Antithrombotic treatment management in low stroke risk patients undergoing cardioversion of atrial fibrillation <48 hours duration: Results of an EHRA survey

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ABSTRACT

Data supporting the safety of cardioversion (CV) of atrial fibrillation (AF) without anticoagulation in patients with AF duration <48 hours are scarce. Observational studies suggest that the risk of stroke in these patients is very low when the definite duration of the AF episode is of <48 hours and the clinical risk profile as estimated through the CHA₂DS₂-VASc score is very low (a score of 0 for men and 1 for women). As the recent 2020 European Society of Cardiology (ESC) guideline indication for this clinical scenario is based mainly on consensus, we sent out a survey to assess the current clinical practice on anticoagulation prior to and post-CV in patients with AF <24-48 hours duration and low stroke risk across centers in Europe. Of the 136 respondents, half were affiliated to university hospitals (68/136; 50%). Non-university hospitals (50/136; 36%) and private hospitals (2/136; 1.4%) accounted over a third of respondents. The main findings of our survey were: (i) heterogeneity in the anticoagulation management both before and post-CV in low-risk stroke patients with AF <48 hours, (ii) higher utilization of periprocedural low-molecular-weight heparin than of DOACs, (iii) higher utilization of pre-CV TOE for electrical CV than for pharmacological CV regardless the duration of AF, (iv) high adherence to a 4-week post-CV oral anticoagulant (OAC) therapy, mainly for electrical CV, and, finally (v) perceived higher acceptance of lack of post-CV OAC in patients with <24 hours than 48 hours episode duration. The results obtained in the present survey highlight the need for more research providing definitive clarification on the safety of CV without anticoagulation in patients with short duration AF.

Keywords: Atrial fibrillation, Anticoagulation, Non-vitamin K antagonist oral anticoagulants, Vitamin K antagonist • EHRA survey
INTRODUCTION

Patients undergoing cardioversion (CV) of atrial fibrillation (AF) are at increased risk of stroke and thromboembolism, especially in the absence of oral anticoagulant (OAC) and if AF has been present for >12 hours (1-3). This risk justifies the use of OAC for at least 4 weeks after cardioversion, independently of the CHA₂DS₂VASc score or the method (electrical or pharmacological) used to restore sinus rhythm, if AF has been present for 48 hours duration or longer (4). However, the rationale for the potential benefit and use of anticoagulation during this time frame comes from the observation of an increased risk of stroke in the first 30 days after conversion (5).

This area of uncertainty and knowledge gap has been addressed in the recent 2020 European Society of Cardiology (ESC) guidelines (6) for the diagnosis and management of AF, which recommend anticoagulation as soon as possible before every CV of AF (Class IIa, level of evidence B), and for a period of 4 weeks whenever the duration of the AF episode is estimated as 24 hours or more (Class IIa, level of evidence B). However, despite the limited evidence and lack of randomized controlled trials (RCTs) evaluating anticoagulation vs no anticoagulation for that particular scenario, the current Guidelines suggest that omission of the 4-week anticoagulation period may be considered in patients with a definite AF duration of 24 hours or less, and with a CHA₂DS₂VASc score of 0 in men, or 1 in women (6).

Observational data suggest that the risk of thromboembolic complication after a CV for AF duration <48 hours is very low (0 to 0.9%) in patients with a low stroke risk (CHA2DS2-VASc 0 in men, 1 in women) (1,7-10). Cardioverting acute AF of less than <48 hours without any anticoagulation before and after CV has therefore been used by some author groups in specific scenarios (11-13). Thus, in the absence of RCTs, the risk of thromboembolic events should be weighed against the risk of anticoagulant-related bleeding for the individual patient.
Because the recommendation for skipping anticoagulation is based mainly on consensus, with no RCTs currently available, we decided to assess the daily clinical practice across centers in Europe regarding anticoagulation prior and post-CV in patients with AF <24-48 hours duration and CHA2DS2-VASc score 0-1. The aim of this European Heart Rhythm Association (EHRA) was to capture the current clinical practice in this less investigated area of AF care.

**METHODS**

The questionnaire was developed by the EHRA Scientific Initiatives Committee. The survey electronic link was sent via emails to the members of EHRA, EHRA Young EP, between 26 November 2020 and 22 January 2021. The online questionnaire was constructed to collect information about antithrombotic treatment in low stroke risk patients undergoing CV of AF of <48 hours duration. The online-based questionnaire consisted 18 of multiple-choice questions including institutional information, in combination of single best answer, multiple answers. The response was voluntary and anonymous (the full questionnaire is provided in Supplementary material online, S1). Categorical variables are presented with actual numbers and frequencies. Continuous variables are expressed as mean ± standard deviation (SD) or median and 25 and 75 percentile. Differences in anticoagulation strategies depending on the type of CV (electrical vs pharmacological) were assessed using the chi-square test or the Fisher exact test as appropriate. All analyses were performed using the SPSS statistic software (version 21.0; SPSS Inc., Chicago, IL, USA).

**RESULTS**

We received 136 responses to the survey. Most responses came from Italy (n =56/136; 41%), and Poland (n= 26/136; 19%) (Supplementary material online Figure S1). Participants were most frequently affiliated to university hospitals (68/136; 50%) followed by non-university hospitals (50/136;36%) and private hospitals (2/136; 1,4%). The mean number of electrical cardioversions per center and year was 285 ±321 (Median 150; 100-375).
Anticoagulation strategy before cardioversion

We asked the respondents to choose the anticoagulant strategy usually adopted in their centers before CV among the alternatives shown in Figure 1, and if there was a different policy according to the type of CV used (i.e. electrical or pharmacological). Respondents were allowed to select more than one answer; 120 replied to the question while 16 skipped it.

Small numerical but non-significant differences were observed in anticoagulant strategy according to the type of adopted CV. Most respondents used low-molecular-weight heparin (LMWH) (electrical CV 80/120, 66% vs. pharmacological CV 77/120, 64%; p=0.68) followed by single dose of non-vitamin K antagonist oral anticoagulant (NOAC) taken ≥ 2-4 h before CV without transesophageal echocardiography (TOE) (electrical CV 33/120, 27% vs. pharmacological CV 28/120; 23%; p=0.46). A sixth of the respondents stated they did not to use anticoagulation therapy before CV (electrical CV 18/120, 15% vs pharmacological CV 20/120, 16%; p=0.72).

In case of AF lasting <24 hours duration, LMWH remained the most frequently adopted anticoagulation strategy followed by NOAC without TOE (Figure 2). CV without previous use anticoagulants increased to 19% for electrical and 17% for pharmacological CV. As for the type of LMWH, the most used is enoxaparin (95/120; 79%) followed by nadroparin (6/120; 5%) and dalteparin (6/120; 5%).

Pre-CV TOE (regardless the antithrombotic therapy adopted) was used more often for electrical CV than for pharmacological CV regardless the duration (48 or 24 hours) of AF (electrical CV 26/120, 21% vs pharmacological CV 7/120, 5%; p<0.001; electrical CV 17/120, 14% vs pharmacological CV 5/120, 4%; p=0.007 respectively).

Duration of anticoagulation management post-cardioversion

We asked the respondents to provide information on the duration of anticoagulation after CV usually utilized in their centers out of the alternatives shown in Figure 3, and if it changed according to the type of CV used (i.e. electrical or pharmacological). More than one answer was
allowed; 113 replied to the question while 23 skipped it. Continuous OAC for at least 4 weeks was the most frequently selected option, and was used more often in electrical CV (electrical CV 92/113, 81% vs. pharmacological CV 78/113, 69%; p=0.03) followed by no anticoagulation therapy (electrical CV 14/113, 12% vs pharmacological CV 17/113, 15%; p=0.58). Continuous anticoagulation for days, 1 week or lifelong were options selected by only a minority of respondents. Regarding the type of anticoagulant therapy post-CV, NOAC was usually the first choice (99/113; 88%) followed by LMWH (12/113; 10%), vitamin K antagonist (1/113; 1%) and antiplatelet agents (1/113; 1%) In case of AF lasting <24 hours duration, continuous OAC for at least 4 weeks was once again the most utilized strategy (electrical 72/113, 63% vs. pharmacological CV 61/113, 54%; p=0.14) (Figure 4). Not performing any anticoagulation increased to 24%-26% for electrical and pharmacological CV, respectively.

**DISCUSSION**

This survey provides an insight into the current clinical practice related to anticoagulation management in patients with short duration AF episodes (less than 48-24 hours) and CHA$_2$DS$_2$-VASc score 0-1 undergoing CV in European centers. The main findings of our survey were: (i) The lack of a homogeneous approach for anticoagulation both before and post-CV; (ii) High utilization of pre-procedural LMWH with markedly lesser use of DOACs, (iii) Little difference in peri-CV anticoagulation regardless of duration of AF, (iv) Higher utilization of pre-CV TOE for electrical CV than for pharmacological CV regardless the duration of AF, (v) No anticoagulation before CV in 1:5 to 1:6 of respondents; (vi) High adherence to a 4-week post-CV OAC therapy, mainly for electrical CV, (vii) Higher acceptance of lack of post-CV OAC in patients < 24 hours than 48 hours duration
Management of stroke risk and anticoagulant therapy in atrial fibrillation patients
undergoing cardioversion

Patients undergoing CV of AF, either pharmacological or electrical, are at increased risk of stroke and thromboembolism, especially in the absence of anticoagulation. This risk justifies starting OAC for at least 3 weeks before CV and continuing it for 4 weeks afterwards, independently of theCHA$_2$DS$_2$VASc score if AF has been present for 48 hours or longer (4, 14,15). However, the “48-hour rule”, is not evidence-based, and has been questioned as a delay of 12 hours or longer from symptom onset to CV was associated with a greater risk of thromboembolic complications compared to CV in less than 12 hours (1.1% versus 0.3%) (1). Underlying mechanisms of the increased propensity for peri-cardioversion thrombo-embolism include the presence of pre-existing thrombus, atrial stunning post-CV, and a transient prothrombotic state (1,15-16). Peri-CV anticoagulation with a VKA results in a significant decrease of stroke and thrombo-embolism, but achieving the necessary therapeutic anticoagulation (INR 2.0 - 3.0) for a minimum of 3 weeks before CV may be difficult and cause further delays. This 3-week period is arbitrary, and based on the time presumably needed for endothelialization or resolution of pre-existing AF thrombus. To shorten this time, TOE-guided CV was introduced. If there is no atrial thrombus on TOE, CV can be performed (17,18). As NOACs act rapidly, in patients with AF undergoing CV, NOACs are recommended with at least similar efficacy and safety to warfarin (19-21).

Interestingly, in this survey, uptake of pre-CV TOE was more frequent in patients undergoing electrical CV, suggesting a higher perceived risk of stroke by the respondents for this particular type of strategy.
Cardioverting atrial fibrillation of <48 hours in patient with low stroke risk (CHA2DS2-VASc score 0-1)

As stated in the 2019 American Heart Association guidelines, for patients with AF of less than 48 hours duration with a CHA2DS2-VASc score of 0 in men or 1 in women, administration of anticoagulation (such as heparin, a factor Xa inhibitor, or a direct thrombin inhibitor) vs no anticoagulant therapy, may be considered before CV (Class IIb recommendation) (22). Otherwise, according to the recent 2020 ESC guidelines, effective anticoagulation should be initiated as soon as possible before every CV of AF (Class IIa recommendation, level of evidence B) (6).

A single dose of LMWH was the most frequently used drug in this setting. Even though data addressing the use of NOACs pre-CV of AF lasting shorter than 48 hours duration is absent (6,15), given the consistent efficacy and safety of NOACs in patients with AF ≥48 hours combined with the similar pharmaco-dynamic and kinetic properties of NOACs and LMWH, the use of a single dose of NOAC 2–4 h before CV to replace LMWH may be justified in patients with AF <48 hours, without a TOE.

The results of the present survey reflected the considerable variability in the anticoagulant strategy among respondents. Anticoagulation before CV is the most usually adopted strategy among European centers and LMWH (mainly enoxaparin) was the most frequently agent used followed by single dose of NOAC before CV without TOE.

The recent ESC guidelines have reinforced the importance of involving patients in treatment decisions through a shared-decision making model. This applies not only to rhythm vs rate control decisions, but also for the choice of anticoagulant. The current suggested pathway for the management of AF patients is the ABC pathway (6) This integrated approach, reinforces the patient role. Taking into account that LMWH probably is not the best option for patient comfort and possible complications (causing pain and leading to frequent bruising and ecchymosis), it seems difficult for physicians to justify their preference for LMWH and not involving patients in this decision. Future research comparing NOAC and LMWH before CV in patients with AF <24-48
hours duration and low-risk stroke will help fill this evidence gap and provide physicians and patients with more sound grounds for decision-making.

**Duration of anticoagulation post-cardioversion for AF of <48 hours in patient with low stroke risk (CHA2DS2-VASc score 0-1)**

As stated in the recent 2020 ESC guidelines (6), 4 weeks of anticoagulation after CV could be omitted in patients at very low risk (CHA2DS2-VASc of 0 in men and 1 in women) with new-onset AF lasting shorter than 24 hours (Class IIb recommendation, level of evidence C). In patients with AF duration of >24 hours duration undergoing CV, therapeutic anticoagulation should be continued for at least 4 weeks, even after successful CV to sinus rhythm (Class IIa recommendation, level of evidence B).

The results of the present survey showed that continuous OAC for at least 4 weeks was the most common option regardless of AF duration. Omitting post-CV anticoagulation was an uncommon strategy. However, this was observed more often in patients with AF <24 hours duration than those with < 48 hours, and in patients undergoing pharmacological cardioversion.

**Limitations**

Due to the relatively low number of respondents, mainly electrophysiologists affiliated to university hospitals, and very high representation from Italy and Poland, it is difficult to extrapolate this survey to different categories of European practitioners and all European countries. This limits the ability of the survey to provide a comprehensive snapshot of current practice regarding antithrombotic management treatment in low stroke risk patients undergoing CV of AF <48 hours duration. Finally, it is often very difficult to be sure of the “true” duration of a new-onset AF and physician’s preference and views on CV safety and thromboembolism is likely to play a role when choosing anticoagulation strategy.
CONCLUSIONS

This survey provided an insight into current clinical practice related to anticoagulation management in patients with AF <48 hours duration and CHA₂DS₂-VASc score 0-1 undergoing CV across European centers. The main finding is the lack of a homogeneous approach for anticoagulation both before and post-CV. LMWH use before CV and continuous anticoagulation for at least 4 weeks are the most common strategies, regardless of AF duration (24 or 48 hours). The results obtained with the present survey highlight the need for more research addressing this area of uncertainty, and clarifying the role and safety of CV without anticoagulation in patients with short duration AF.

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Data availability

Data are stored by European Society of Cardiology (ESC) and only ESC staff, European Heart Rhythm Association Scientific Initiatives Committee Chair and authors of the survey have access to the data. Data would be made available upon reasonable request to the senior author.
REFERENCES


3. Husted S, Torp-Pedersen C. Thromboembolic risk in 16274 atrial fibrillation patients undergoing direct current cardioversion with and without oral anticoagulant therapy. Europace 2015;17:18-23


FIGURE LEGENDS

Supplementary material online, Figure S1. Geographic distribution of respondents to the EHRA survey on antithrombotic treatment management in low stroke risk patients undergoing cardioversion of atrial fibrillation <48 hours duration.

Figure 1. Anticoagulation strategy before cardioversion in patient with nonvalvular AF <48 hours duration not on oral anticoagulation and CHA2DS2-VASc score of 0 (m) – 1 (f). LMWH: low-molecular-weight heparin; NOAC: Non-vitamin K antagonist oral anticoagulant; UFH: unfractionated heparin; TOE: transesophageal echocardiography.
Figure 2. Anticoagulation strategy before cardioversion in patient with nonvalvular AF <24 hours duration not on oral anticoagulation and CHA2DS2-VASc score of 0 (m) – 1 (f). LMWH: low-molecular-weight heparin; NOAC: Non-vitamin K antagonist oral anticoagulant; UFH: unfractionated heparin; TOE: transesophageal echocardiography.

Figure 3. Duration of anticoagulation post-cardioversion for nonvalvular AF of <48 hours not on oral anticoagulation and CHA2DS2-VASc score of 0 (m) – 1 (f). LMWH: low-molecular-weight heparin; NOAC: Non-vitamin K antagonist oral anticoagulant; UFH: unfractionated heparin; TOE: transesophageal echocardiography.
Figure 4. Duration of anticoagulation post-cardioversion for nonvalvular AF of <24 hours duration not on oral anticoagulation and CHA2DS2-VASc score of 0 (m) – 1 (f). LMWH: low-molecular-weight heparin; NOAC: Non-vitamin K antagonist oral anticoagulant; UFH: unfractionated heparin; TOE: transesophageal echocardiography.
QUESTIONNAIRE

1. In which country is your centre based?
   (drop-down list)

2. Would you like the acknowledgment of your centre in the EP Europace Journal and on the website?
   Yes
   No

3. Your email address is
   (text box)

4. What type of institution do you work in?
   a) University Hospital
   b) Non-University Hospital
   c) Private Hospital
   d) Private practice
   e) Other (please specify); (text box)

5. Which is the estimated number of electrical cardioversions performed per year in your Centre?
   ……

6. In your Centre, the elective electrical cardioversion is performed:
   a) in an outpatient setting
   b) in the emergency ward/department
   c) the patients are admitted to the cardiology/intensive care unit (inpatient setting)

7. Which anticoagulation strategy is usually adopted in your center before cardioversion (CV) in a patient with recent onset nonvalvular AF of <48 h duration not on oral anticoagulation and with CHA2DS2-VASc score of 0 (m) – 1 (f) ?

<table>
<thead>
<tr>
<th>Anticoagulation Strategy</th>
<th>Electrical CV</th>
<th>Pharmacological CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administering LMWH</td>
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<tr>
<td>Administering UFH</td>
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<tr>
<td>Fondaparinux</td>
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<tr>
<td>Single dose of NOAC taken ≥ 2–4 h before CV with a TOE-guided approach</td>
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<tr>
<td>Single dose of NOAC taken ≥ 2–4 h before CV without TOE</td>
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<td>TOE regardless of the antithrombotic therapy adopted</td>
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<td>TOE before deciding anticoagulation</td>
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<tr>
<td>No anticoagulation</td>
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</table>

8. If your institutional practice is administering LMWH before CV, which LMWH do you use?
   a) Bemiparin
   b) Nadroparin
   c) Reviparin
   d) Reviparin
   e) Tinzaparin
   f) Dalteparin
   g) Enoxaparin
   h) We do not use LMWH before CV
9. If your institutional practice is administering Enoxaparin (LMWH) before CV, which dose do you use?
   a) A subcutaneous single dose of 4000 UI
   b) A subcutaneous single dose of 6000 UI
   c) 1mg/Kg subcutaneous single dose
   d) A subcutaneous dose of 1 mg/kg twice daily
   e) I use other alternative imaging (please specify)

10. Do you routinely use alternative imaging to TOE before CV?
   a) No, I do not use any alternative imaging
   b) Yes, I use CT scan
   c) Yes, I use MRI only in unclear TOE
   d) I use other alternative imaging (please specify)

11. If the recent onset of AF is <24 h, which is your strategy?

<table>
<thead>
<tr>
<th>Administering LMWH</th>
<th>Electrical CV</th>
<th>Pharmacological CV</th>
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<tbody>
<tr>
<td>Administering UFH</td>
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<td>Fondaparinux</td>
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<tr>
<td>No anticoagulation</td>
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</table>

12. In your practice, in a patient with recent onset AF <12 h, in applying cardioversion do you prefer:
   a) To wait for 12 before CV
   b) To wait 24 before
   c) To wait for 48 h
   d) To defer cardioversion after 4 weeks of anticoagulation

13. In case of spontaneous cardioversion of the recent onset nonvalvular AF of <48 h duration not on oral anticoagulation and with CHA2DS2-VASc score of 0 (m) – 1 (f), what is your institutional anticoagulation protocol immediately after the conversion?
   a) Administration of LMWH/UFH, no TOE
   b) Administration of NOAC, no TOE
   c) No immediate anticoagulation, no TOE
   d) TOE, than decision on immediate anticoagulation
   e) Other?

14. Which is your institutional practice regarding duration of anticoagulation management of patients post-cardioversion for nonvalvular AF of <48 h and a CHA2DS2-VASc score of 0 (m) – 1 (f)?

<table>
<thead>
<tr>
<th>Lifelong</th>
<th>Electrical CV</th>
<th>Pharmacological CV</th>
<th>Spontaneous CV</th>
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<tbody>
<tr>
<td>At least 4 weeks OAC</td>
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<td>1 week</td>
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<td>1-2 days</td>
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<td>3 days</td>
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<tr>
<td>No anticoagulation</td>
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15. If the recent onset of AF is <24 h, which is your strategy?

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<thead>
<tr>
<th></th>
<th>Electrical CV</th>
<th>Pharmacological CV</th>
<th>Spontaneous CV</th>
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<tr>
<td>Lifelong</td>
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<tr>
<td>At least 4 weeks</td>
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<td>3 days</td>
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<tr>
<td>No anticoagulation</td>
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</table>

16. Which anticoagulant therapy is usually the first choice in your center after CV?

a) LMWH  
b) Antiplatelet agents  
c) Vitamin K antagonist  
d) NOAC  
e) Other

17. The recently published 2020 ESC guidelines on management of FA stated that in patients with a definite duration of AF <24 h and a very low stroke risk (CHA2DS2-VASc of 0 in men or 1 in women) post-CV anticoagulation for 4 weeks may be omitted. Does this recommendation change your current practice?

a) Strongly agree  
b) Midly agree  
c) Midly disagree  
d) Strongly disagree  
e) I don’t know