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

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Data supporting the safety of cardioversion (CV) of atrial fibrillation (AF) without anticoagulation in patients with AF duration <48 h 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 h and the clinical risk profile as estimated through the CHA_2DS_2VASc score is low (a score of 0 for men and 1 for women). As the recent 2020 European Society of Cardiology (ESC) guidelines 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 h duration and low stroke risk across centres 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 stroke-risk patients with AF <48 h, (ii) higher utilization of periprocedural low-molecular-weight heparin than of non-vitamin K antagonist oral anticoagulant, (iii) higher utilization of pre-CV transoesophageal echocardiography for electrical CV than for pharmacological CV regardless of 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 therapy in patients with <24 h than 24-48 h episode duration. The results obtained in this 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 • Low stroke risk • Cardioversion • 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) therapy and if AF has been present for >12 h.[1–3] This risk justifies the use of OAC therapy for at least 4 weeks after cardioversion, independently of the CHA_2DS_2VASc score or the method (electrical or pharmacological) used to restore sinus rhythm, if AF has been present for 48 h duration or longer.[4] However, the rationale for the potential benefit and use

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of anticoagulation during this time frame comes from the observation of an increased risk of stroke in the first 30 days after CV.[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 h 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 ESC Guidelines suggest that omission of the 4-week anticoagulation period may be considered in patients with a definite AF duration of 24 h or less, and with a CHA_2DS_2VASc score of 0 in men, or 1 in women.[6]

Observational data suggest that the risk of thromboembolic complications after CV for AF duration <48 h is very low (0–0.9%) in patients with a low stroke risk (CHA_2DS_2-VASc 0 in men, 1 in women).[1,7–10] Cardioverting acute AF of <48 h without any anticoagulation before and after CV has, therefore, been used by some author groups in specific scenarios.[1,7,8,11–13] 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 centres in Europe regarding anticoagulation prior and post-CV in patients with AF <24–48 h duration and CHA_2DS_2-VASc score 0–1. The aim of this European Heart Rhythm Association (EHRA) survey 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 informations about antithrombotic treatment in low stroke risk patients undergoing CV of AF of <48 h duration. The online-based questionnaire consisted of 18 multiple-choice questions including institutional information, in combination of single best answer or 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 χ^2 test or the Fisher's 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 centre 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 centres 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 transoesophageal 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 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 h duration, LMWH remained the most frequently adopted anticoagulation strategy followed by NOAC without TOE (*Figure 2*). Cardioversion without previous use anticoagulants increased to 19% for electrical and 17% for pharmacological CV. As for the type of LMWH, the most frequently used was enoxaparin (95/120; 79%) followed by nadroparin (6/120; 5%) and dalteparin (6/120; 5%).

Pre-CV TOE (regardless of the antithrombotic therapy adopted) was used more often for electrical CV than for pharmacological CV indipendently from duration (48 or 24 h) 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 centres 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 therapy 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 h duration, continuous OAC therapy 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.

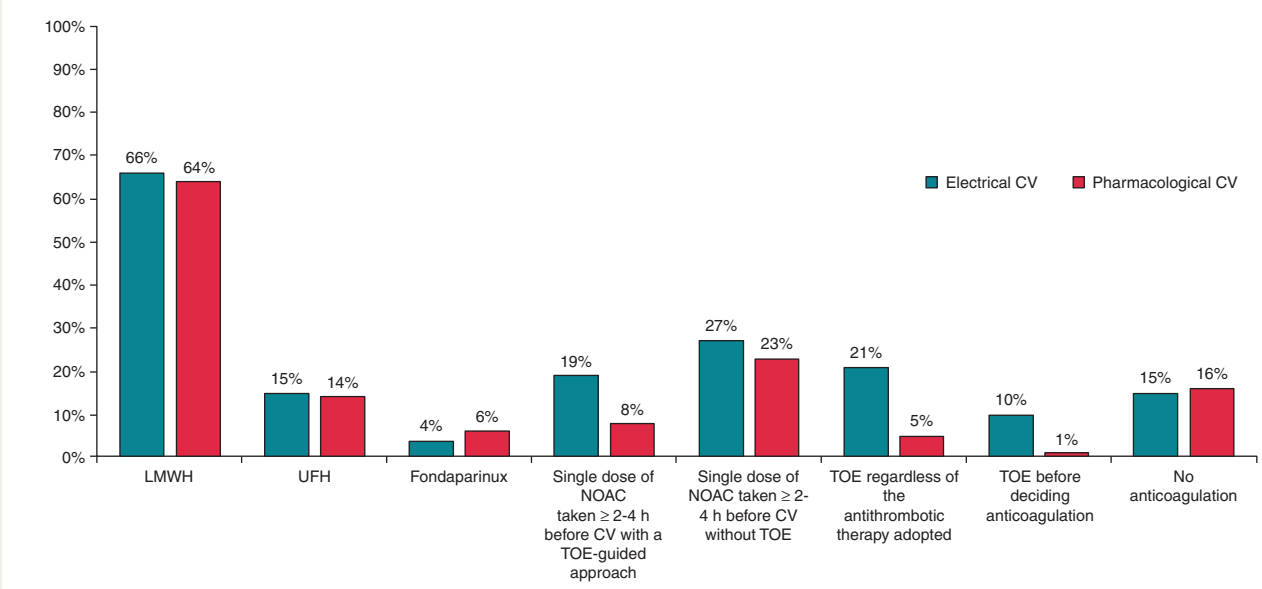

Figure 1 Anticoagulation strategy before cardioversion in patient with non-valvular AF <48 h duration and CHA_2DS_2-VASc score of 0 (m) – 1 (f). CV, cardioversion; LMWH, low-molecular-weight heparin; NOAC, non-vitamin K antagonist oral anticoagulant; TOE, transoesophageal echocardiography; UFH, unfractionated heparin.

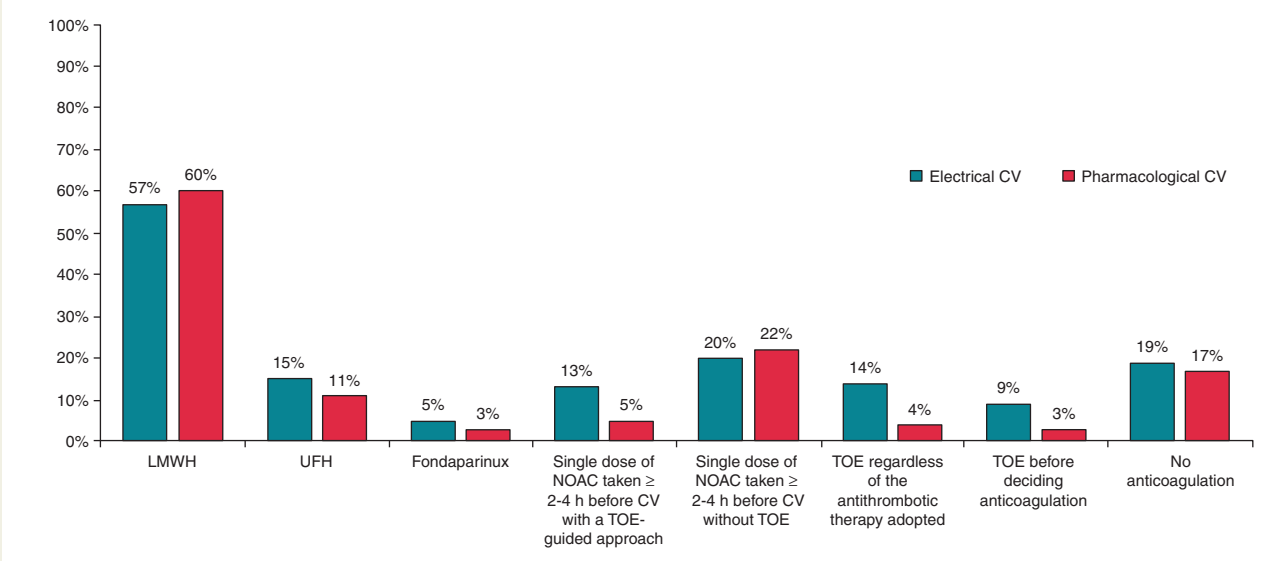

Figure 2 Anticoagulation strategy before cardioversion in patient with non-valvular AF <24 h duration and CHA_2DS_2-VASc score of 0 (m) – 1 (f). CV, cardioversion; LMWH, low-molecular-weight heparin; NOAC, non-vitamin K antagonist oral anticoagulant; TOE, transoesophageal echocardiography; UFH, unfractionated heparin.

Discussion

This survey provides an insight into the current clinical practice of anticoagulation management in patients with short duration AF episodes (<48–24 h) and CHA_2DS_2-VASc score 0–1 undergoing CV in European centres. The main findings were:

i. the lack of a homogeneous approach for anticoagulation both before and post-CV;
ii. high use of pre-procedural LMWH with markedly lower use of NOACs;
iii. little difference in peri-CV anticoagulation regardless of duration of AF;

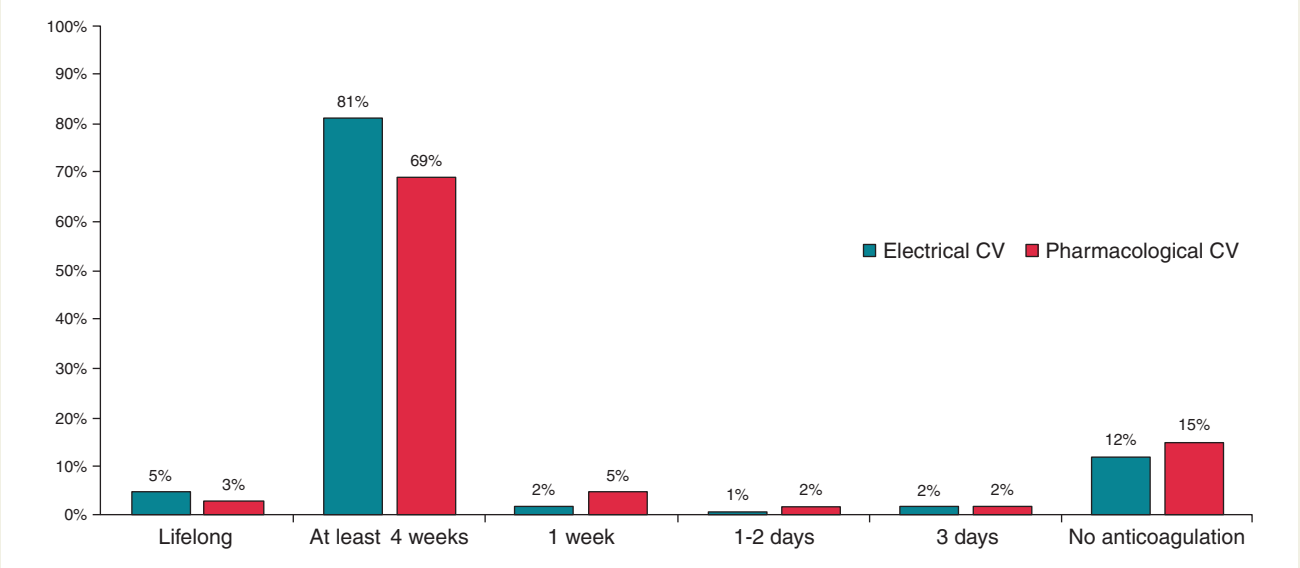

Figure 3 Duration of anticoagulation post-cardioversion for non-valvular AF of <48 h and CHA_2DS_2-VASc score of 0 (m) – 1 (f).

iv. higher utilization of pre-CV TOE for electrical CV than for pharmacological CV regardless of the duration of AF;
v. no anticoagulation before CV in 1:5–1:6 of respondents;
vi. high adherence to a 4-week post-CV OAC therapy, mainly for electrical CV; and
vii. lower prescription of post-CV OAC therapy in patients <24 than 24-48 h 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 the CHA_2DS_2VASc score if AF has been present for 48 h or longer.[4,14,15] However, the '48-h rule', is not evidence-based, and has been questioned as a delay of 12 h or longer from symptom onset to CV was associated with a greater risk of thromboembolic complications compared to CV in <12 h (1.1% vs. 0.3%).[1] Underlying mechanisms of the increased propensity for peri-CV thromboembolism include the presence of pre-existing thrombus, atrial stunning post-CV, and a transient prothrombotic state.[1,15–17] Peri-CV anticoagulation with a VKA results in a significant decrease of stroke and thromboembolism, 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.[18,19] As NOACs act rapidly, in patients with AF undergoing CV, NOACs are recommended with at least similar efficacy and safety to warfarin.[20–22]

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 h in patient with low stroke risk (CHA_2DS_2-VASc score 0–1)

As stated in the 2019 American Heart Association guidelines, for patients with AF of less than 48 h duration and a CHA_2DS_2-VASc score of 0 in men or 1 in women, administration of anticoagulant therapy (such as heparin, a factor Xa inhibitor, or a direct thrombin inhibitor) vs. no anticoagulation, may be considered before CV (Class IIb recommendation).[23] 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 h duration is absent,[6,15] given the consistent efficacy and safety of NOACs in patients with AF ≥48 h 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 h.

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

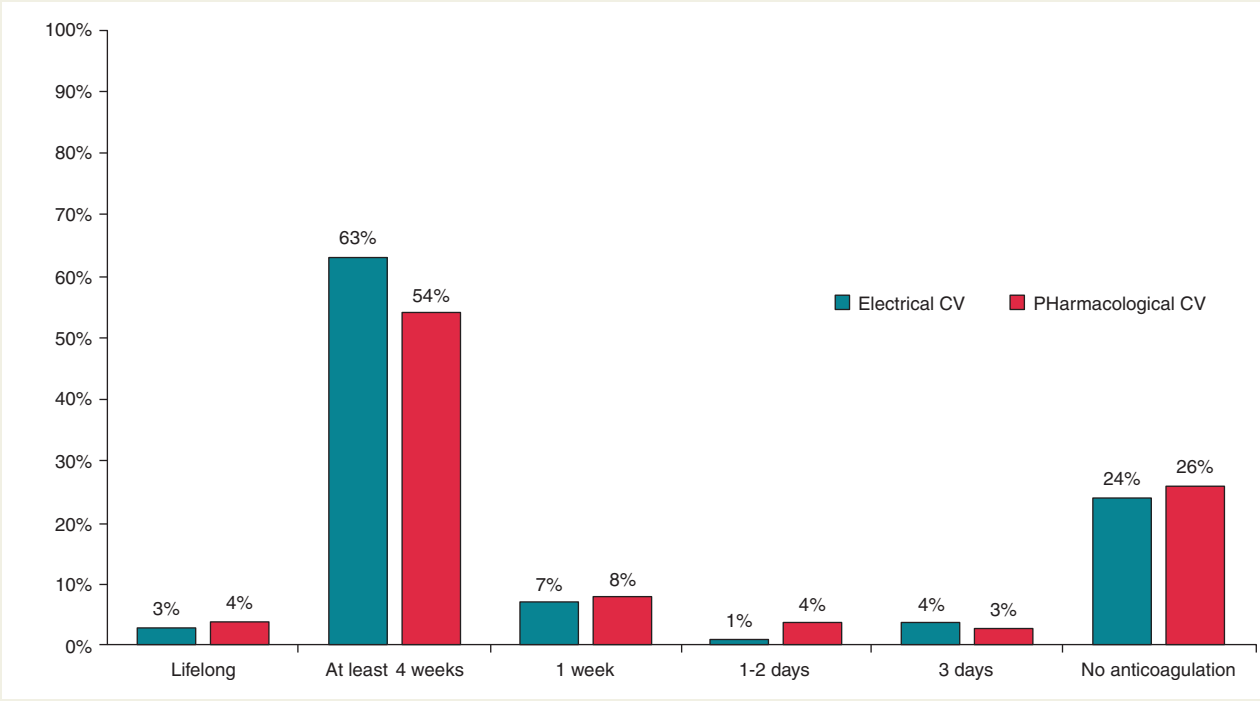

Figure 4 Duration of anticoagulation post-cardioversion for non-valvular AF of <24 h duration and CHA_2DS_2-VASc score of 0 (m) – 1 (f).

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 h 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 h in patients with low stroke risk (CHA_2DS_2-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 (CHA_2DS_2VASc of 0 in men and 1 in women) with new-onset AF lasting shorter than 24 h (Class IIb recommendation, level of evidence C). In patients with AF duration of >24 h 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 h duration than those with <48 h, 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 generalize the results of 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 h 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 h duration and CHA_2DS_2-VASc score 0–1 undergoing CV across European centres. The main finding is the lack of a homogeneous approach for anticoagulation both before and post-CV. The use of LMWH before CV and continuous anticoagulation for at least 4 weeks are the most

common strategies, regardless of AF duration (<24 or <48 h). 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.

Supplementary material

Supplementary material is available at *Europace* online.

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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.

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