

# Non-vitamin K antagonist oral anticoagulants therapy for atrial fibrillation patients undergoing electrophysiologic procedures

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## KEYWORDS

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Over the last 10 years since the introduction of non-vitamin K antagonist oral anticoagulants (NOACs) into routine clinical practice our experience with these drugs has increased tremendously, also in the context of patients undergoing electrophysiology procedures. While some open questions remain, the available evidence indicates that for the majority of cases, these interventions can safely be performed on NOACs if study-based standard operating procedures are in place and followed. This review summarizes the most current trial evidence and guidelines on the use of NOACs for patients undergoing cardioversion, atrial fibrillation ablation, and device implantations, based on previous work of the author and others.

## Introduction

Based on the outcomes of four landmark randomized clinical trials, non-vitamin K antagonist oral anticoagulants (NOACs) have become the standard of care for stroke prevention in atrial fibrillation (AF).<sup>1-6</sup> As a result, many patients undergoing electrophysiological procedures, including cardioversion, ablation, and device implantations, are treated with NOACs. The management of these patients may differ from peri-interventional management around other procedures such as general or orthopaedic surgery in that they involve direct (ablation) or indirect (cardioversion, device implantation) manipulation of the heart and, importantly, the left atrium. As such, anticoagulation management requires an even more refined balance between stroke prevention and the risk of peri-interventional bleeding. Over the last years, experience on the efficacy and safety of NOACs in the context of patients undergoing electrophysiology (EP) procedures has increased tremendously. This review summarizes the most current trial evidence, guidelines, and open questions regarding the use of NOACs for patients undergoing

cardioversion, AF ablation, and device implantations, based on previous work of the author and others.<sup>7</sup>

## Cardioversion

Patients with AF of  $\geq 48$  h (or unknown) duration who are undergoing electrical or pharmacological cardioversion need to have effective oral anticoagulation established for at least 3 weeks prior to cardioversion based on current ESC guidelines.<sup>5</sup> Alternatively, LA/LAA thrombus may be ruled out, e.g. by transoesophageal echocardiography (TOE). Oral anticoagulation has to be continued for at least another 4 weeks following cardioversion. These recommendations are independent of the mode of cardioversion (electrical vs. medical) as well as the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and have hence to be followed also in patients with a score of 0 who otherwise do not qualify for long-term anticoagulation.<sup>5,6</sup> The rationale behind this seeming inconsistency has traditionally been the belief that the risk of thromboembolism is increased after cardioversion due to dislodgement of a pre-existing thrombus or temporary reduction in atrial function resulting in new thrombus formation.<sup>8</sup> Recent evidence has challenged the causal relationship of the increased thrombo-embolic risk around the time of

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cardioversion indicating that the latter may at least in part be due to overall clinical deterioration of these patients (resulting in the need for cardioversion).<sup>9</sup> As such, the mere necessity for cardioversion may (also) be a marker of a larger overall disease burden rather of than (purely) a causal factor for ischaemic events.

In patients requiring cardioversion, two different scenarios have to be distinguished:

- (1) Cardioversion in patients newly diagnosed with AF and naïve to anticoagulation.
- (2) Cardioversion in patients on chronic treatment with a NOAC

### Cardioversion in patients not on non-vitamin K antagonist oral anticoagulants therapy

Dedicated studies have been performed for the scenario of cardioversion in AF patients not on a NOAC. The EMANATE,<sup>10</sup> ENSURE-AF,<sup>11</sup> and X-VerT<sup>12</sup> trials with apixaban, edoxaban, and rivaroxaban, respectively, included 100%, 27%, and 57% of oral anticoagulation (OAC)-naïve patients, respectively.<sup>7</sup> The majority of patients included in these trials had AF of  $\geq 48$  h (or unknown) duration. Two different strategies were investigated: Patients were either cardioverted early (after exclusion of LA/LAA thrombus via TOE) or delayed after 3–8 weeks of anticoagulation before cardioversion. Except for a lower rate of ischaemic events with apixaban in the EMANATE trial, there were no differences in ischaemic or bleeding events between the NOAC- and the group using VKA. Similarly, no difference between the early and delayed group was observed. Overall, event rates were (expectedly) low and as such, the trials were formally not powered for non-inferiority. In the EMANATE trial, an initial loading dose of 10 mg of apixaban (5 mg if does-adjustment criteria were met) was administered in 45% of patients.

Taken together, these data indicate that performing a cardioversion in a patient with AF of  $\geq 48$  h duration either after 3 weeks of NOAC therapy or using at least a single NOAC dose  $\geq 4$  h before cardioversion ( $\geq 2$  h after apixaban loading dose) after exclusion of a LA/LAA thrombus appears safe and effective.<sup>7</sup> Importantly, adherence needs to be assured in patients cardioverted after 3 weeks of NOAC therapy and, if in doubt, exclusion of LA/LAA thrombus is nonetheless recommended.

Observational studies have indicated a lower incidence of ischaemic events using anticoagulation even in patients with AF duration of  $< 48$  h, especially in individuals with an elevated CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  and AF duration  $\geq 12$  h.<sup>7,13,14</sup> These patients were not included to a great enough extent in the above-mentioned pivotal cardioversion trials in order to make any firm recommendations. In the pre-NOAC era, they were usually cardioverted following administration of a single dose of LMWH, followed by VKA treatment for at least 4 weeks (if CHA<sub>2</sub>DS<sub>2</sub>-VASc score 0 in men or 1 in women) or life-long (in all other patients). In view of the similar pharmacokinetic and pharmacodynamic properties of NOACs vs. LMWH and the similar results in patients on NOACs vs. LMWH/VKA in patients cardioverted after  $\geq 48$  h duration AF, the use of NOACs appears justifiable also in these situations.<sup>7</sup> Independent of the

mode of therapy, LA/LAA thrombus should be ruled out or anticoagulation installed for  $\geq 3$  weeks prior to cardioversion in very high risk patients (i.e. CHA<sub>2</sub>DS<sub>2</sub>-VASc  $\geq 4$ ) and in those in whom there is any doubt about the onset of AF.<sup>7</sup>

### Cardioversion in atrial fibrillation patients on non-vitamin K antagonist oral anticoagulant therapy for $\geq 3$ weeks

Several thousand cardioversions were performed in the landmark phase III NOAC trials in patients on apixaban,<sup>3</sup> dabigatran,<sup>1</sup> edoxaban,<sup>15</sup> or rivaroxaban.<sup>2</sup> Overall, the risk of ischaemic as well as bleeding events following cardioversion were very low and similar compared to patients undergoing cardioversion under warfarin. These results were later confirmed in the above-discussed dedicated cardioversion trials as well as in various meta-analyses and ‘real world’ studies.<sup>16–18</sup> Although none of these studies include sufficient patient numbers to formally demonstrate statistically non-inferiority, the available evidence strongly suggests that cardioversion under regular and continued NOAC intake is reasonably safe.<sup>5,7</sup> One important prerequisite, however, is adequate adherence and correct (on-label) dosing of NOAC therapy prior to cardioversion. If this cannot be guaranteed LA/LAA thrombus should be ruled out with imaging prior to cardioversion. Finally, thrombi may also develop under adequate anticoagulation therapy,<sup>19,21</sup> which is why one may opt to anyways perform imaging even in case of long-standing anticoagulation prior to cardioversion. Conversely, not all strokes in patients with AF may be due to thrombi in the LA/LAA; as such, any (rare) ischaemic event in the time period after cardioversion—even on adequate anticoagulation—may not be the result of an undetected LA/LAA thrombus.

### Duration of anticoagulation post-cardioversion

Patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of  $\geq 2$  (women) or  $\geq 1$  (men) have a Class IIa indication for life-long anticoagulation independent of cardioversion, while a Class I indication is given in case of a score  $\geq 3$  (women) and  $\geq 2$  (men).<sup>5</sup> However, in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 (women) or 0 (men), the situation is less clear. While current guidelines recommend 4 weeks of anticoagulation if AF duration was  $\geq 48$  h prior to cardioversion data are scarce for patients with shorter durations, especially  $< 12$  h.<sup>7</sup> Importantly, these patients may in addition have self-limiting (i.e. ‘self-cardioverting’) bouts of AF of several hours’ duration (which may be asymptomatic) for which it is unclear whether OAC should be recommended. Given the overall very low risk of thromboembolism in these patients and the usually comparatively good general health, longer and particularly life-long anticoagulation does generally not seem to be mandated, but further studies are necessary.

### Management of left atrial/left atrial appendage thrombus

In the absence of an emergency indication cardioversion should be deferred in patients in whom an LA/LAA thrombus is detected. There are no (and likely never will be any) adequately powered endpoint trials comparing a LMWH/

VKA based regimen to NOACs for the treatment of LA/LAA thrombi. Increasing observational evidence is indicating a similar degree of thrombus resolution using a NOAC vs. a LMWH/VKA based regimen.<sup>22-24</sup> In the prospective X-TRA study, thrombus resolution was observed in 22 out of 53 patients (41.5%) with standard dose rivaroxaban,<sup>25</sup> which is comparable to the resolution rate under heparin/VKA in the retrospective CLOT-AF registry (60/96 patients, 62.5%).<sup>25</sup> Similarly the rate of thrombus resolution was similar in patients treated with apixaban (52%, 12/23) as compared to LMWH/VKA (56%, 10/18) in the EMANATE trial.<sup>26</sup> The prospective RE-LATED AF study with dabigatran has recently been terminated due to recruitment problems (NCT02256683, accessed 10 January 2020). Importantly, mal-adherence as well as off-label use of reduced NOAC dose were shown to be among the main predictors for the development of LA/LAA thrombus ‘under’ NOAC therapy.<sup>24</sup> Conversely, increased dosage or changing the anticoagulant strategy appeared to be successful in thrombus resolution.<sup>24</sup>

Taken together, increasing evidence indicates that NOACs may be a valid option for LA/LAA thrombus resolution. This appears particularly appealing in patients in whom VKA are not well tolerated or in whom an adequate time in therapeutic range cannot be achieved.<sup>7</sup>

### Atrial fibrillation ablation

Although the absolute incidence in experienced hands is decreasing, left atrial catheter ablation still carries a risk of both severe ischaemic and bleeding complications, mainly related to transseptal puncture and ablation in the left atrium.<sup>27,28</sup> In patients on VKA, ablation is recommended to be performed on uninterrupted therapy with a target international normalized ratio 2-2.5,<sup>5,27</sup> as this has been shown to lead to less thromboembolic as well as bleeding complications compared to a LMWH/UFH heparin-based bridging strategy.<sup>29</sup> Over the last years, dedicated randomized clinical trials for apixaban (AXAFA),<sup>30</sup> dabigatran (RE-CIRCUIT),<sup>31</sup> edoxaban (ELIMINATE),<sup>32</sup> and rivaroxaban<sup>33</sup> have been performed each comparing uninterrupted NOAC to uninterrupted VKA treatment around catheter ablation for AF. Importantly, bid-based NOACs (apixaban, dabigatran) were administered in the morning of the procedure, whereas the last dose of once-daily based NOACs were recommended (rivaroxaban) or mandated (edoxaban) to be administered in the evening before the procedure (Figure 1). Although the studies were

underpowered to detect statistically significant differences in hard endpoints, the overall event rate in the NOAC arms of the trials were low, while large variations in the event rate in the VKA arm of the trials were observed. A lower rate of bleeding events was confirmed in a recent meta-analysis of 29 studies comprising over 12 000 patients.<sup>34</sup> As such, it may be concluded that the use of uninterrupted NOAC therapy can be considered safe and effective and should likely be preferred to uninterrupted VKA treatment in patients undergoing AF ablation. Whether to give or withhold the morning dose before ablation may depend on various factors. In spite of the positive trial evidence operators may not be entirely comfortable performing groyne puncture, transseptal puncture and left-sided ablation at peak NOAC plasma levels. On the flip-side, however, patients may be exposed to very low anticoagulant levels following the procedure if the morning dose is withheld, particularly if protamine is delivered prior to sheath removal. It may therefore be advisable to administer the morning dose prior to ablation if intraprocedural heparin administration is routinely reversed prior to sheath removal, or if the first dose of heparin is administered only *after* successful transseptal puncture. If, conversely, the peri-interventional protocol includes administration of a first bolus of unfractionated heparin just *prior* to the first transseptal puncture, closure of the groyne puncture (e.g. with a figure-of-eight stitch or a dedicated closure device) *without* administration of protamine, and resumption of full dose NOAC therapy 4-6 h post sheath removal, withholding the morning dose of the NOAC appears justifiable as the patient is unlikely to be exposed to low anticoagulant levels at any point in time. Randomized clinical trial evidence comparing these two approaches, however, are not available. In once-daily based NOACs, switching NOAC intake to the evening well in advance (e.g. 1 week) of the intervention appears reasonable in order to follow a similar protocol as in the respective clinical trials.<sup>32,33</sup>

Current expert consensus statements generally recommend to routinely consider exclusion of an LA/LAA thrombus prior to AF ablation.<sup>7,27</sup> While TOE (or intracardiac imaging) is currently considered the standard of care to rule out LA/LAA thrombus, computed tomography (CT) may represent an attractive alternative<sup>35</sup> especially since a large number of patients will anyways undergo CT imaging prior to ablation for LA anatomy assessment and 3D reconstruction. Performance of the CT shortly prior to the ablation (as for TOE), implementation of a dedicated CT scanning protocol, and extensive experience in the

	Day -2	Day -1	Day of ablation	Day +1
Dabi / Apix	● ●	● ●	No bridging <b>&lt; 4-6 hours &gt;</b>	● ●
Edo / Riva (PM intake)*	●	●	<b>&lt; 4-6 hours &gt;</b>	●

**Figure 1:** Management of non-vitamin K antagonist oral anticoagulants around atrial fibrillation ablation (based on reference 7). See text for details. Consider administration of twice-daily dosed non-vitamin K antagonist oral anticoagulants in the morning of the procedure especially if no administration of heparin prior to transseptal puncture is administered and when periprocedural heparin anticoagulation is reversed prior to sheath removal. \*Patients on once-daily dosed non-vitamin K antagonist oral anticoagulants (edoxaban, rivaroxaban) are recommended to be switched to evening intake well before the planned atrial fibrillation ablation.

	Day -2	Day -1	Day of surgery	Day +1
Dabi / Apix	● ●	● ●	(●) ★	● ●
Edo / Riva (AM intake)	●	●	★	●
Edo / Riva (PM intake)	●	●	★ (●)	●

**Figure 2:** Management of non-vitamin K antagonist oral anticoagulants around cardiac device implantation/generator exchange (based on reference 7). See text for details.

interpretation of CTs in this indication are crucial prerequisites. In case of doubts or inconclusive CT imaging results, performance of a TOE is mandatory.

During AF ablation, intravenous heparin with a target activated clotting time (ACT) of 300-350 s should be administered.<sup>7,27,36</sup> The total dose of heparin and time to reach the target ACT is generally higher in patients undergoing AF ablation on NOACs vs. VKA,<sup>37-39</sup> reflecting a difference in whole blood coagulability.

## Device implantation procedures

In experienced hands, implantation of cardiac device (i.e. pacemaker, implantable cardioverter defibrillator (ICD), and cardiac resynchronization therapy (CRT) devices) and generator exchanges are generally procedures with a low bleeding risk. Uninterrupted VKA treatment has been shown to lead to fewer bleeding events as compared to heparin-based bridging in patients undergoing device implantation on VKA in the prospective randomized BRUISE-CONTROL trial.<sup>40</sup> The BRUISE-CONTROL 2 trial demonstrated that patients on uninterrupted NOAC therapy (including intake in the morning of the procedure) have a similarly low rate of relevant bleeding complications as those with a last intake 48 h before the procedure.<sup>41</sup> Other complications were rare, including one stroke and one symptomatic pericardial effusion. Further evidence for a low overall complication rate, including both bleeding and ischaemic events, comes from several registries<sup>42</sup> as well as from the PAUSE<sup>43</sup> and the EMIT studies in which a various amount of patients undergoing cardiac device procedures on either continued or minimally uninterrupted NOAC therapy have been included, and in which low incidence of bleeding and ischaemic event rates were confirmed. As such, the standard strategy suggested for ‘low bleeding risk’ procedures in the current EHRA<sup>44</sup> Practical Guide on the use of NOACs with intake of the last NOAC dose in the morning or evening of the day before the procedure seems reasonable in most cases, followed by restarting one day afterwards (adequate haemostasis provided, *Figure 2*).<sup>7</sup>

The role of NOAC plasma level measurements prior to device surgery (or, for that matter, any type of surgery) is currently unclear due to the lack of adequately powered prospective clinical trial data. Importantly, it is unclear whether the benefit of withholding NOACs for a longer time period based on an elevated NOAC plasma level outweighs the risk of prolonged interruption of

anticoagulation.<sup>7</sup> Based on the available evidence discussed above, routine NOAC plasma level assessments are not recommended. Whether such a strategy may be of use in very high risk situations such as severe renal insufficiency, multiple possible drug-drug interactions, very high risk interventions (including difficult lead extractions) etc. will require further studies.

## Summary and conclusions

Over the last 10 years since the introduction of NOACs into routine clinical practice, our experience with these drugs has increased tremendously, also in the context of patients undergoing EP procedures. Some open questions remain: how long should low-risk patients (CHA<sub>2</sub>DS<sub>2</sub>-VASc 0 in men, 1 in women) be anticoagulated following cardioversion? Can NOACs safely and effectively be used to ‘dissolve’ a thrombus in the LA/LAA? Is ‘truly’ uninterrupted NOAC therapy safer and more effective as leaving out the morning dose of the NOAC before AF ablation? What is the optimal NOAC treatment strategy around higher risk cardiac device interventions such as transvenous lead extraction? These questions will require further data, ideally in the form of dedicated randomized trials to be solved; additionally, data from partly already ongoing large registries will be of value (with the main limitation of unmeasured confounding). This notwithstanding the available evidence today indicates that for the majority of cases, EP procedures like cardioversion, ablation, and device implantations can safely be performed on NOACs if study-based standard operating procedures are in place and followed.

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