Novel oral anticoagulants in the electrophysiology lab: are we really ready to forget warfarin?

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This editorial refers to ‘Novel oral anticoagulants in a real-world cohort of patients undergoing catheter ablation of atrial fibrillation’ by C. Eitel et al., on page 1587.

Atrial fibrillation (AF) is the most common arrhythmia, affecting over 6 million people in Europe. Subjects suffering from this arrhythmia have a five-fold higher risk of stroke than those in stable sinus rhythm, and anticoagulation with vitamin K antagonists has proven able to reduce this risk by about 60%.

Recently, new oral anticoagulants (NOACs) have been introduced in the clinical practice and have proven non-inferior to warfarin in preventing thromboembolic risk in patients affected by non-valvular AF. Moreover, NOACs significantly reduce the risk of cerebral haemorrhage, act rapidly, and are easier to administer, considering that monitoring of the international normalized ratio (INR) is not required and a lower interaction with food and other drugs is described. However, these drugs display the limitation to have no antidote and the difficulty to assess patient compliance.

In the last 10 years, catheter ablation has become an effective therapeutic option for treatment of symptomatic and drug-refractory AF. Nevertheless, this therapy may be associated with complications, mainly thromboembolic events, cardiac tamponade, and vascular complications. Over the years, various antithrombotic treatments for use either during or after the procedure have been proposed to maximize protection against thromboembolic events and to reduce the risk of bleeding. However, the lack of prospective, randomized, large-scale studies has led to the emergence of different approaches, which are largely based on the operator’s experience. There is a general agreement on the need to anticoagulate the patient in the period prior to the procedure following the same recommendations that pertain to AF cardioversion. The most widely adopted strategy is discontinuation of warfarin and bridging with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) for several days before ablation. During the procedure, optimal anticoagulation with UFH is regarded as essentially maintaining the activated clotting time (ACT) at 300–400 s. After ablation, oral anticoagulation is promptly restarted and maintained for at least 3 months in all patients due to high risk of thromboembolism in the early post-procedural period. The restoration of anticoagulation with warfarin, however, requires LMWH or UFH as bridging therapy in the post-operative period which increases the risk of vascular complications.

In the last few years, several studies have suggested that AF ablation can be safely performed in patients who are continuously therapeutically anticoagulated with warfarin. This strategy also requires UFH administration during the procedure to maintain ACT equal or above 350 s. Santangeli et al. conducted a meta-analysis of the data from over 27,000 patients, in which the strategy of discontinuing warfarin before ablation was retrospectively compared with that of performing the procedure under therapeutic INR. Their results confirmed that performing radiofrequency catheter ablation on warfarin is an effective strategy for reducing thromboembolic risk without increasing major bleedings. However, in the event of persistent bleeding or cardiac tamponade, fresh frozen plasma, prothrombin complex concentrate, or recombinant activated factor VII should be available for replacement of coagulation factors reduced by warfarin in addition to protamine for reversal of heparin.

The availability of NOACs has opened up new anticoagulation protocols during AF ablation. Given the rapid onset of action, these drugs have the potential advantage of not requiring any bridging with heparin in the immediate post-operative period. At the same time, however, the lack of an antidote makes it difficult to manage any major bleeding. In the last 2 years, several retrospective analyses have been undertaken to glean information on the possible use of NOACs during AF ablation. Dabigatran has been most extensively studied in this setting. Winkle et al. described their experience of using dabigatran after AF ablation on 123 consecutive patients. In their series, < 30% of patients were taking dabigatran before the procedure. In this subgroup of patients, dabigatran was discontinued 36–60 h before the procedure depending on renal function. During ablation, UFH was administered in all patients to maintain a target ACT value of 225 s. Immediately after the procedure, all the patients received LMWH, and dabigatran was started after 22 h. No thromboembolic or haemorrhagic events were recorded with...
this approach. Later, Lakkireddy et al. reported the results of a multi-
centre observational study in 145 patients in whom dabigatran was
discontinued on the morning of ablation and resumed within 3 h
after haemostasis. This population was matched with an equal
number of patients who had undergone ablation in the same
period on uninterrupted warfarin therapy. In the dabigatran group,
there was a significantly higher incidence of major bleeding (6 vs.
1% \( P = 0.019 \); the thromboembolic risk was also higher, albeit not
significantly (2.1 vs. 0% \( P = 0.25 \)). Increased bleeding rates observed
in this study may have been due to overlapping of pharmacodynamic
effects of dabigatran and UFH adjusted to maintain an ACT target
higher than described in the previous study (300–400 s). On the
other hand, a higher thromboembolic risk observed in patients
taking dabigatran can be explained by a possible greater resistance
to UFH described with this treatment. Of note, all patients who suf-
f ered a thromboembolic event had undergone extensive ablation for
non-paroxysmal AF suggesting that the role of atrial substrate, type of
AF, or ablation strategy in peri-procedural thromboembolic events in
patients taking dabigatran needs to be explored further.

These findings remain controversial and have not been confirmed
in further studies. Indeed, Snipelsky et al, adopting the same anti-
coagulation protocol described by Lakkireddy et al, in a smaller popu-
lation of patients, mainly with paroxysmal AF, found a similar
complication rate between patients in whom dabigatran was sus-
pended and those on therapeutic warfarin during the procedure.
By contrast, Kaseno et al. reported a higher haemorrhagic risk in
patients undergoing ablation during therapeutic INR than in those
treated with dabigatran discontinued on the morning of the proced-
ure and restarted the day after at a dosage of 110 mg every 12 h. Sur-
prisingly, the authors continued UFH for 24 h after the procedure in
both patient groups; in our opinion, this could justify their findings
more than the low dosage of dabigatran discontinued for the day of
the procedure.

Several subsequent retrospective single-centre studies, including
some with fairly large patient populations, have shown that an abla-
tion procedure performed after the discontinuation of dabigatran,
mainly 24 h before the procedure, is similar to the strategy of ablation
during therapeutic INR, particularly in patients affected by paroxys-
mal AF and at low thromboembolic risk. The only study in
which uninterrupted anticoagulation with dabigatran was compared
with therapeutic warfarin continued throughout the ablation pro-
cedure was performed by Maddox et al. in 463 patients and
showed no significant differences in the safety and efficacy between
protocols.

In this issue of the Journal, Eitel et al. reported that, in a real-world
cohort of low-to-intermediate risk patients, NOACs (dabigatran and
rivaroxaban) administered in the immediate post-ablation period
have shown a good safety profile. The authors prospectively col-
lected data on 259 patients generally undergoing AF ablation using
bridge therapy with LMWH. In a small group of patients (n = 54),
who had already received NOACs prior to ablation, therapy was dis-
continued the day before the procedure. Patients treated with war-
farin and stable INR values before the procedure were excluded
from the study. After ablation, the majority of patients received dabi-
gatran 110 mg (38%) or 150 mg (56%) twice daily, while the remain-
der (6%) received rivaroxaban 20 mg daily. Therapy with NOACs
was started on the evening of the procedure or the day after
depending on haemostasis. In the latter case, enoxaparin 0.5 mg/kg
was given on the evening of the procedure as bridging therapy.
Patients treated with dabigatran 110 mg were older, had a higher
haemorrhagic risk, and a lower body weight. None of the patients
had a bleeding or thromboembolic complication during follow-up.
The authors found therapy with NOACs, a reasonably safe option
after ablation, even in patients with periprocedural complications
considering a lower risk of cerebral haemorrhage reported in previ-
sous studies and fast onset of action that allows a quick achievement of
therapeutic anticoagulation.

This study adds further data on the safety of NOACs following
radiofrequency catheter ablation for paroxysmal AF in patients at
low—intermediate thromboembolic risk, whereas the possibility to
avoid any bridging with heparin makes this approach attractive.
However, these data do not improve the knowledge on the safety of
AF ablation without discontinuation of NOACs.

In summary, three anticoagulation protocols using NOACs have
been tested: (i) discontinuation of warfarin and pre-operative
bridging with LMWH, UFH during the procedure, and NOACs
post-operatively; (ii) pre-operative discontinuation of NOACs 3–4
half-lives before the procedure, bridging with LMWH, UFH during
ablation, and subsequent resumption of NOACs; and (iii) ablation
performed without NOAC discontinuation and administration of
UFH during the procedure. The presence of controversial retro-
spective data with different anticoagulation protocols and the lack
of randomized studies conducted on large patient populations
suggest that, at this stage, a certain amount of caution should be exer-
cised with regard to the use of dabigatran as a periprocedural antith-
rombotic therapy. Moreover, given the current lack of significant
studies on ablation procedure performed on rivaroxaban or apixa-
ban, the results obtained so far cannot be generalized to all the
NOACs. Ablation of AF using uninterrupted warfarin seems to be
the most appropriate strategy. Alternatively, discontinuation of
NOACs 24 h before the procedure and their resumption a few
hours after ablation to avoid the bridge with LMWH seems pru-
dent. Further data from prospective randomized studies will
be necessary to obtain a clearer picture on the periprocedural man-
agement of NOACs in patients undergoing AF ablation and, if appro-
priate, to propose these new drugs as alternatives to warfarin in
electrophysiology laboratories.

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