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REVIEW ARTICLE

# Are Some Anticoagulants More Equal Than Others? - Evaluating the Role of Novel Oral Anticoagulants in AF Ablation

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**Abstract:** Left atrial ablation strategies are being increasingly performed as a Class 1 therapeutic indication for drug refractory paroxysmal atrial fibrillation (AF). Traditionally AF ablation has been performed with patients on uninterrupted warfarin therapy, however over the last few years, novel oral anticoagulants (NOACs) have emerged as attractive alternatives to warfarin in order to reduce stroke risk due to AF. NOACs are therefore increasingly being used instead of warfarin in the management of AF. There is also mounting evidence mainly in the form of small randomised studies and meta-analysis that have demonstrated that the use of NOACs for AF ablation is efficacious, safe and convenient. However the peri-procedural dosing protocols used in various studies especially in terms of whether NOAC use is interrupted or uninterrupted during AF ablation, have significant inter-operator and inter-institution variability. Currently there is also a lack of randomised controlled trials to validate the data obtained from meta-analyses. There is also evidence that use of NOACs may increase the requirement of unfractionated heparin during the procedure. This review article shall examine the currently available evidence-base, appraise the gaps in the current evidence and also underscore the need for larger randomised clinical trials in this rapidly developing field.

**Keywords:** Atrial fibrillation, anticoagulation, thromboembolism, stroke, bleeding, ablation.

## 1. INTRODUCTION

AF ablation is associated with a risk of thrombo-embolic and haemorrhagic complications with recent surveys reporting an incidence between 0.25 - 1% [1]. Thrombo-embolic phenomena during AF ablation, are due to a multitude of factors such as the ablation catheter dislodging pre-existing atrial thrombi, clot formation on the ablation catheter or the sheath following trans-septal puncture [2, 3], the endothelial ablation lesion itself activating the clotting cascade, or the restored atrial contractility which potentiates dislodgement of thrombi [4, 5]. This risk also extends to the post-ablation period due to factors such as "atrial stunning", inflammation and the pro-thrombotic milieu induced by the ablation lesions. Therefore, guidelines recommend a minimum of four weeks (w) of therapeutic anticoagulation prior to AF ablation and continuation for up to two months (m) post-procedure [6]. During the AF ablation procedure, prior to or immediately following trans-septal puncture unfractionated intravenous heparin loading bolus is administered and repeated at intervals in order to keep the activated clotting time (ACT) 300-400 seconds (s) [6]. As AF ablation techniques have evolved over the last decade, uninterrupted warfarin therapy has been the "gold-standard treatment" to minimise this peri-procedural risk [6, 7]. However optimal peri-procedural anticoagulation is a balancing act between preventing both thrombo-embolic as well as bleeding complications as anticoagulation can contribute to haemopericardium, cardiac tamponade or vascular access site complications [1].

Increasingly, NOACs (dabigatran, rivaroxaban and apixaban) are rapidly gaining popularity over warfarin in view of the lack of need for regular haematological monitoring due to their predictable pharmacological effects, fixed dose regimens and rapid onset and offset of action. Robust clinical trial data have demonstrated non-inferiority and possibly even superiority of NOACs over warfarin [8-10]. There is increasing world-wide evidence for the use of NOACs in the setting of AF ablation. A recent European survey of Oral anticoagulant therapy for stroke prevention in patients with AF undergoing ablation, showed that NOACs are used in nearly 33% patients [11]. However this evidence is mainly in the form of non-randomised studies or small randomised trials and meta-analysis. In view of the relatively rare incidence of thrombo-embolic and haemorrhagic complications, studies with large sample sizes are required in order to establish the safety of NOACs in the setting of AF ablation and also to analyse end-points effectively. Meta-analyses by pooling several small studies increase the effective sample size in order to examine outcomes. However analysis of rare outcomes is likely to be erroneous if mainly retrospective or non-randomised studies are included which were not a priori

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powered enough to detect rare outcomes such as thrombo-embolic or haemorrhagic. In addition meta-analyses may also magnify the heterogeneity inherent in individual studies. We shall therefore review the available evidence and establish a requirement for more robust randomised trial data, so clear guidelines can be formulated to enable uniformity of dosage regimens for NOACs in AF ablation. In order to review the available evidence, we performed a systematic review of clinical trials that have been published in the PUBMED and MEDLINE database from inception till June 2015, using the keywords "atrial fibrillation", "ablation", and "anticoagulation".

### 1.1. Advantages and disadvantages of warfarin in the context of AF ablation

Warfarin has a slow onset and offset of action, with the maximum anticoagulant effect not reached before 4 to 5 days (d) [12]. At the dawn of the AF ablation era, an "interrupted warfarin and heparin-bridging strategy" was employed whereby warfarin would be discontinued 3-5 d prior to the procedure and bridged with heparin. However more recent studies have demonstrated that continuous warfarin therapy is superior to the "bridging strategy" in terms of preventing thrombo-embolic and bleeding complications in patients undergoing AF ablation [7, 13]. Over the last decade, a robust evidence base of clinical trials on AF ablation with patients on warfarin has been accumulated and has underlined the safety as well as efficacy of warfarin in this setting. In order to monitor compliance of warfarin and therapeutic efficacy, there is also availability of a simple lab assay (INR). Urgent reversal of warfarin using an antidote (vitamin K plus prothrombin complex concentrate) is also possible in case of major haemorrhagic complication [14].

The disadvantages of warfarin include a narrow therapeutic window with scope for interactions with several drugs and diet leading to labile INR readings and thus therapeutic efficacy, thereby necessitating the need for consecutive therapeutic INR readings (2-3) for at least 4 w prior to the AF ablation procedure and on the day of procedure. Sub-therapeutic INR leads to need for trans-oesophageal echocardiography in order to rule out atrial thrombus or even cancellation of the AF ablation procedure, as does INR $\geq$4.

## 2. NOVEL ORAL ANTI-COAGULANTS FOR AF ABLATION

A recent survey on procedural routines for AF ablation in Europe has shown that whilst the majority of patients who underwent AF ablation were on warfarin, the use of NOACs is steadily increasing [11]. NOACs have a short half life and a rapid onset as well as offset of action. This abbreviates the “thrombo-embolic window of risk” and in addition to the reliable, efficacious pharmacological profile, makes them particularly attractive as anti-coagulants for AF ablation

### 2.1. Dabigatran

Dabigatran is a direct thrombin inhibitor which has a serum half life of 12 to 17 hours (h) (therefore requiring twice daily dosing) and reaches peak plasma level 2 h after ingestion [15]. The RE-LY trial showed that the 150 mg twice daily dose of dabigatran was superior to warfarin in terms of lower thrombo-embolic complications but non-inferior in terms of major bleeding [8]. The 110 mg twice daily dose was non-inferior to warfarin in preventing thrombo-embolic complications but led to a significantly lower incidence of haemorrhagic stroke.

A recent meta-analysis that included 17 (1 randomised control trial, 11 retrospective observational and 5 prospective observational) studies of AF ablation (2714 patients on dabigatran and 4436 patients on warfarin) illustrated that there was no significant difference between the incidence of thrombo-embolic or bleeding complications between the two treatment arms [16]. There was significant heterogeneity in the peri-procedural dosing protocols for dabigatran used in AF ablation. Amongst the 17 studies included in the meta-analyses, 3 studies used the 110 mg dose [17-19]. A minority of the studies continued dabigatran uninterrupted [20-22] and these studies did not show a significant difference between thrombo-embolic or bleeding outcomes between the dabigatran or warfarin arms. Other studies which interrupted dabigatran varied in the timing of the last dose withheld - several studies dose withheld dabigatran on the morning of the procedure [17-19, 23-26], whereas the last pre-ablation dose in other studies varied from 12 h to 5 d prior to the procedure [22, 27-33]. Similarly the timing of re-starting dabigatran also varied significantly amongst the studies (from a few hours after the procedure to the morning after the procedure).

Similar results were obtained from a previous meta-analysis which did not show any significant difference in the incidence of thrombo-embolic or bleeding complications [34]. However 2 previous meta-analyses which analysed a smaller number of AF ablation studies, showed a significantly higher incidence of thrombo-embolic complications in patients who were on dabigatran in comparison to those who were on warfarin [35, 36]. It is probable that interruptions in dabigatran therapy could have contributed to the increased incidence of thrombo-embolic complications [37], although individual studies also showed a higher incidence of significant haemorrhage, suggesting that an interplay between dabigatran and peri-procedural heparin could have been causative [23, 26]. A multi-centre observational study by Lakkireddy *et al.* (n=145 in the dabigatran arm with 1 dose withheld pre-ablation versus n=145 in the uninterrupted warfarin arm) found a significantly higher incidence of bleeding and thrombo-embolic complications in the dabigatran arm compared to the warfarin arm [major bleeding rate (6% vs. 1%; $p = 0.019$), total bleeding rate (14% vs. 6%; $p = 0.031$), and composite of bleeding and thrombo-embolic complications (16% vs. 6%; $p = 0.009$)] [23]. However a significant proportion of dabigatran patients in this study were older than 75 years and hence had a higher bleeding risk per se. Data regarding ACT levels during the procedure or heparin requirement were not reported.

### 2.2. Rivaroxaban

Rivaroxaban is a Factor Xa inhibitor that has a rapid onset of action of 2-4 h, short half life of 7-13 h. A recent meta-analysis analysed outcomes of patients on rivaroxaban versus warfarin included 15 studies (1 randomised trial, 1 post-hoc analysis of a randomised trial and 13 observational stud-

ies) of AF ablation (13 studies) and cardioversion (2 studies) including 8872 patients (2898 on rivaroxaban and 5974 on warfarin) [38]. Two ablation studies employed a continuous rivaroxaban administration strategy [39, 40], whereas the others withheld the NOAC for a period of time ranging from 2-48 h prior to the procedure. Similarly there was heterogeneity in warfarin administration as well with 8/15 studies using an uninterrupted strategy. Results showed a significantly lower incidence of stroke events (Peto Odds Ratio (POR) 0.33, 95% confidence interval (CI) [0.11, 0.95]; P=0.04), as well as thrombo-embolic phenomena (POR 0.46, 95% CI [0.21, 0.97]; p=0.04) in patients on rivaroxaban but the incidence of bleeding complications was not significantly different from patients on warfarin. Another meta-analysis analysed 8 studies and showed no significant difference in the incidence of thrombo-embolic or haemorrhagic complications between patients on rivaroxaban versus dabigatran or on warfarin [41]. Recent results from the VENTURE AF study which was the first prospective randomized trial of uninterrupted rivaroxaban (n=124) and uninterrupted warfarin (n=124), have shown no significant difference in thrombo-embolic or bleeding complications between the two treatment arms, thereby suggesting that uninterrupted rivaroxaban is safe and efficacious for AF ablation [42].

### 2.3. Apixaban

Apixaban like rivaroxaban is also a Factor Xa inhibitor. There are fewer studies that have looked at the feasibility of the use of apixaban in the setting of AF ablation. A prospective multi-centre registry that analysed 200 patients on warfarin and 200 patients on uninterrupted apixaban found no significant difference in the incidence of symptomatic or asymptomatic thrombo-embolic or bleeding complications [43]. Outcomes from uninterrupted apixaban (n=105) in AF ablation were compared to warfarin (n=237) in a recent retrospective study and no difference was found in terms of bleeding or thrombo-embolic complications [37]. Another retrospective single centre study from a prospective registry analysed 374 AF ablation cases (173 warfarin, 123 dabigatran, 61 rivaroxaban, and 17 apixaban) found that there was no significant difference in the incidence of major haemorrhage or thrombosis amongst warfarin, apixaban and rivaroxaban, however there was a lower incidence of minor haemorrhage in the dabigatran group [44]. Some of the limitations of this study other than the retrospective nature, include the small sample size (especially of patients on rivaroxaban and apixaban) and the fact that whilst warfarin was continued uninterrupted, one or more doses (variable) of the NOAC were withheld.

### 2.4. Edoxaban

Edoxaban is the latest Factor Xa inhibitor that received FDA approval earlier this year for stroke prevention in non-valvular AF. There is however currently a lack of clinical data evaluating its safety and efficacy during AF ablation.

## 3. GAPS IN THE EVIDENCE

### 3.1. Monitoring of Compliance

Unlike warfarin, there is currently a lack of a reliable coagulation assay to determine therapeutic levels of NOACs. This is especially important in patients where drug compliance is in doubt and therefore warfarin may be more appropriate. Many centres therefore perform a TOE pre-procedure in patients on NOAC. Awareness of the effects of NOACs on coagulation assays may be required in haemorrhagic emergencies or need for emergency surgery. A study by Cuker *et al.* systematically analysed the laboratory measurement of the anticoagulant activity of dabigatran (17 studies), rivaroxaban (15 studies), and apixaban (4 studies) [45]. Analysis of dabigatran showed that prothrombin time (PT), activated partial thromboplastin time (APTT) and activated clotting time (ACT) are usually normal despite therapeutic plasma dabigatran levels, however a normal thrombin time excludes clinically relevant drug concentrations. The dilute thrombin time and ecarin based assays shows a linear relationship with a wide range of drug plasma levels and could be useful for drug quantification, anti-Factor IIa chromogenic assay is emerging as a useful test for dabigatran activity. Anti-Factor Xa chromogenic assay levels could similarly be used for plasma drug quantification of rivaroxaban and apixaban, whereas PT and aPTT are less sensitive. However chromogenic assays may not be widely available thus limiting their use.

### 3.2. Interrupted Versus Continuous NOAC Strategy

The European Heart Rhythm Association guidance on the use of NOAC in AF ablation advises that the last dose pre-ablation be taken no later than 48 h prior to the procedure [46]. However based on the studies on AF ablation using NOACs, there is no consensus as yet which strategy ("interrupted NOAC or continued NOAC") is the safest and this has led to significant heterogeneity in pre-procedural doing protocols. Abrupt discontinuation of anticoagulation could lead rebound thrombo-embolic phenomena [47] and might explain the increased thrombo-embolic complications noted in some studies which interrupted NOACs prior to AF ablation [36, 37]. One of the studies of AF ablation using an interrupted rivaroxaban strategy showed a significantly higher incidence of left atrial thrombi in the rivaroxaban arm (4.6%) in comparison to the warfarin arm (1.4%) with a higher prevalence when the dose was withheld >36 h prior to ablation [33]. It has been suggested that an "uninterrupted NOAC strategy" could lead to a lower incidence of silent thrombo-embolic events [48, 49] and indeed this protocol has not shown a higher incidence of bleeding complications in several recent studies [20, 39, 42, 43, 50, 51].

### 3.3. Interplay Between NOACs and Unfractionated Heparin

Guidelines recommend that the ACT be maintained between 300-400 seconds during AF ablation [6]. This is usually achieved by administering heparin boluses prior to or immediately after the trans-septal puncture [6]. ACT<250 s has been demonstrated to be an independent predictor of thrombo-embolic events during AF ablation [5]. Several studies have shown that use of NOACs can increase the requirement of heparin during AF ablation, thereby suggesting an interaction between the two agents [21, 24, 25, 42, 48]. A variety of explanations have been postulated including the continued use followed by sudden stoppage of dabigatran or

interference of dabigatran with the ACT test itself [25]. Irrespective of the mechanism, this interaction could theoretically lead to a greater period of time spent below the recommended therapeutic ACT range in these patients and thus increase the potential risk for thrombo-embolic complications. For instance, a study by Bassiouny *et al.* showed that the time to reach target ACT was significantly longer in patients who had withheld 2 doses of dabigatran (50 min), compared to those who had withheld 1 dose (20 min) or those on warfarin (20 min) [25]. Authors from this study suggest that the higher doses of heparin were directly related to the longer length of dabigatran interruption rather than due to the interaction of dabigatran with heparin. Interestingly this observation is not limited to dabigatran alone and the above possible explanation is contradicted by findings from a recent study of 869 consecutive AF ablation patients [48] on uninterrupted anticoagulation (370 patients on warfarin, 239 on dabigatran, 102 on rivaroxaban and 158 on apixaban) showed that the average time to achieve target ACT>300 seconds was significantly greater in the dabigatran and apixaban groups (60 and 70 minrespectively) compared to the warfarin and rivaroxaban groups (8 and 9 minrespectively). Pre-procedure aPTT was similar in patients on warfarin and rivaroxaban, thereby possibly leading to a similar response to heparin. However pre-procedure aPTT was significantly higher in the dabigatran group and this was explained by the down-regulation of anti-thrombin (to which heparin is bound) due to continuous administration of dabigatran [21]. Konduru *et al.* also propose that dabigatran along with the heparin/antithrombin complex compete for binding to thrombin, thereby leading to a need for higher doses of heparin in order to prolong the ACT [21]. Whilst the above study did not show a significant interaction between rivaroxaban and heparin, results from the VENTURE-AF study that compared uninterrupted rivaroxaban versus uninterrupted warfarin showed a significantly higher total heparin dose required to achieve target ACT and lower mean ACT in the rivaroxaban arm [42]. The existing evidence therefore suggests a possible interaction of heparin with all the currently available NOACs and more research is necessary in order to unravel the exact mechanisms involved. Although this interaction did not seemingly result in clinically apparent thrombo-embolic complications in the majority of the studies, it is possible the studies were under-powered to detect these relatively rare complications. It is currently also unknown whether this interaction could lead to a higher incidence of clinically silent thrombo-embolic brain lesions.

### 3.4. Reversal Agents for NOACs

In the case of need for emergency reversal of the anticoagulant effects of warfarin such as due to major bleeding complicating AF ablation, a combination of vitamin K and prothrombin complex concentrates (PCC) are usually effective as specific antidotes. However currently there is a lack of sufficient clinical experience with the available antidote for NOACs in clinical use. Management of major bleeding emergencies in the context of AF ablation (such as tamponade and access site haemorrhage), include supportive measures and PCC. In many studies that reported haemorrhagic complications during AF ablation whilst on NOAC, the bleeding was self-limiting and the patients did not require surgery or haemodialysis [23, 25]. A specific antidote for dabigatran, idarucizumab that binds specifically with dabigatran and prevents its interaction with thrombin, is current undergoing evaluation in a Phase 3 study [52]. It has recently undergone clinical studies and has been approved for clinical use. Andexanet alfa is an injectable antidote for factor Xa inhibitors which is currently undergoing Phase 3 clinical studies. Iraparantag (PER977) is a universal antidote that reverses the effects of dabigatran, rivaroxaban, apixaban, edoxaban, fondaparinux, and heparin in animal studies [53].

### 3.5. Lack of Large Randomised Studies

The current evidence base is limited to meta-analyses of mainly observational non-randomised studies and thus susceptibility to selection bias but the studies included also had significant heterogeneity in enrolment criteria, baseline patient characteristics, NOAC dosing protocols, operator experience and ablation protocols. There is therefore an imminent need for large randomised controlled trials to validate the above evidence. Currently several randomised controlled trials are recruiting patients with results expected within the next 2 years. Amongst these is the RE-CIRCUIT study [54] (Randomized Evaluation of dabigatran etexilate Compared to warfarIn in pulmonaRy vein ablation: assessment of an uninterrupted peri-proCedUral antIcoagulation sTrategy) that aims to recruit 610 patients with either paroxysmal or persistent AF undergoing ablation whilst on uninterrupted anticoagulation. The AXAFA-AFNET 5 study is a multi-centre (Europe and USA) trial that is recruiting 630 AF ablation patients randomised to either continuous warfarin or uninterrupted apixaban.

## 4. CONCLUSIONS

Currently there is rapidly increasing worldwide use of NOACs in AF ablation. The available evidence that is limited to small randomised trials, observational studies and meta-analyses, suggests that the use of NOACs for AF ablation appears to be safe and efficacious. However there are significant heterogeneities in terms of peri-procedural NOAC dosing protocols. There is also some evidence suggesting a possible interaction of NOACs leading to higher intra-procedural heparin requirements. Further *in vitro* and *in vivo* studies are required to establish the exact mechanism and consequences of this interplay. NOAC use in the setting of AF ablation heralds an exciting new era, there is therefore a need for large randomised trials to establish a robust evidence base in order to help formulate guidelines and thus enable uniformity in practice.

## ABBREVIATIONS

| | | |
|---|---|---|
| AF | = | Atrial Fibrillation |
| NOAC | = | Novel Oral Anti-Coagulant |
| ACT | = | Activated Clotting Time |
| PT | = | Prothrombin Time |
| APTT | = | activated partial thromboplastin time |
| w | = | weeks |

m = months

s = seconds

d = days

h = hours

min = minutes

## CONFLICT OF INTEREST

D. J. Fox has received speaker fees from the drug companies that manufacture NOACs (Bayer, Pfizer/Bristol-Myers Squibb,Boehringer Ingelheim) Rajiv Sankaranarayanan has no conflicts of interest to declare.

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