REVIEW ARTICLE

Anticoagulation management in nonvalvular atrial fibrillation: current and future directions

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KEY WORDS

anticoagulation management, atrial fibrillation, bleeding, novel oral anticoagulants, thromboembolism

ABSTRACT

Oral anticoagulant therapy, either with vitamin K antagonists (VKAs) or with novel oral anticoagulants such as dabigatran, rivaroxaban, and apixaban, is the mainstay for thromboprophylaxis in patients with atrial fibrillation (AF). Thromboembolic risk factors associated with AF and risk factors for bleeding associated with oral anticoagulant therapy are largely the same, and bleeding risk very rarely outweighs individual benefit of thrombosis prevention, thus resulting in positive net clinical benefit of oral anticoagulant therapy in almost all AF patients.

Prevention of AF-related thromboembolic events most commonly requires long-term oral anticoagulant therapy. Over time, various clinical situations may occur in a given patient (e.g., a need for an urgent surgery or invasive intervention, acute stroke, etc.), which may require a temporary or permanent modification of anticoagulant therapy regardless of which anticoagulant drug has been used. This may be particularly challenging for physicians because many issues regarding optimal use of oral anticoagulant drugs in specific clinical situations still remain to be solved.

In this review article, we discuss the periprocedural management of oral anticoagulant therapy, bridging, transition to another oral anticoagulant, the occurrence of acute stroke in a patient already taking an oral anticoagulant, and decision when it is safe to resume oral anticoagulation therapy after stroke. We summarize the available evidence and current (and future) approaches to oral anticoagulation management in such clinical situations.

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Introduction Oral anticoagulant therapy, either with vitamin K antagonists (VKAs) or with novel oral anticoagulants (NOACs) such as dabigatran, rivaroxaban and apixaban, is the mainstay for thromboprophylaxis in patients with atrial fibrillation (AF).[1-3] Thromboembolic risk factors associated with AF and risk factors for bleeding associated with oral anticoagulant therapy are largely the same (e.g., older age, hypertension, prior stroke, etc.) and bleeding risk very rarely outweighs individual benefit of thrombosis prevention, thus resulting in positive net clinical benefit of oral anticoagulant therapy in almost all AF patients.[4-7]

Recent randomized clinical trials on stroke prevention in nonvalvular AF have shown that compared with warfarin, NOACs are at least equally effective and safer (particularly regarding the risk for intracranial hemorrhage [ICH]).[8-10] NOACs offer a rapid, predictable, and stable anticoagulation with fixed-dose regime, few clinically relevant drug interactions and no need for routine laboratory monitoring of anticoagulant intensity, which makes a long-term oral anticoagulant treatment with NOACs more convenient in comparison to VKAs, both for physicians and patients (TABLE 1).[11-13] However, NOACs have no specific antidote available in clinical setting and none of the routinely used coagulation tests can precisely quantify their anticoagulation effect.[12-14] Nonetheless, increasing experience with NOACs will help learn how to use these drugs effectively and safely in daily clinical practice.

Prevention of AF-related thromboembolic events most commonly requires long-term oral anticoagulant therapy.[1-4] Over time, various

TABLE 1 Novel oral anticoagulant drugs for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation

		Dabigatran	Rivaroxaban	Apixaban
mechanisms		thrombin (factor II) inhibitor	factor Xa inhibitor	factor Xa inhibitor
dosage (daily)		twice	once	twice
bioavailability		~6%	>66%	>50%
protein binding in plasma		35%	~90%	~90%
control assays		aPTT, dTT, ECT	aPTT, PT[a], anti-Xa chromogenic assay	none
antidote		none	none	none
clearance		80% renal	66% renal	25% renal
half-live (h) in patients with normal renal function				
		12–14	5–9 (young) 11–13 (elderly)	8–13
half-lives (h) in renal dysfunction (eGFR in ml/min/1.73 m^2)[12]				
stage II (eGFR, 60–90)		14	8.5	no data
stage III (eGFR, 30–60)		18	9	no data
stage IV (eGFR, 15–30)		28	9.5	no data
stage V (eGFR, <15)		no data	no data	no data
last intake before elective surgical intervention (hours)				
low risk	stage I (eGFR, >90)	>24	>24	>24
	stage II (eGFR, 60–90)	>36	>24	>24
	stage III (eGFR, 30–60)	>48	>24	>24
	stage IV (eGFR, 15–30)	not known	>36	>36
high risk	stage I (eGFR, >90)	>48	>48	>48
	stage II (eGFR, 60–90)	>72	>48	>48
	stage III (eGFR, 30–60)	>96	>48	>48
	stage IV (eGFR, 15–30)	not known	>48	>48

a prolonged aPTT but unknown relation with bleeding risk

Abbreviations: aPTT – activated partial thromboplastin time, dTT – diluted thrombin time, ECT – ecarin clotting time, eGFR – estimated glomerular filtration rate, PCCs – prothrombin complex concentrates, P-gp – P-glycoprotein, PT – prothrombin time

clinical situations may occur in a given patient (e.g., a need for an urgent surgery or invasive intervention, acute stroke, etc.), which may require a temporary or permanent modification of anticoagulant therapy regardless of which anticoagulant drug has been used. This may be particularly challenging for physicians, as many issues regarding optimal use of oral anticoagulant drugs in specific clinical situations still remain to be solved.[12-14]

In this review article, we discuss the periprocedural management of oral anticoagulant therapy, bridging, transition to another oral anticoagulant, the occurrence of acute stroke in a patient already taking an oral anticoagulant and decision when it is safe to resume oral anticoagulation therapy after stroke, and we summarize available evidence and current approaches to oral anticoagulation management in such clinical situations.

Why, when, and how to stop anticoagulation

Annually, at least 1 of 10 AF patients taking an oral anticoagulant needs a surgery or an invasive procedure.[15] Although a common task, the periprocedural management of long-term oral anticoagulant therapy is a complex clinical problem, with sparse high-quality evidence to inform clinical practice. The ultimate goal is to minimize both thromboembolic events and major hemorrhage in the periprocedural period, and clinicians must carefully balance the risk of thromboembolic events with oral anticoagulation interruption against the risk of periprocedural bleeding with continued treatment, taking into account both patient-related and procedure-related risk factors.[16,17] In addition, there are some differences in the periprocedural management of oral anticoagulant therapy between elective and emergency procedures.

Elective surgery The elective setting allows for a careful planning of periprocedural management of oral anticoagulant therapy, and appropriate decision making should include the assessment of thrombotic and bleeding risk, consideration of the need for bridging anticoagulation therapy and planning of the timing of cessation and reinitiation of oral anticoagulant therapy.[16-19] This area has been subject to much debate and discussion.[20,21]

Periprocedural thromboembolic risk assessment

Periprocedural risk for thromboembolic events with oral anticoagulation interruption in

TABLE 2 Stroke and bleeding risk assessment in patients with nonvalvular atrial fibrillation

Thromboembolic risk assessment using the $CHADS_2$ score							
	clinical parameter	risk category for TE	score	TE rate during 1 year	postoperative 30-day stroke rates according to $CHADS_2$[16]	risk category for postoperative TE	recommendation for bridging
	max 6 points	low ($CHADS_2$ 0)	0	1.9 (1.2–3.0)	1.01 (0.83–1.21)	low ($CHADS_2$ 0–2)	no bridging (grade 2C)
C	**C**hronic heart failure		1	2.8 (2.0–3.8)	1.62 (1.46–1.79)		
H	**H**ypertension	moderate ($CHADS_2$ 1)	2	4.0 (3.1–5.1)	2.05 (1.87–2.24)		
A	**A**ge >75 y	high ($CHADS_2$ ≥2)	3	5.9 (4.6–7.3)	2.63 (2.26–3.04)	moderate ($CHADS_2$ 3–4)	no recommendation
D	**D**iabetes mellitus		4	8.5 (6.3–11.1)	3.62 (2.66–4.80)		
S	**S**troke/TIA (2 points)		5	12.5 (8.2–17.5)	3.65 (1.83–6.45)	high ($CHADS_2$ 5–6)	bridging recommended (grade 2C)
			6	18.2 (10.5–27.4)	7.35 (2.43–16.3)		

thromboembolic risk assessment using the CHA_2DS_2–VASc score					hemorrhagic risk assessment		risk for bleeding
	max 9 points	truly low (CHA_2DS_2–VASc 0)	0	0.0		max 11 points	
C	**C**hronic heart failure	moderate (CHA_2DS_2–VASc 1)	1	0.46 (0.10–1.34)	H	**H**ypertension	low (HAS-BLED 0–2)
H	**H**ypertension	high (CHA_2DS_2–VASc ≥2)	2	0.78 (0.44–1.29)	A	**A**bnormal renal or lever	
A	**A**ge >75 y (2 points)		3	1.16 (0.79–1.64)		function (1 point each)	high (HAS-BLED ≥3)
D	**D**iabetes mellitus		4	1.43 (1.01–1.95)	S	**S**troke	
S	**S**troke/TIA (2 points)		5	2.42 (1.75–3.26)	B	**B**leeding	
V	**V**ascular disease		6	3.54 (2.49–4.87)	L	**L**abile INR	
A	**A**ge 65–74 y		7	3.44 (1.94–5.62)	E	**E**lderly (age >65 y)	
Sc	**S**ex **c**ategory (female)		8	2.41 (0.53–6.88)	D	**D**rugs or alcohol	
			9	5.57 (0.91–27.0)		(1 point each)	

Abbreviations: INR – international normalized ratio, TE – thromboembolism, TIA – transient ischemic attack

TABLE 3 Periprocedural bleeding with continued oral anticoagulation in surgical or invasive procedures

	Low risk	High risk
discontinuation of OAC not recommended	discontinuation of OAC and bridging could be considered	discontinuation of OAC and bridging recommended
– superficial surgery (dermatologic excisions)	– SVT catheter ablation	– AF catheter ablation
– endoscopy without surgery	– pacemaker/ICD implantation	– thoracic surgery (cardiac surgery)
– cataract or glaucoma intervention	– angiography	– abdominal surgery
– dental interventions	– endoscopy with biopsy	– major orthopedic surgery
– paradontal surgery		– liver biopsy
– implant positioning		– kidney biopsy
– extraction of 1-to-3 teeth		– prostate resection
		– lumbar diagnostic puncture
		– spinal and epidural anesthesia
		– operations >1 h

Abbreviations: AF – atrial fibrillation, ICD – implantable cardioverter/defibrillator, OAC – oral anticoagulants, SVT – supraventricular tachycardia

nonvalvular AF patients is essentially derived from the patient's 'regular' risk for thromboembolism, as estimated outside the periprocedural period using the $CHADS_2$ or CHA_2DS_2–VASc score (TABLE 2), whereby increasing score values indicate progressively higher risk of stroke. Although these scores have been less well validated in the periprocedural setting, periprocedural thromboembolic risk in older recommendations thus far have been graded as low, intermediate, or high according to the $CHADS_2$ values of 0–2, 3–4, and 5-6, respectively.[15-17] In addition to patient-related risk factors, several procedure-related thrombotic risk factors have been described (e.g., major surgery, laparoscopic procedures, etc.), and it has been suggested that major surgery per se may increase the pre-existing thromboembolic risk up to 10-fold.[22,23]

Periprocedural bleeding risk assessment The risk of major periprocedural bleeding with continued oral anticoagulation primarily depends on the type of procedure (TABLE 3). In general, any procedure that can result in intracranial, intraspinal, intraocular, intrathoracic, pericardial, or retroperitoneal bleeding is considered a high bleeding risk procedure and those are, essentially, all major surgery (e.g., cardiac, vascular, brain, spinal, orthopedic, urologic, intrathoracic or intra-abdominal surgery), some invasive procedures such as AF ablation, arthroscopy, kidney or liver biopsy, lumbar puncture, large polypectomy, etc., or any surgery or procedure lasting ≥45 min.[15,16,23] Additional risk factors, such as history of bleeding with invasive procedures or trauma, or concomitant use of antiplatelet and nonsteroidal anti-inflammatory medications may further increase the procedure-related bleeding risk.[24] A HASBLED score ≥3 (TABLE 2) was found to be an independent predictors of bleeding in both AF and non-AF patients in a prospective, observational, multicenter registry of patients undergoing invasive procedures.[25]

Periprocedural cessation of oral anticoagulant therapy Any periprocedural antithrombotic strategy is essentially a 'trade-off' between the clinical consequences of a stroke versus a bleeding event.[26] Of note, AF-related stroke is twice as likely to be fatal as non-AF stroke, and cause permanent disability in 40% of stroke survivors.[27] Given that stroke usually results in more severe consequences than most major bleedings, a strategy that includes a few more major bleeds to prevent one stroke is generally deemed reasonable.[28] Thus, minor procedures with low bleeding risk including dental, dermatologic and ophthalmologic procedures can be performed under uninterrupted oral anticoagulation therapy either with VKAs or with NOACs (TABLE 3). For example, tooth extractions, minor dermatologic procedures including skin cancer excision, and ophthalmologic procedures (i.e., cataract surgery) under continued VKA were associated with low bleeding rates (<5%).[29-31] However, the international normalized ratio (INR) immediately before procedures with uninterrupted VKAs should be closer to the lower end of therapeutic range of 2.0 to 3.5 (i.e., 2.0–2.5). Importantly, minor procedures should not be performed at peak concentrations of NOACs, but should be scheduled to coincide with the trough concentration of a NOAC – at the time when the next dose is due (i.e., 12 to 24 h after the last drug intake, depending on once or twice daily dosing) or even postponed to 18–24 h after the last intake, with the NOAC restarted 6 h later (thus skipping 1 dose of a twice daily dosed NOAC).[14,32]

When a procedure-related bleeding risk necessitates periprocedural interruption of oral anticoagulation, the time interval without anticoagulation therapy should be the shortest possible in high-risk AF patients. An INR of ≤1.5 is generally considered safe regarding the risk of periprocedural bleeding, and is usually achieved from 4 to 6 days following warfarin cessation (indeed, 93% of the patients with an INR within the therapeutic range will have an INR of <1.5 5 days after warfarin discontinuation).[33] Nonetheless, the INR should be re-checked within 24 h before the procedure, as the INR normalization may take longer in patients receiving higher-intensity anticoagulation (INR of 2.5–3.5) and

TABLE 4 Thromboembolic risk factors related to ablation of atrial fibrillation

preprocedural risk factors
risk factors inherent to the individual patient:
– CHA_2DS_2–VASc score
arrhythmia-related risk factors:
– endothelial/endocardial dysfunction
– reduced left atrial contractile function
periprocedural risk factors
risk factors inherent to the individual patient:
– CHA_2DS_2–VASc score
procedure-related risk factors:
– introduction of the foreign material (catheter) into the blood stream
– catheter manipulation (risk of displacement of pre-existing thrombi)
– application of radio-frequency energy – creation of highly thrombogenic endothelial damage and activation of coagulation factors
– atrial stunning
– transient mechanical dysfunction
– paradoxical decrease of left atrial and left atrial appendage blood flow velocities
postprocedural thromboembolic risk factors
risk factors inherent to the individual patient:
– CHA_2DS_2–VASc score
arrhythmia-related risk factors and periprocedural endocardial damage (particularly significant during the first 2 weeks after the procedure):
– endothelial damage and activation of coagulation factors
– transient mechanical dysfunction
– paradoxical decrease of left atrial and left atrial appendage blood flow velocities

in elderly.[34] In addition, an INR of ≤1.2 is recommended for procedures with increased risk of bleeding into closed spaces (e.g., intracranial surgery).

A rapid onset and predictable duration of anticoagulant effect of NOACs allow a more precise proper timing of short-term cessation and reinitiation of NOACs therapy compared with VKAs in the periprocedural setting. The optimal timing of discontinuation of NOAC before surgery depends on renal function. In patients with normal kidney function, the last NOAC dose should be taken 24 h before the elective procedures with a low bleeding risk and 48 h before procedures with a high risk of bleeding. In patients with impaired renal function, NOACs must be discontinued earlier than 24 h before a procedure (TABLE 1).[12-14,32,35,36]

Bridging anticoagulation When a high bleeding risk procedure is needed, temporary cessation of oral anticoagulation therapy is mandatory. Given the cumbersome pharmacology of VKAs,[37,38] bridging was designed to replace warfarin by a parenteral agent with rapid onset of action and short half-life such as unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), which can be discontinued and restarted only a few hours before and after the procedure, respectively.[39] Due to a predictable and relatively short duration of the NOACs effect, bridging is probably not necessary in NOAC-treated patients.[32] Currently, bridging is recommended for VKA-treated AF patients at a high risk of thromboembolic events undergoing high-bleeding-risk procedures, while the individualized balancing of thromboembolic vs. bleeding risk is recommended for patients at a moderate risk of thromboembolism.[15] However, both recommendations have been provided with low-grade evidence (2C), derived mostly from retrospective observational studies with heterogeneous groups of patients undergoing various procedures.

A recent systematic review and meta-analysis of 34 studies on perioperative thromboembolic and bleeding events in patients undergoing elective surgical or invasive procedures has evaluated the safety and efficacy of periprocedural bridging anticoagulation in a total of >12,000 patients of whom 7118 had received any periprocedural bridging therapy.[40] In this currently the largest analysis of the periprocedural management of patients taking VKAs, heparin bridging was associated with more than a 5-fold greater risk of any bleeding, 3-fold greater risk of major bleeding, and similar risk of thromboembolic events compared with nonbridging periprocedural strategy. In addition, the risk of bleeding was higher with therapeutic vs. prophylactic or intermediate LMWH dosing, again with no significant difference in the risk of thromboembolic events.[40]

A recent randomized trial compared continued warfarin treatment to bridging therapy with heparin in patients at a high risk of thromboembolism (>5% per year) undergoing elective pacemaker or implantable cardioverter-defibrillator (ICD) implantation.[41] Nearly 90% of the patients had AF, and the trial was terminated after the second prespecified interim analysis due to remarkably greater incidence of the primary study outcome (i.e., clinically significant device-pocket hematoma) in the bridging group vs. continued warfarin

group (16.0% vs. 3.5%, respectively), while major surgical or thromboembolic complications were rare in both groups (1 stroke and 1 transient ischemic attack [TIA] only, and both occurred in the continued-warfarin group).[41]

Observational data suggested that brief periprocedural warfarin interruptions (for ≤5–7 days) without bridging anticoagulant therapy were associated with a low incidence of thromboembolic events in AF patients at a low-to-intermediate risk of thromboembolism,[42,43] and this was confirmed by a retrospective analysis of the randomized RE-LY trial of dabigatran vs. warfarin in nonvalvular AF, which included 4591 patients who underwent at least 1 invasive procedure with warfarin or dabigatran temporary interruption (bridging anticoagulation was used in 15.3% to 28.5% of those procedures).[44] The incidence of thromboembolic events was as low as 0.5%, whilst the incidence of major periprocedural bleeding ranged from 3.8% to 5.1%, thus further challenging the benefits of bridging anticoagulant therapy in patients with nonvalvular AF. Nonetheless, definite conclusions must await the results of ongoing randomized clinical trials comparing bridging vs. no bridging perioperative strategies (e.g., the BRIDGE [NCT00 786 474] and PERIOP2 [NCT00 432 796] trials).

When the decision to use bridging anticoagulant therapy has been made, UFH should be preferred over LMWH in patients with significantly impaired renal function and creatinine clearance (CrCl) <30 ml/min.[15] In addition, scarce nonrandomized data suggest that subtherapeutic (i.e., prophylactic, low-dose) LMWH is safe and effective bridging therapy at least in patients with low--to-moderate thromboembolic risk.[15,45,46] However, in moderate-risk patients, the intensity of bridging anticoagulation should be individualized.[15]

Postprocedural reinitiation of oral anticoagulant therapy In general, the resumption of antithrombotic therapy is a major determinant of postprocedural bleeding risk.[16] Whilst the prophylactic-dose heparin can be restarted when hemostasis is secured, a therapeutic-dose heparin use should be postponed for 48 h after the high bleeding risk procedure or for a shorter period after the procedures with lower risk of bleeding.[15-17] Given the slow onset of action, VKAs should be restarted the evening of the procedure day or the next day (unless a reoperation is anticipated), and the INR should be within the therapeutic range for at least 48 h before heparin is discontinued.[15]

NOACs can be restarted 6–8 h after procedures with immediate and complete hemostasis (including atraumatic spinal/epidural anesthesia or clean lumbar puncture). However, NOACs should be postponed for 48–72 h after most of other procedures.[12-14] It should be kept in mind that full therapeutic anticoagulation with NOACs will be achieved within 2 h of intake, and the postoperative use of a reduced dose of the NOACs has not been studied in AF patients.

Periprocedural anticoagulation for atrial fibrillation ablation Catheter ablation is an established AF treatment strategy, which employs constantly developing technologies and is increasingly used even in patients with nonparoxysmal AF or advanced left atrial remodeling, who commonly undergo more extensive, complex AF ablation procedures.[47] In addition to the underlying AF-related risk of thromboembolic events, AF ablation per se bears a high thromboembolic potential, both during the intervention and for some time thereafter (**TABLE 4**).[47,48] Since AF ablation is an elective procedure, a carefully planned thromboprophylactic strategy must be conducted during the pre-, intra-, and post-procedural period, with mandatory intraprocedural use of heparin.

A large world-wide survey on safety and efficacy of AF ablation reported a 0.94% periprocedural incidence of stroke/TIA.[49] Although optimal anticoagulation protocols for AF ablation are still a matter of debate, growing evidence show that uninterrupted warfarin at an INR between 2 to 3 decreases the rates of thromboembolic events and minor bleedings, without increase in major bleeding rates compared to discontinuation of warfarin with heparin bridging.[47,50] Importantly, it has been shown that the optimal INR range during uninterrupted periprocedural anticoagulation with warfarin is rather narrow (2.1–2.5), which necessitates particularly careful INR monitoring during the periprocedural period.[51] A recent survey of clinical practice in Europe showed that common practice when approaching an anticoagulated patient was to stop oral anticoagulant and bridge with heparin, but as many as 53.6% of centers would perform the procedure with uninterrupted oral anticoagulation.[52]

Regarding the periablation use of NOACs, data accumulated over the past few years mostly rely upon small, often retrospective, observational studies on dabigatran (there are no published data on factor Xa inhibitors in patients undergoing AF ablation, as yet), with significant differences in study design, patients' characteristics or procedure-related factors, all of which might have contributed to the contrasting results of those studies.[53-60] In general, late discontinuation of dabigatran (<24 h) before ablation and/or too early reinitiation of dabigatran (within first several hours after the procedure) were associated with increased risk of both thromboembolic and bleeding events compared with uninterrupted warfarin, while an earlier dabigatran discontinuation and later reinitiation (≥4 h after the procedure), with appropriate LMWH bridging, appeared to be as safe and effective as uninterrupted warfarin. However, the most recent study (also retrospective, but the largest published so far) found that uninterrupted administration of dabigatran 150 mg twice daily (including the day of the procedure), was as safe and effective as uninterrupted warfarin.[59] Indeed, a recent meta-analysis of the published literature on the efficacy and safety of dabigatran for anticoagulation during AF

ablation found no significant differences in the efficacy and safety of dabigatran vs. uninterrupted warfarin, and no particular pattern of dabigatran interruption or continuation were associated with increased incidence of thromboembolic or bleeding events.[60]

Of note, several reports with standard intraprocedural heparin protocol described delayed and lower levels of activated clotting time (ACT) in the dabigatran group compared with uninterrupted warfarin (i.e., a higher bolus of heparin was needed to achieve the goal ACT level in the dabigatran group).[61] Despite the unclear mechanism(s) of potential dabigatran interaction with heparin, it may result in increased risk of bleeding (due to higher heparin bolus) or additional risk of thromboembolism (if the ACT levels are suboptimal).

Overall, current evidence suggest that dabigatran can usually be discontinued 12–30 h before AF ablation and then safely resumed 3–4 h after achieving hemostasis.[60] Shorter discontinuation intervals or even uninterrupted dabigatran therapy during AF ablation should also be further investigated, and a large-scale clinical trial is needed to establish the safety (and efficacy) of dabigatran and other NOACs in the setting of AF ablation.

Oral anticoagulant therapy in patients undergoing percutaneous coronary interventions Patients with coexistent coronary artery disease (CAD) and AF have significantly higher mortality rates and increased risk of adverse cardiovascular events.[62] Such patients commonly need a combination of anticoagulant and antiplatelet therapy for a variable length of time,[63-66] and management of such dual or triple treatment may be particularly challenging in the absence of sufficient high-quality data to guide clinical practice.

Available data suggest that a percutaneous coronary intervention (PCI) is safe in patients taking a VKA, without bridging and additional periprocedural heparin.[67] Continuation of VKA (with the INR within the therapeutic range) is also recommended for PCI in the setting of an acute coronary syndrome (ACS).[64-66,68] However, NOACs should be temporarily discontinued in all patients presenting with an ACS.[14] Unless contraindicated for other reasons, all ACS patients should be immediately given low-dose aspirin (150–300 mg) and a thienopyridine. Primary PCI using radial approach is strongly preferred over fibronolysis in patients with an acute ST-elevation myocardial infarction, and additional parenteral anticoagulation should be used during the procedure, regardless of the timing of the last NOAC dose.[14] Alternatively, if primary PCI is not available, fibrinolysis might be considered, provided that coagulation tests (TABLE 5) indicate that the NOAC anticoagulation effect has faded out.[14]

In patients with a non-ST-elevation ACS, every effort should be made to reduce the need for long-term dual or triple therapy (e.g., radial approach, bare-metal instead of drug-eluting stents, sole balloon angioplasty, bypass surgery, etc.), and coronary angiography should be postponed for ≥24 h after the last NOAC dose, if possible. Once the patient with ACS is stabilized (i.e., no recurrent ischemia, no need for additional invasive treatment), anticoagulation with NOAC can be restarted after safe discontinuation of parenteral anticoagulant therapy.[14] During a PCI, UFH or bivalirudin are generally preferred over enoxaparin, owing to their short-lasting action and lower risk of bleeding.[14]

Post-ACS treatment of an AF patient who underwent a PCI with stenting should be highly personalized, based on the individual atherothrombotic, thromboembolic, and bleeding risks which should be estimated using the GRACE, CHA_2DS_2–VASc and HASBLED scores.[1,69] Balancing the risk of stroke/systemic embolism (which is best reduced by oral anticoagulant therapy, with superior efficacy compared with any other antithrombotic treatment)[70] and stent thrombosis or recurrent ischemic events (best reduced using dual antiplatelet therapy)[71,72] vs. the risk of bleeding (which is the highest with triple antithrombotic therapy),[72] triple therapy (i.e., oral anticoagulation with a lower target INR of 2.0 to 2.5 and aspirin plus clopidogrel) is generally prescribed as short as possible depending on the stent type, followed by an oral anticoagulant plus 1 antiplatelet agent and, ultimately, an oral anticoagulant long-term monotherapy.[64-66] However, these recommendations are based mostly on the expert consensus opinion.

Any combination of antithrombotic drugs increases the risk of bleeding compared with a single-drug therapy. For example, in a nationwide registry of AF patients admitted for myocardial infarction or PCI, the rates of bleeding within 30 days were 22.6% per 100 person-years with triple therapy, 20.3% with warfarin plus aspirin and 14.3% with dual antiplatelet therapy.[72] A recent open-label, randomized study with anticoagulated patients (not all had AF) undergoing PCI/stenting suggested that, compared with triple therapy, warfarin plus clopidogrel could be safer in terms of bleeding (HR = 0.36, 95% CI, 0.26–0.50, P <0.001) and all-cause mortality (6.4% vs. 2.5%, respectively, P = 0.03), with no increase in the rate of thrombotic events.[73] Unfortunately, the study was not powered to assess the efficacy of warfarin plus clopidogrel for the prevention of stroke, stent thrombosis, or recurrent ischemic events.

A post-hoc substudy of the RE-LY trial showed that concomitant use of dabigatran with a single or dual antiplatelet therapy increased bleeding risk by approximately 60% and 130%, respectively.[74] Until more data become available, it seems prudent to avoid a prolonged use of any NOAC with a single or dual antiplatelet therapy, particularly in very old patients, those with impaired renal function and patients requiring ticagrelor or prasugrel (newer P2Y12 inhibitors).[14]

TABLE 5 Interpretation of coagulation assays for the estimation of drug exposure in patients treated with NOACs (modified from Turpie et al.)[12]

NOAC	Plasma concentration of NOAC after ingestion		Coagulation assays					
	peak plasma concentration	trough plasma concentration	PT	INR	aPTT	dTT	anti-FXa	ECT
dabigatran	2 h	12–24 h	NA	NA	>2 × ULN at trough plasma concentration suggests excessive bleeding risk	>65 s at trough plasma concentration suggests excessive bleeding risk	NA	≥3 × ULN at trough plasma concentration suggests excessive bleeding risk
rivaroxaban	2–4 h	16–24 h	prolonged PT[a] may indicate increased bleeding risk, but calibration at local laboratory needed	NA	NA	NA	quantitative; no data on the threshold values for bleeding/ thrombotic risk	NA
apixaban	1–4 h	12–24 h	NA	NA	NA	NA	no data on the threshold values for bleeding/ thrombotic risk	NA
edoxaban	1–2 h	12–24 h	no available data on the relation with bleeding risk[a]	NA	no available data on the relation with bleeding risk[b]	NA	quantitative; no data on the threshold values for bleeding/ thrombotic risk	NA

a drug exposure produces prolonged PT
b drug exposure produces prolonged aPTT

Abbreviations: NOAC – novel oral anticoagulant, ECT – ecarin clotting time, NA – not applicable, ULN – upper limit of normal, others – see TABLES 1 and 2

The ongoing open-label, randomized, controlled, multicenter PIONEER AF-PCI study (NCT01830543), will investigate 2 strategies of rivaroxaban and 1 of oral VKA in patients with nonvalvular AF who undergo PCI with stent placement. The primary purpose of this study is to evaluate the safety for 2 different rivaroxaban treatment strategies and 1 VKA treatment strategy utilizing various combinations of dual antiplatelet therapy or low-dose aspirin or clopidogrel (or prasugrel or ticagrelor).

Urgent surgery In patients taking oral anticoagulant therapy (either a VKA or a NOAC), urgent surgery is generally associated with much higher bleeding rates compared with elective interventions. However, bleeding rates with dabigatran were not higher than with warfarin in patients undergoing an urgent intervention in the RE-LY trial.[44]

If an emergency intervention is required in patient taking a VKA, anticoagulant intensity can be easily measured by the INR, and, if needed, anticoagulation effect can be reversed using parenteral vitamin K, fresh frozen plasma, and/or prothrombin complex concentrate.[75] However, in patient taking a NOAC, the drug should be discontinued and surgery should be delayed (if possible) until at least 12 to 24 h after the last dose to allow anticoagulant effect to diminish sufficiently.[14] If the intervention cannot be postponed, the risk of bleeding will be increased, which should be weighed against the urgency of operation. Common or NOAC-specific coagulation tests, if available, should be considered to assess the presence of anticoagulant effect and to roughly estimate its extent (i.e., therapeutic or excessive anticoagulation) (TABLE 5).

Switching between different anticoagulants In certain clinical situations, a transition from one to another anticoagulant drug might be needed for a variety of reasons. It is of crucial importance to safeguard the continuation of optimal anticoagulation and to minimize the risk of bleeding during the transition, as the ultimate goal would be to keep the patient protected from stroke but not at the expense of an excessive anticoagulation with unnecessarily increased risk of bleeding complications. To keep the transition as safe as possible, physicians should be familiar with basic pharmacological properties of oral anticoagulant drugs.

The transition from warfarin (or any other VKA) to a NOAC is simple – the drug can be started as soon as the INR falls to ≤2.0 after warfarin discontinuation. If the INR is 2.0–2.5, NOACs may be started immediately (or better the next day) without further INR measurement. However, if the INR is above 2.5, the initiation of a NOAC should be postponed and the INR measurement should be repeated. The time of next INR measurement should be estimated from the present INR value and half-life of the VKA, ranging

from 8 to 14 h for acenocoumarol, 38–42 h for warfarin and as much as 120–200 h for phenprocoumon. For the transition from LMWH to a NOAC, the oral drug should be started at the time when the next LMWH dose is due. Given the short half-life of UFH (approximately 2 h), NOAC should be started at the moment of UFH discontinuation.

If the transition from a NOAC to warfarin (or any other VKA) is needed, the process is not so straightforward, since VKAs need some time to reach the optimal intensity of anticoagulation, owing to a delayed onset of action. Hence, a VKA and a NOAC should be given concomitantly for several days (most commonly 2 days), until the INR reaches the appropriate range. As NOACs may increase the INR value, INR should be measured just before the next intake of a NOAC (trough concentration), and rechecked 24 h after the last NOAC intake. If the patient has been taking dabigatran, the drug half-time may range from 15 to 28 h, depending on a renal function, and warfarin should be started 3, 2, or even just 1 day before dabigatran discontinuation if the CrCl is above 50 ml/min, 30–50 ml/min, or below 30 ml/min, respectively.[14]

Acute stroke in patients taking oral anticoagulant therapy First step in the management of patients presenting with an acute cerebrovascular event is to differentiate between ischemic stroke, hemorrhagic stroke, or other ICH and TIA.

The annual rates of ICH in AF patients taking VKAs are lower than 1%, and NOACs impressively decrease the risk of hemorrhagic stroke or any ICH compared with warfarin.[8-10] Nonetheless, patients with ICH had the same poor prognosis regardless of whether they were taking warfarin or dabigatran in the RE-LY trial.[76]

A recent meta-analysis of 8 contemporary randomized trials on stroke prevention in AF including the trials with NOACs found a 1.66% residual annual rate of ischemic stroke in patients taking warfarin at a mean time in therapeutic range (TTR) of 55% to 68% (all trials were conducted between 2003 and 2011),[77] and NOACs were at least as effective as warfarin for stroke prevention in randomized AF trials.[8-10] In patients already taking warfarin, stroke rates are higher with older age, female sex, previous stroke/TIA, VKA-naive status, renal impairment, previous aspirin use, and higher $CHADS_2$ score.[78] In addition, poor TTR with warfarin or noncompliance to NOAC therapy increase the risk of cardioembolic stroke. However, up to 25% of AF-related strokes may result from intrinsic cerebrovascular disease or noncardiac sources of embolism.[79]

Acute ischemic stroke Thrombolytic therapy with recombinant tissue plasminogen activator (rTPA) in the first 4.5 h from onset of stroke symptoms is not recommended for patients under optimal oral anticoagulation. Indeed, thrombolysis should not be attempted in the first 48 h after the last administration of NOAC.[14] If the timing of last NOAC intake cannot be elucidated, common coagulation tests (**TABLE 5**) should be considered and mechanical recanalization of the occluded vessel could be employed if the tests are not available or when the results suggest clinically relevant anticoagulant effect.[14]

Oral anticoagulant therapy (VKA or NOAC) should be restarted as soon as possible, depending on the cerebral infarct size (and estimated risk of hemorrhagic transformation), after 1day in patients with TIA, after 3 days in patients with small infarct, after 5–6 days following a moderate-sized stroke, and 2–3 weeks after large cerebral infarcts.[14] When NOACs are used, bridging with heparin is not required. The use of NOACs for secondary prevention in AF have recently been the subject of debate and discussion.[80,81]

Acute hemorrhagic stroke ICH is the most feared, devastating complication of oral anticoagulant therapy with a 50% mortality rate.[82] Reversal of VKAs should be attempted using fresh frozen plasma or PCC, since vitamin K acts too slowly to affect the brain hemorrhagic expansion.[83] As there are no routinely available specific antidotes for NOACs at present, the drug should be discontinued and supportive therapy should be applied, including PCC and activated factor VII (however, the latter strategy needs further evaluation in clinical studies).[14]

Similar to prior ischemic stroke being the single strongest predictor of recurrent stroke, any anticoagulation-related ICH (also including subdural or epidural hemorrhage) is an independent risk factor for new ICH, and a history of spontaneous ICH is a contraindication against anticoagulation.[14,82-84] The decision to reinitiate oral anticoagulation therapy after any anticoagulation-related ICH is always very difficult, since the stroke and bleeding risk parallel one another in the majority of AF patients, and the optimal timing for resumption of anticoagulation after ICH is still unresolved. However, recurrent ICH after VKA reinstitution occurs less frequently than recurrent thromboembolic events in patients who do not restart warfarin, particularly in patients requiring secondary stroke prevention.[85] In general, in patients at high risk of thromboembolism and low risk of a recurrent bleeding event, reinstitution of oral anticoagulation from 7 to 14 days after ICH is recommended.[14,86] Alternatively, nonpharmacological thromboprophylactic strategies such as left auricular ablation or occlusion should be considered.[1,2,14]

Conclusions Optimal prevention of AF-related thromboembolic events most commonly requires long-term oral anticoagulant therapy, and the availability of multiple oral anticoagulants facilitates a more personalized thromboprophylaxis in AF patients. However, various clinical situations may necessitate a temporary or permanent modification of anticoagulant therapy regardless

of which anticoagulant drug has been used. This may be particularly challenging for physicians, as many issues regarding optimal use of oral anticoagulant drugs in specific clinical situations still remain to be solved, and several ongoing randomized trials as well as the growing clinical experience with NOACs should provide some answers in the near future.

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ARTYKUŁ POGLĄDOWY

Leczenie przeciwkrzepliwe w niezastawkowym migotaniu przedsionków – stan obecny i przyszość

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SŁOWA KLUCZOWE

incydenty zakrzepowo-zatorowe, krwawienie, leczenie przeciwkrzepliwe, migotanie przedsionków, nowe doustne antykoagulanty

STRESZCZENIE

Doustne leczenie przeciwkrzepliwe za pomocą antagonistów witaminy K (*vitamin K antagonists* – VKA) lub nowych doustnych antykoagulantów, takich jak dabigatran, rywaroksaban czy apiksaban, to podstawa profilaktyki incydentów zakrzepowo-zatorowych u chorych z migotaniem przedsionków (*atrial fibrillation* – AF). Czynniki ryzyka zakrzepicy związanej z AF są w większości te same co czynniki ryzyka krwawienia związanego z doustnym leczeniem przeciwkrzepliwym, przy czym ryzyko krwawienia bardzo rzadko przewyższa indywidualną korzyść w postaci zapobiegania incydentom zakrzepowym, co przekłada się na dodatni bilans korzyści z doustnej antykoagulacji u niemal wszystkich chorych z AF.

Zapobieganie powikłaniom zakrzepowo-zatorowym związanym z AF wymaga zazwyczaj długotrwałej terapii przeciwkrzepliwej. Wraz z upływem czasu mogą pojawić się u chorego różne sytuacje (np. konieczność wykonania pilnego zabiegu operacyjnego lub innej interwencji inwazyjnej, udar mózgu itd.), które mogą wymagać tymczasowej lub stałej modyfikacji schematu antykoagulacji, niezależnie od stosowanego leku. Mogą one być szczególnym wyzwaniem dla lekarza, ponieważ wiele problemów związanych z dawkowaniem doustnych leków przeciwzrepliwych w szczególnych sytuacjach klinicznych nie zostało jak dotąd rozwiązanych.

W tym artykule przeglądowym rozważamy kwestie: okołozabiegowego postępowania u chorych otrzymujących doustne leki przeciwkrzepliwe, stosowania terapii pomostowej, zmiany jednego doustnego antykoagulantu na inny, występowania udaru mózgu u chorych leczonych doustnie przeciwkrzepliwie oraz decyzji, kiedy można po udarze mózgu ponownie włączyć takie leczenie. Podsumowujemy dostępne dane oraz obecny (i przyszły) sposób podejścia do doustnego leczenia przeciwkrzepliwego w takich sytuacjach klinicznych.

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