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REVIEW

Periprocedural Management of Novel Oral Anticoagulants During Atrial Fibrillation Ablation: Controversies and Review of the Current Evidence

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Oral anticoagulation (OAC) has been the cornerstone for the prevention of thromboembolic complications in patients with atrial fibrillation (AF) at significant risk of stroke. Catheter ablation is an established efficacious technique for the treatment of AF. Ameliorating the risk of stroke or transient ischaemic attack (TIA) in patients with AF undergoing ablation requires meticulous planning of pharmacotherapy. The advent of non-vitamin K oral anticoagulants (NOACs) has broadened the therapeutic scope, representing a viable alternative to traditional vitamin K antagonists (VKA) in non-valvular AF. Potential advantages of NOACs include greater pharmacokinetic predictability, at least comparable efficacy as compared to VKA and a superior haemorrhagic complication profile. However, robust evidence for the safety and efficacy of periprocedural NOAC use for AF ablation remains uncertain with a non-uniform clinical approach between and within institutions.

The following review will summarise the current and emerging evidence on periprocedural management of NOACs in patients undergoing catheter ablation of AF. An overview of NOAC pharmacology will provide a foundation for the review of reversal agents in the context of catheter ablation of AF. The purpose of the review is to outline key studies and identify key areas for further critical research with the ultimate aim of developing evidence-based guidelines for optimal care.

Keywords Non-vitamin K antagonists • Atrial fibrillation ablation • Peri-procedural

Introduction

Traditional use of VKAs has been fraught with difficulties in compliance with periodic blood sampling and maintenance of a therapeutic international normalised ratio (INR). The emergence of NOACs appears to have simplified anticoagulation therapy for patients and physicians, primarily through more predictable pharmacodynamics. Current NOACs are either direct inhibitors of Factor IIa (FIIa) or Factor Xa (FXa). The pharmacological and pharmacokinetic profiles of the four currently available agents; dabigatran, rivaroxaban, apixaban and most recently edoxaban, are outlined in Table 1.

Atrial fibrillation confers a cerebral thromboembolic risk of 1% to 18% per annum, depending on validated scoring

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Table 1 Pharmacokinetic and pharmacodynamic profiles of currently available NOACs non-valvular AF.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dosage (mg) and frequency	150 twice daily *(CrCl≥50mL/min)* **OR** 110 twice daily *(CrCl 30-50mL/min or age ≥75 years)*	20 once daily *(CrCl≥50mL/min)* **OR** 15 once daily *(CrCl 30-50mL/min)*	5 twice daily **OR** 2.5 twice daily *(Age≥80 or weight≤60 kg or serum Cr≥133 umol/L)*	60 daily **OR** 30 daily *(CrCl 15-50mL/min or weight≤60kg)*
Mechanism of action	Direct thrombin inhibition of bound and fibrin free	Direct factor Xa inhibition	Direct factor Xa inhibition	Direct factor Xa inhibition
T_{max} (Time to peak concentration, hr)	2	2.5-4	1-3	1-2
$T_{1/2}$ (Half-life, hr)	12-17	5-9	8-15	10-14
Plasma protein binding (%)	35	95	87	55
Cellular efflux protein P-glycoprotein ligand	Yes	Yes	Yes	Yes (but no inhibition of pump function)
Hepatic cytochrome binding	No effect on plasma levels in moderate hepatic impairment	CYP3A4, CYP 2J2 and non-cytochrome dependent pathways	CYP3A4, CYP3A5	Minimal metabolism by CYP3A4
Metabolism and excretion	Renal 85% unchanged excretion	66% metabolised and renal 33% unchanged excretion	25% metabolised, 27% renal clearance, gastrointestinal excretion	Renal 50% unchanged excretion, 50% unchanged gastrointestinal excretion
Effects of renal impairment	Increase in AUC, T_{max} and $T_{1/2}$ with decreased in CrCL*	Inverse relationship between CrCL and AUC, anti-factor Xa activity and PT*	Inverse relationship between CrCL and AUC, however no correlation with anti-factor Xa activity*	Inverse relationship between CrCL and AUC§
Weight impact on trough levels	50% greater trough levels in <50 kg compared to >100kg	Negligible effect. No dose adjustment necessary	<50 kg associated with 30% increase in AUC and >120 kg associated with 30% decrease in AUC‡	13% greater AUC in <55 kg compared to >84kg
Impact of age	Compared to <65yrs, 28% higher trough levels in 65-75yrs, 68% higher in >75yrs	AUC 1.5-fold higher in elderly but no dose adjustment necessary	AUC 32% higher in >65yrs compared to <65yrs‡	No impact independent of age-related changes in body weight and renal function

‡ No dose adjustment required unless weight ≤60 kg, age ≥80yrs or renal impairment (creatinine ≥133umol/L). * Contraindicated in severe renal impairment (CrCL < 30 mL/min). § Absolute contraindication in non-valvular atrial fibrillation patients with CrCl >95 mL/min., based on clinical trial data. AUC denotes area under curve. CrCL denotes creatinine clearance.

algorithms incorporating ancillary demographic, vascular and other cardiometabolic risk factors. Recent large international surveys of patients undergoing catheter ablation of AF, estimate a periprocedural risk of cerebral thromboembolism and cardiac tamponade at 0.94% and 1.31%, respectively [1]. Mitigating these risks requires a systematic approach to pre-, intra- and post-procedural management of NOAC therapy. Current areas of significant uncertainty are:

- The safety and efficacy of peri-procedural NOAC therapy. Specifically, the impact on minor bleeding, major bleeding and thromboembolic complications, including ''silent'' cerebral ischaemia.
- A unified definition of ''uninterrupted therapy'' and ''minimally interrupted therapy'', the latter implying dose omission or modification pre-procedure.
- The role of pre-procedural transoesophageal echocardiography to evaluate for LA thrombus.
- The effect of OACs on intra-procedural in vivo anticoagulation and/or potential interference with various coagulation assays in vitro, in particular the activated clotting time (ACT).
- The optimal NOAC resumption strategy post-procedure.
- The management of bleeding complications and potential clinical use of ligand-specific reversal agents.

Pre-Procedural Planning

Uninterrupted therapeutic anticoagulation for more than three weeks is considered a prerequisite for instrumentation of the left atrium (LA) and delivery of ablation energy within the LA [2]. Prior to the ablation procedure, transoesophageal echocardiography (TOE) is often used to exclude LA thrombus. Confirmation of the weekly INR readings >2.0 in the preceding 30 days may, in low risk patients, obviate the need for a TOE. However, strict NOAC therapy adherence cannot be objectively verified using a validated assay due to the short half-life of the drugs. Therefore a TOE may be required if there is any doubt about continuous NOAC compliance in the pre-procedural period. Likewise, any known or deliberate interruption of therapeutic anticoagulation may presage the need for a TOE. A TOE may also be preferable in high-risk patients, such as those with a high CHADS2 score ($\geq$1) and/or persistent AF, and presenting in AF at the time of the procedure [3]. Conversely, observational data supports the omission of pre-procedural TOE in patients with a CHADS2 score <1 [2,3].

More recently, there has been a shift towards uninterrupted VKA therapy in the peri-procedural period. The strategy has been demonstrated to lower peri-procedural thromboembolic complications without an increase in haemorrhagic complications [4]. With accumulating data suggesting a superior safety profile, such an uninterrupted strategy has been increasingly adopted by electrophysiologists. It is estimated that interruption of VKA increases thromboembolic risk 12-fold as compared to an uninterrupted strategy [5].

One approach for patients on NOACs requires transitioning to VKA several weeks prior to the procedure and then continuing uninterrupted VKA for the procedure. Strict patient adherence is paramount to achieving a desirable INR, and reducing the risk of bleeding or thrombotic complications [6,7]. With these issues in mind, there is an effort towards a more simplified approach with either minimal interruption of the NOAC pre-procedure or completely uninterrupted NOAC therapy throughout the peri-procedural period. The existing data, including meta-analyses, will be discussed later in this review. At this point, studies have disclosed significant variability in clinical practice and areas of uncertainty. Randomised and masked prospective clinical trials will provide the unified evidence-base to inform recommendations and guidelines.

Intra-Procedural Anticoagulation

Intra-procedural thromboembolism is a rare but devastating complication that may be related to transseptal access and the presence of catheters in the LA, ablation-related and mechanical stunning of the LA following reversion to sinus rhythm [8]. Conventional anticoagulation following LA access (or immediately prior to transseptal puncture) is via parenteral heparin (UFH) to achieve an ACT between 300 and 400 seconds. Algorithms for determination of the initial UFH bolus have been developed, based on body weight and pre-procedural INR [9]. Periodic ACT sampling then guides further boluses or continuous infusion rates. Failure to sustain continuous therapeutic anticoagulation (therapeutic INR) in the preceding three weeks, or failure to achieve and maintain an intra-procedural ACT $\geq$300 seconds has generally been associated with an increased peri-procedural thromboembolic risk [10]. However, a specific ACT threshold for risk has not been clearly defined.

The ACT is a non-standardised test that is sensitive to deficiencies in FVIII (<25% of normal), IX, X, XI and XII. Thus it is expected that the ACT will be prolonged in patients receiving VKAs, via a reduction in FX and FIX activity. The impact of a therapeutic INR ($\geq$2.0) on ACT and UFH dosing in patients undergoing AF ablation on uninterrupted VKA has been previously described [11]. Patients on therapeutic VKA require less total UFH dose, and attain a target ACT $\geq$350 seconds more rapidly, than those with sub-therapeutic (<2.0) or interrupted VKA therapy. These observations have been confirmed in an observational retrospective study by Nagao et al. [12].

There is less experience and data to guide the management of intra-procedural anti-coagulation in the setting of uninterrupted (or minimally interrupted) NOAC therapy. As with VKA, the baseline ACT will be prolonged also in patients taking NOACs, but this is due to inhibition of FX and FII, rather than decreased clotting activities. The optimal monitoring strategy for NOACs remains unknown since in vivo anticoagulant effect and plasma drug levels do not consistently show a linear relationship. Thus it is unlikely that experience with VKA can be directly applied to the NOACs. Moreover, there is increasing recognition of an interaction between NOACs and UFH [12,13].

While drug-specific laboratory assays are available for the NOACs, the influence of concomitant UFH infusion on the FXa activity measurement is not clear and the presence of UFH will render the thrombin time-based monitoring assays for dabigatran uninterpretable without a UFH neutralisation step. Conversely, the influence of the NOACs on the utility of the ACT to guide UFH therapy is also unclear. Recent studies have shown that higher doses of UFH are required to maintain a target ACT of >350 seconds in the context of uninterrupted NOACs compared to uninterrupted VKA [12]. Importantly, the interpretation of the ACT with combined NOAC (direct FIIa and FXa inhibition) and UFH (indirect FIIa and FXa inhibition) is unlikely to be a simple additive effect [14–17]. Table 2 outlines the effect of the NOACs on commonly used in-vitro coagulation assays. This apparent interaction may in part reflect the proceduralist's modified UFH administration protocol and the target ACT, in patients who have been on an uninterrupted or minimally interrupted NOAC strategy. Nonetheless, it is unknown if patients on NOACs require an alteration of the UFH protocol to achieve a target ACT, or conversely if the target ACT should be re-evaluated for patients specifically taking NOACS. The observed differences may be a function of the drug's effect on the in vitro assay rather than an in vivo

Table 2 Effects of NOACs on various in-vitro coagulation assays.

	Dabigatran	Rivaroxaban	Apixiban
International Normalised Ratio (INR) and Prothrombin Time (PT)	Insensitive for anticoagulant effect at therapeutic levels. Prolonged with supra therapeutic levels	PT prolonged. Weak correlation with plasma Rivaroxaban levels dependent on assay reagent used.	Minor prolongation without plasma concentration correlation. Elevated levels suggestive of high dose ingestion
Activated Partial Thromboplastin Time (aPTT)	Prolonged, but non-linear relationship between plasma levels and anticoagulant assay at plasma levels >200ng/mL	Dose dependent non-linear increase in aPTT. Poor correlation at high plasma levels	Non-linear correlation with plasma drug levels
Activated Clotting Time (ACT)	Crude correlation between ACT and drug levels	Limited experience	Limited experience
Thrombin Time (TT)	Linear relationship between plasma levels and anticoagulant assay	Not affected	Not affected
Chromogenic FXa assay	No effect	Dose-dependent prolonged anti-Factor Xa activity	Curvilinear relationship between assay and plasma drug levels
†Mean time (min) taken to achieve intra-procedural ACT>300sec	60	10	60
†UFH units (U/kg/hr) required to reach intra-procedural ACT>300sec	59±20	57±15	71±28

†Based on retrospective analysis of 869 patients by Nagao et al., Heart Rhythm, 2015.
FXa Factor Xa; ACT activated clotting time; UFH unfractionated heparin. Insufficient data is available for Edoxaban.

augmentation or amelioration of the anticoagulant effect of UFH. Regardless, recent retrospective and prospective studies of CA with uninterrupted NOAC therapy have aimed for an ACT 300s-400s based upon historical targets with VKAs and heparin, and they have not shown a difference in adverse outcomes [18].

Post-Procedural Care

There is a thrombogenic state in the LA post-ablation, partly due to stasis (especially following acute reversion to sinus rhythm) and endocardial pro-inflammatory and pro-coagulant cascade activation [19]. This pro-coagulant state persists for a number of weeks. It is therefore critical that anticoagulation is recommenced with minimal or no interruption, and maintained for a minimum duration of one to three months based on expert consensus recommendations [2,20]. Long-term administration or cessation of anticoagulation will depend on multiple patient and procedural factors, including the patient's baseline risk of stroke (CHADS2 score).

The optimal timing for restarting anticoagulation following ablation must take into account the risk of bleeding related to the peripheral access site, the potential for acute or subacute haemopericardium and oesophageal haematoma. Common post-procedural clinical practices are as follows: In patients on uninterrupted VKA therapy, simply continuing VKA in the post-procedure period is usually straightforward. In patients with interrupted VKA therapy, the usual practice is to re-commence VKA and bridge with intravenous UFH infusion (often without a bolus dose) or subcutaneous enoxaparin four to six hours after removal of the sheaths if haemostasis has been established.

In patients on an uninterrupted or minimally interrupted NOAC strategy, the NOAC is recommenced four to six hours after removal of the vascular sheaths if haemostasis has been established. In the latter strategy, bridging with parenteral heparin is usually not required because of the rapid onset of action of the NOACs. Real-world practice is often influenced by physician experience and patient factors such as compliance, duration of hospital stay, rural or remote dwelling, and access to an INR clinic. In addition, the administration of protamine at the conclusion of LA access is often used to expedite safe removal of the vascular sheaths, establishing haemostasis, and allow earlier recommencement of OAC. Non-randomised studies have shown that administration of IV protamine at the conclusion of the catheter ablation procedure facilitates early removal of the intravascular sheaths and patient mobilisation, without any compromise to patient safety or procedural outcomes [21,22]. In addition to protamine administration, the figure-of-eight femoral suture appears to be a simple, effective and safe mechanical

approach to hasten reestablishment of therapeutic anticoagulation thereby minimising anticoagulation interruption [23–25].

Within the first 24 hours post-ablation, pericardial effusion is observed in up to 14% of patients [26], ranging from a mild effusion to overt tamponade. With early reinstitution of OAC post-procedure, some ablationists consider a day 1 transthoracic echocardiogram to exclude pericardial effusion, prudent clinical care. Notably however, this has not been systematically studied.

Use of NOACs in the Peri-Ablation Period – Key Studies

Dabigatran vs VKA

Non-randomised studies have compared peri-procedural interruption (or minimal interruption) of *dabigatran* to uninterrupted VKA. Although the studies have pointed towards superior efficacy and safety in the former strategy, caution is warranted as these studies have been observational and non-randomised. Furthermore, amongst the studies, there is significant variability in dosage of dabigatran, days of dabigatran cessation pre-procedure and the mean intra-procedural ACT achieved and maintained. Individual studies and meta-analyses have suggested that dabigatran and uninterrupted VKA have similar peri-procedural bleeding and thromboembolic complications rates (Table 3). In prospectively collected data from a PVI registry [27], 376 patients were on dabigatran which was withheld for one to two days pre-procedure and 623 patients on uninterrupted VKA. The study found no evidence of increased thromboembolic or haemorrhagic risk with either strategy. Similarly, a case-control study, showed equivalent safety and efficacy between dabigatran withheld for 24 hours pre-procedure (resumed four hours post-procedure) and uninterrupted VKA [28]. Furthermore, in a multicentre retrospective analysis of 882 patients, Arshad et al. [29] showed that uninterrupted dabigatran was not associated with increased adverse risk, whilst VKA with UFH bridging was associated with an increase in total complications. A randomised controlled trial comparing dabigatran (45 patients) and VKA (45 patients), both using an interrupted strategy, demonstrated a higher risk of minor bleeding in the VKA group [30]. Of note however, in a multicentre, observational and prospective study, Lakkireddy et al. showed a higher incidence of bleeding complications including late-onset pericardial tamponade and the composite outcome of bleeding and thromboembolism, in the dabigatran group [31]. In univariate analysis, dabigatran use and age >75 years were independent predictors of bleeding and combined bleeding and thromboembolism. These observations were not reproduced in other similar studies. A potential explanation is the dabigatran dosage omission on the morning of the procedure and the uniform use of the 150 mg twice-daily dosage. Another reason for caution is that the risk of procedure-related thromboembolic complications is exceedingly low. Therefore, observational studies with limited patient numbers are not adequately powered to detect differences in thromboembolic risk between the study groups. A recent meta-analysis of peri-ablation dabigatran vs VKA highlighted the non-randomised observational nature of the studies and variability in the drug administration protocol [32]. Despite this, the analysis suggested similar safety and efficacy between dabigatran and VKA.

Rivaroxaban vs VKA

Similarly, the majority of studies related to uninterrupted *rivaroxaban* (a FXa inhibitor), have suggested at least non-inferior safety outcomes, when compared to uninterrupted VKA. In a single centre observational study by Diller et al., no differences were noted for major bleeding or thromboembolism, however there was a slight but significant increased incidence of non-tamponade pericardial bleeding in the VKA group [33]. Moreover, the UFH administration protocol was different between groups, as was the baseline and mean intra procedural ACT. A larger multicentre observational study comparing rivaroxaban to VKA, both uninterrupted, showed no differences in all predefined safety outcomes. However, the HAS-BLED score was higher in the VKA cohort as compared to the rivaroxaban arm of the study [34]. Two meta-analyses, each incorporating eight studies, showed equivalent peri-procedural efficacy, risk of bleeding and risk of thromboembolism, when compared to VKA and dabigatran [35,36]. However, significant variation in the dosage administration protocol in the various studies, limited interpretability of the study.

The recent VENTURE-AF [18] trial was an exploratory randomised prospective study comparing uninterrupted VKA to rivaroxaban in the peri-ablation period in 250 patients. Using an intention-to-treat analysis, both strategies demonstrated comparably very low thromboembolic and bleeding rates. Major bleeding (0.4% in rivaroxaban group) and thromboembolic events (0.8% in rivaroxaban group; one vascular death and one ischaemic stroke) occurred post-procedure in the VKA arm. In addition, more IV UFH units were required in the rivaroxaban group to achieve and maintain the target ACT when compared to the VKA group. Moreover, the mean procedural ACT achieved was higher in the latter group, as compared to the former. The open-label exploratory nature of the design, small sample size and recruitment from highly experienced labs introduces significant confounders and biases. Nevertheless, the results substantiated observations made in preceding clinical studies.

Apixaban vs VKA

Apixaban, a FXa inhibitor similar to rivaroxaban, has likewise demonstrated a comparable safety profile to VKA when used in an uninterrupted protocol in the peri-ablation period [37,38]. However, heterogeneity in the UFH protocol and ACT profiles were again observed between the study groups. The Apixaban Evaluation of Interrupted Or Uninterrupted Anticoagulation for Ablation of Atrial Fibrillation (AEIOU: NCT02608099) is a phase 4 prospective randomised cohort

Table 3 Summary of studies evaluating the safety and efficacy of peri procedural NOAC use.

Study	Design	Comparisons	Key findings	Comments
Dabigatran				
Lakkireddy, 2012	Multicentre, prospective registry	Interrupted D vs uninterrupted VKA	Greater risk of major bleeding, total bleeding and composite of bleeding and thromboembolism	Dabigatran use and age >75 yrs predictive of bleeding and embolic risk
Imamura, 2013	Single centre, prospective observational	Interrupted D vs Interrupted VKA	No differences between groups for safety endpoint	Dabigatran shortened the hospital stay
Bin Abdulhak, 2013	Meta-analysis of 9 observational studies	Interrupted D vs Uninterrupted VKA	Interrupted D as safe as VKA with regards to bleeding and thromboembolism	Significant practice variation in amongst centres
Providencia, 2013	Meta-analysis of observational controlled studies (14 citations)	Mix of interrupted and uninterrupted D vs VKA mostly uninterrupted	No differences between groups, and no differences between the 2 dosage regimens of D, for all safety endpoints	Significant practice variation in amongst centres
Maddox, 2013	Single centre, prospective observational	Uninterrupted D vs Uninterrupted VKA	No differences between groups for all safety endpoints	Non-randomised, single centre study
Kim, 2012	Single centre, case-control	Interrupted D vs Uninterrupted VKA	No thromboembolic complications in either group. No differences in major or minor bleeding	INR, clopidogrel use and CHADS2-VASc score were independent predictors of bleeding in VKA group
Arshad, 2014	Retrospective, single centre	Uninterrupted D vs Uninterrupted VKA vs Interrupted VKA (UFH bridging)	Uninterrupted VKA associated with major bleeding/transfusion	Concurrent antiplatelet use and UFH bridging associated with greater complications
Bassiouny, 2013	Case-control single centre	Interrupted D vs Uninterrupted VKA	No differences in all bleeding and thromboembolic events	1 VKA patient stroke, 0 in D
Phan, 2015	Meta-analysis (17 studies)	D vs VKA, mixed administration protocols	No differences in thromboembolism or bleeding events	Mostly retrospective observational studies
Nin, 2012	Prospective randomised single centre	Interrupted D vs Interrupted VKA	VKA significantly higher venepuncture bleeding risk. One fatal mesenteric thromboembolic event in VKA group	Small sample size (45 in each arm)
Rivaroxaban				
Lakkireddy, 2014	Multicentre, prospective observational	Uninterrupted R vs Uninterrupted VKA	No differences between groups for all safety endpoints	VKA group higher HAS-BLED score
Dillier, 2014	Single centre, prospective observational	Uninterrupted R vs Uninterrupted VKA	No differences between groups for major bleeding, thromboembolism or death. Higher risk of non-tamponade pericardial haemorrhage in VKA group	Mean ACT lower in R group. Greater UFH requirement in VKA group
Winkle, 2014	Single centre observational	VKA, D, R, Aspirin and none. All interrupted	Interrupted D and R were safe to use peri-ablation for AF	No anticoagulation or aspirin was a safe option for low risk patients
Phan, 2015	Meta-analysis of 8 studies	R vs D vs VKA, mixed administration protocols	No differences when comparing R vs VKA, and R vs D for thromboembolism and bleeding events	5 prospective studies. Heterogeneous administration protocols, including UFH bridging

Table 3. (continued).

Study	Design	Comparisons	Key findings	Comments
Apixaban				
Kaess et al 2015	Single centre, prospective observational	Uninterrupted A vs Uninterrupted VKA	No differences between groups for all safety endpoints	Greater UFH required in A group to achieve and maintain target ACT
Aryal, 2014	Systematic review	R vs VKA and R vs D	No difference in bleeding or thromboembolism when comparing R vs VKA, and R vs D	Heterogeneous administration protocols, including UFH bridging
Cappato, 2015	Prospective, randomised, multi-centre	Uninterrupted R vs Uninterrupted VKA	No differences between groups for all bleeding and thromboembolic events	All adverse events occurred in VKA group
Di Biase, 2015	Prospective multicentre registry	Uninterrupted A vs Uninterrupted VKA	No differences between groups for all safety endpoints.	No differences in ''silent'' MRI evidence of cerebral ischaemia
Nairooz, 2015	Meta-analysis of 8 studies	Uninterrupted D/R/A vs Uninterrupted VKA	No differences in all bleeding and thromboembolic events between groups	7 of 8 studies were observational in nature
Wu, 2016	Meta-analysis of 25 studies	Uninterrupted or Interrupted D/R/A vs Uninterrupted VKA	Compared to VKA, either NOAC strategy, interrupted or not, was associated with lower risk minor bleeding, but equivalent major bleeding and thromboembolic risk	Majority of studies observational. Analysis includes conference abstracts with incomplete data. Significant heterogeneity between studies in administration protocols

VKA vitamin K antagonist, D dabigatran, R rivaroxaban, A apixaban, UFH unfractionated heparin, ACT activated clotting time, TOE transoesophageal echocardiography. Safety endpoints specific minor bleeding, major bleeding and thromboembolism.

study, assessing an uninterrupted vs interrupted apixaban administration protocol currently in the recruitment phase. In addition, there will be a retrospective cohort of 300 VKA-treated patients as a benchmark comparison with either peri-ablation apixaban strategy.

It is noteworthy that there were a small number of delayed pericardial effusions (occurring >48 hours post-ablation) amongst the patient cohorts undergoing ablation on NOACs [31,37]. This phenomenon has not been observed in the VKA literature. Moreover, delayed pericardial effusion may be under-detected because it is standard practice in most centres to discharge patients within 24 hours of the ablation procedure. While some of these occurrences may represent a reactive inflammatory pericarditis, further surveillance for this particular complication is required in ongoing studies of NOACs. Prolonging hospitalisation, or an early outpatient echocardiogram may be considerations in the meantime.

In addition, the risk of symptomatic cerebral ischaemic events peri-ablation is relatively small and the existing studies are underpowered to detect a difference in the event rate of this complication. While symptomatic strokes are rare, asymptomatic cerebral embolism (ACE) associated with AF ablation has an estimated incidence of 14% and is therefore of increasing concern [39]. The clinical course of these lesions is unclear, however the size of the acute lesion likely determines the likelihood of subsequent glial scarring [40]. In a prospective observational study, failure to maintain a therapeutic pre-ablation INR was associated with a greater than three-fold increase in ACE, while interruption of VKA and UFH bridging resulted in a seven-fold increase in ACE [41]. In light of these findings, the use of universal cerebral imaging for ''silent'' cerebral embolism as a surrogate marker of stroke may allow subtle differences in event rates to be detected in future studies.

In view of the non-randomised observational nature of the available data and variability in study protocols, several prospective, randomised and controlled studies are currently underway comparing uninterrupted NOAC use to uninterrupted VKA use. The RE-CIRCUIT (*phase 4*, NCT02348723) and AXAFA (*phase 4*, NCT02227550) studies will study the use of dabigatran and apixaban, respectively, in the peri-ablation period. The latter will utilise cerebral imaging to detect ACE.

Management of NOAC-Related Bleeding

Peripheral access site haemorrhage and haematoma are the most common complications in AF ablation procedures and rarely require surgical repair. Rare but potential life threatening haemorrhagic complications include pericardial bleeding and tamponade due to catheter or ablation energy-related trauma, mediastinal bleeding from great vein or arterial laceration, oesophageal haematoma, cerebral haemorrhage (including thromboembolism with haemorrhagic transformation) and exacerbation of pre-existing gastrointestinal bleeding diathesis such as peptic ulcer. These emergency situations often require resuscitation measures. In addition, baseline evaluation of coagulation status, blood count and renal function and verification of the last NOAC dose administered, may determine subsequent management and whether specific reversal or bypass agents are required. Normal APTT and PT levels cannot be used to exclude the contribution of NOACs to bleeding. However, NOAC activity assays are available in tertiary referral hospital laboratories across Australia; the dilute thrombin time or ecarin-based assays can be used to assess dabigatran concentrations while calibrated anti-Xa activity assays are used for rivaroxaban and apixaban. These assays can detect active NOACs in the circulation at the time of active bleeding to aid in the clinical decision if ongoing bypass or reversal agents (when available) are indicated. Undetectable anti-Xa or dilute thrombin activity likely excludes clinically relevant drug concentrations. It is worth emphasising that these assays are only validated in the absence of UFH.

In the setting of CA with combined heparin and VKA or NOAC, protamine can reverse the heparin effect. It should be kept in mind that the ACT cannot be used to extrapolate the heparin dose when the patient is concurrently on a VKA or NOAC. NOACs and VKA increase the ACT in a crudely dose-dependent manner; however, the interaction between NOACs and heparin on the ACT is unknown.

In this context, it is important that centres develop and become familiar with a strategy for managing emergency bleeding in patients taking NOACs. Involvement of an expert haematologist will provide invaluable guidance on the use of haemostatic agents and interpretation of complex laboratory assays. Figure 1 provides a proposed protocol for managing emergent peri-procedural bleeding in patients taking NOACs. It is important to note that in the absence of randomised clinical trials, recommendations are based on expert opinion and are likely to vary between different institutions. It is also important to consider the heightened thromboembolic risk specific to the post-ablation setting, when initiating reversal or antagonist agents for use in the EP laboratory. These haemostatic agents may further increase the post-ablation pro-thrombotic or pro-coagulant state and should be used with great caution and following expert consultation.

Dabigatran is the only NOAC amenable to removal by dialysis and haemodialysis may be used in patients with plasma dabigatran levels >500ng/mL. Until the direct reversal agents for the NOACs become widely available, the pharmacological control of bleeding has focussed upon the efficacy of various bypassing agents such as combinations of prothromin complex concentrates. The recommendations are based on limited data extrapolated from pre-clinical animal studies, pilot studies in healthy volunteers and ex-vivo laboratory-based assays. Table 4 shows the pharmacological profiles of several haemostatic agents that bypass or reverse NOACs.

An ideal reversal agent would have the characteristics of being rapidly acting, amenable to titration and with minimal or absent pro-coagulant effects. Most recently, rational drug

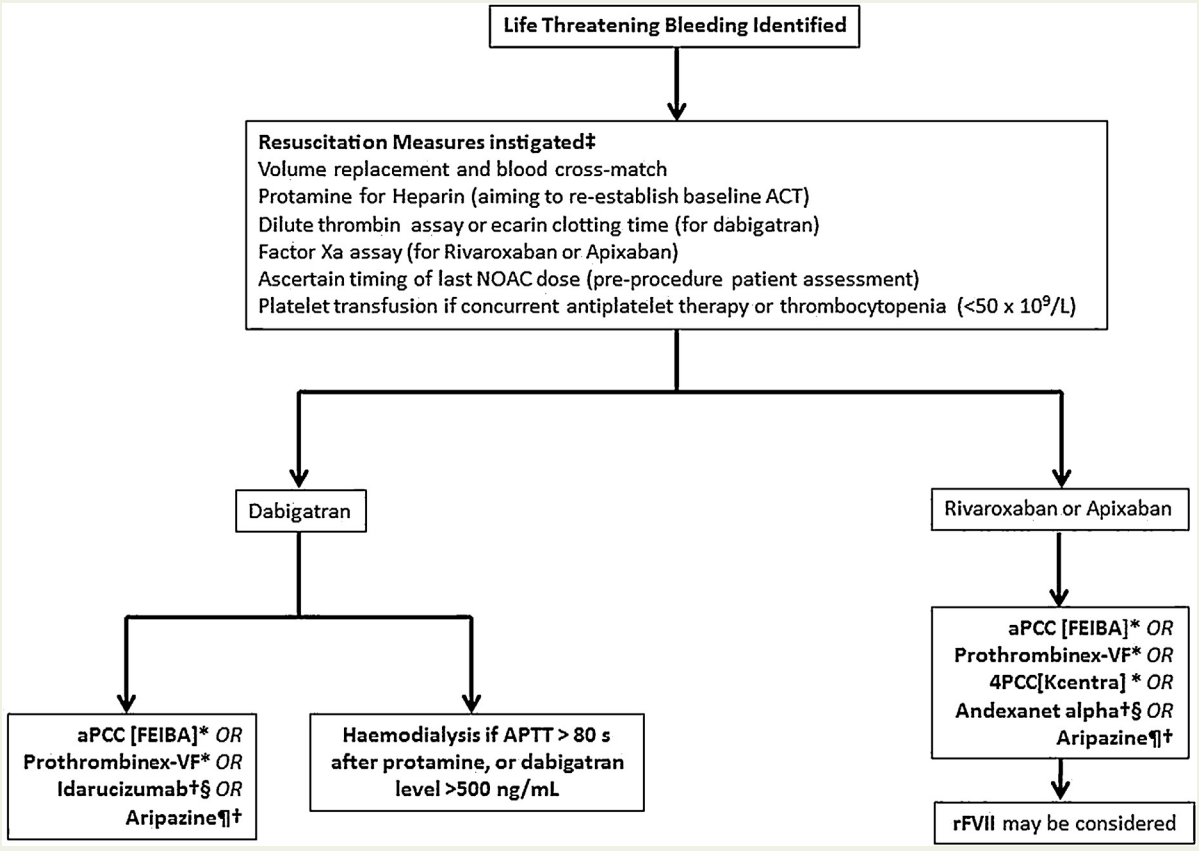

Figure 1 Proposed protocol for managing emergent peri-procedural bleeding in patients taking NOACs.
‡Acute resuscitation measures (e.g.: pericardiocentesis) may be taken simultaneously.
*aPCC activated Protein Complex Concentrate; FEIBA Factor VIII Inhibitor Bypassing Fraction; Prothrombinex-VF 3-factor PCC (3PCC);
†Not to be used with other haemostatic agents,
§Currently in phase III trials (At the time of manuscript submission, drug approved in the United States and Europe. Only available in Australia through the Special Access Scheme), ¶Currently in phase II trials (not approved).

development has led to two avenues for rational NOAC-specific reversal drug development; monoclonal antibody fragments that bind to and neutralise the drug (idarucizumab), and a decoy of the molecular target of the drug which lacks enzymatic activity (andexanet alpha). These agents bind intravascular NOACs, and neutralise them before the *neo* hapten is renally excreted. Extravascular bound drug equilibrates with the plasma drug pool thus allowing continued redistribution and leaching of the drug from the body. These protein drugs are parenterally administered with rapid onset and offset, thus allowing re-dosing if needed or recommencement of effective anticoagulation when the risk of re-bleeding is reduced. A potential inherent risk of these protein drugs is immunogenicity although early experience has shown an absence of immunological abnormalities. Ongoing data collection is also required regarding potential pro-thrombotic complications.

The RE-VERSE AD prospective cohort study (NCT02104947) recently reported its interim analysis [42] of 90 patients receiving 5 g intravenous infusion of idarucizumab (2 x 2.5 g idarucizumab in 50 mL infusions, administered within 15 minutes of each other), for either serious bleeding or urgent surgery, requiring reversal of dabigatran taken for stroke prevention in AF. The percentage of dabigatran reversal, assessed by dilute thrombin time or ecarin clotting time at a central laboratory, was 88-98% within minutes. The leeching effect was demonstrated by the 80% decrease in plasma dabigatran by four hours after administration of idarucizumab, and this diminutive effect was sustained at 24 hours. Under the trade name of Praxbind, idarucizumab has been approved by the U.S. FDA and European Medicines Agency for the European Union. At the time of writing, the drug was not approved, but is being evaluated by the Australian Therapeutic Goods Administration (TGA). The drug is currently available in Australia strictly through the Special Access Scheme of the TGA.

Andexanet has recently shown pharmacodynamic and pharmacokinetic efficacy for reversing the anticoagulant effects of rivaroxaban and apixaban, and restoring near-complete thrombin generation without any serious adverse or pro-thrombotic effects [43].

Table 4 **Pharmacological profile of haemostatic agents used for bypass or reversal of NOACs.**

Agent	Pharmacology	NOAC	Dosage and titration	Laboratory evidence
Bypass agents				
aPCC (FEIBA™)	Activated factors II, IX, X, VIIa	Dabigatran, Rivaroxaban, Apixaban and Edoxaban	50 IU/kg. Maximum single dose of 100 Units/kg or maximum daily dose 200 Units/kg. Not amenable to titration against standard coagulation assays	Daigatran: Khoo TL, Int J Lab Hematol 2013 Rivaroxaban: Eerenberg, Circulation 2011
4F-PCC	Non-activated factors II, IX, X, VII	Dabigatran, Rivaroxaban, Apixaban and Edoxaban	25-50IU/kg	Apixaban: Martin, Int J Cardiol 2013
3F-PCC (Prothrombinex-VF™)	Non-activated factors II, IX and X (low levels of factors V and VII)	Rivaroxaban, Apixaban and Edoxaban Variable evidence for dabigatran	25-50 IU/kg.	Australasian Society of Thrombosis and Haemostasis (ASTH)
rFVIIa	Activated factor VIIa	In vitro data indicates limited role in NOACs bypass	0.5 or 1 mg/kg	Not currently recommended considering poor in-vitro efficacy and increased thrombogenicity
Tranexamic acid	Dose-dependent inhibition of plasminogen activation and Plasmin. No pro-thrombotic effects, but may augment pro-thrombosis when co-administered with other factor concentrates	No specific evidence. Anecdotally used for mucosal bleeding	15-30 mg/kg IV and possible infusion for mucosal life-threatening bleeds. Not amenable to titration against coagulation in-vitro assay. Titrated against clinical response and renal function	Australasian Society of Thrombosis and Haemostasis (ASTH)
Reversal agents				
Idarucizumab	Monoclonal antibody fragment with high affinity to Dabigatran (free and hapten)	Dabigatran	No pro- or anti-coagulant effect of agent demonstrated. Reversal of dabigatran effect measured by TT and serum drug levels	Phase 3 interim analysis (RE-VERSE AD); Dabigatran in bleeding patients: Pollack, NEJM 2015
Andexanet alpha	Modified recombinant FXa (rFXa). Decoy receptor for oral FXa inhibitors but devoid of enzymatic activity	Rivaroxaban, Apixaban and Edoxaban	Bolus and infusion dose dependent on plasma anti-factor Xa activity.	Phase 2; Apixaban NCT02207725 and Rivaroxaban NCT02220725 Phase 3; Bleeding on oral FXa inhibitors NCT02329327
Aripazine (Ciraparantag)	Pan-antagonist (except VKA). Small cation molecule with multiple hydrogen-bonding binding sites	All NOACs, heparin and LMWH (not VKA)	Pre-clinical	Phase 1; Edoxaban NCT01826266 and Phase 2; Edoxaban NCT02207257. Recently fast track approved for haemorrhage in the United States (Phase 3 NCT02329327)
Modified thrombin (T-S195A-IIa)	Decoy receptor for oral FIIa inhibitors but devoid of enzymatic activity	Dabigatran	Pre-clinical	Currently in *pre-clinical* studies

aPCC activated Protein Complex Concentrate; 4F-PCC 4 -factor Protein Complex Concentrate; 3F-PCC 3-factor Protein Complex Concentrate; rFVII recombinant factor VII; VKA vitamin K antagonist; LMWH low molecular weight heparin. Consultation of local guidelines is recommended.

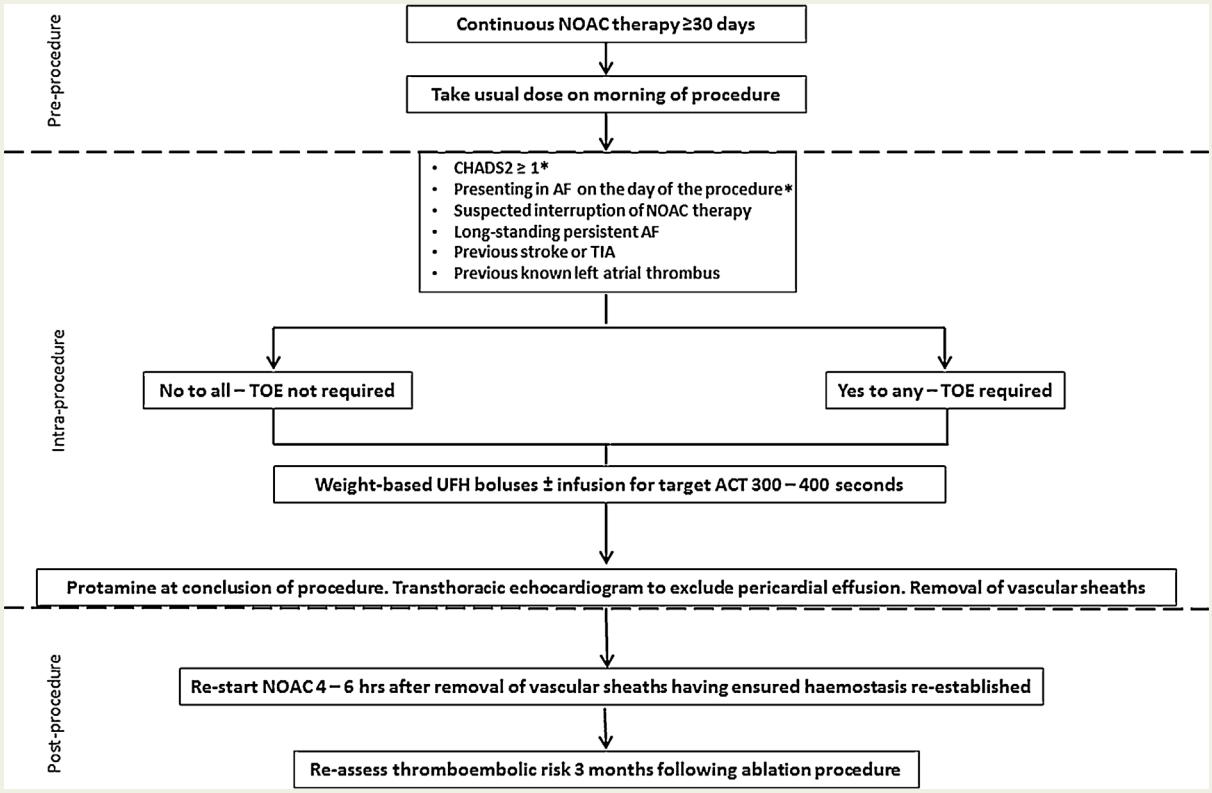

Figure 2 Research algorithm proposed for NOAC management peri-ablation. A prospective randomised study comparing uninterrupted NOAC therapy vs. uninterrupted VKA therapy.
*Puwanant et al., J Am Coll Cardiol. 2009 [3].
CHADS2 Cardiac failure, Hypertension, Age > 75 years, Diabetes, Stroke; TIA Transient ischaemic attack; TOE Transoesophageal echocardiography; UFH Unfractionated heparin;
ACT Activated clotting time.

A third agent, known as aripazine, is a small molecule pan-reversal agent. Aripazine (PER977, Ciraparantag) is a cation with multiple hydrogen bonding binding sites for UFH, enoxaparin and the currently available NOACs. Aripazine (PER977, Ciraparantag) is currently in phase 2 trials (NCT02207257) and has recently been fast-tracked approved for edoxaban-related haemorrhage management (phase 3, NCT02329327).

The safety of combination therapy, in particular using the NOAC-specific reversal agents with bypass agents, is unknown and such use is therefore discouraged until further data is available.

Summary and Future Directions

Catheter ablation of AF is an effective procedure for the long-term maintenance of sinus rhythm. Procedural safety relies on meticulous OAC management in the peri-procedural period. The superior safety and efficacy of uninterrupted therapeutic VKA therapy peri-ablation has further simplified this therapeutic modality. The superior pharmacokinetic and adverse effects profiles of NOACs has translated into greater patient convenience and therefore enhanced therapeutic compliance.

However, we would caution against the universal adoption of uninterrupted NOAC use in the peri-ablation period based on the existing data, particularly in the absence of readily available reversal agents. Adequately powered prospective randomised controlled trials are critically needed for comparing uninterrupted VKA and uninterrupted NOAC strategies, and this may be an ideal subject for collaborative research in Australia and New Zealand. To this end, we propose a schedule which may act as a starting point for developing methods for such studies (outlined in Figure 2). Such a trial would provide the necessary data to either support or refute a switch to NOACs in the peri-ablation period.

In addition, identification of sensitive and specific laboratory assays to assess the quantitative pharmacological aspect of the specific NOAC being studied is also critical for uniform titration and target ACT achievement intra-procedurally. Finally, rational drug design and development of rapid onset, ligand-specific agents or anticoagulation reversal factor, without an inherent pro-thrombotic tendency will affirm a paradigm shift in peri-ablation OAC management.

Disclosures and Declarations

The authors have no external financial support to declare and no relevant disclosures to make.

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