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Abstract

Background. Controversy exists regarding anticoagulation management following acute cardioversion in patients with early-onset (< 48 hours) atrial fibrillation without class I guideline indication for long-term oral anticoagulation (CHA2DS2-VASc 0-1).

Methods and Results. A random-effect meta-analysis of observational studies reporting 30-day incidence of thromboembolic complications after cardioversion without post-procedural oral anticoagulation therapy in patients at low-moderate thromboembolic risk (CHA2DS2-VASc 0-1) was performed. Four studies were included, encompassing 3276 cardioversions. The analysis revealed that the pooled risk of 30-day incidence of thromboembolic complications in this subset of patients is low (0.10%, 95% confidence interval: 0.00-0.30%).

Conclusions. Given these data, considering the bleeding risk unavoidably conferred by OAT, which is known to be higher in the first month from treatment onset, short-term anticoagulation limited to 4 weeks post-cardioversion of early-onset (< 48 hours) atrial fibrillation in patients with low-moderate risk of stroke (CHA2DS2-VASc 0-1) should be discouraged.

Keywords

Atrial fibrillation; Early-onset; Cardioversion; Oral Anticoagulation.

Introduction

Atrial fibrillation (AFib) cardioversion (CV) carries an inherent short-term increase in the risk of clinical thromboembolism, both in acute and in elective settings [1, 2]. In case of acute cardioversion of early-onset (< 48 hours) AFib, oral anticoagulation therapy (OAT) apparently overrides this extra-risk, reducing it to the baseline thromboembolic risk of AFib patients[3]. However, being unanimously accepted that AFib patients not assuming OAT and presenting with high thromboembolic risk (CHA_2DS_2-VASc score ≥ 2) should start anticoagulation as soon as possible before CV and continue it long-term [4, 5], uncertainty regarding the best management in case of non-anticoagulated individuals with low-moderate thromboembolic risk (CHA_2DS_2-VASc score 0-1) exists. In fact, European guidelines [4] advocate peri-procedural anticoagulation followed by short-term OAT (4 weeks) also in patients without stroke risk factors (CHA_2DS_2-VASc 0), while the American guidelines [5] propose a less aggressive approach, suggesting that patients without additional risk factors other than female sex (CHA_2DS_2-VASc 0 in male, CHA_2DS_2-VASc 1 in female) do not necessarily need 4-week OAT post-CV. Due to this inconsistency, the aim of the present study was to perform a meta-analysis of observational studies reporting the 30-day rate of thromboembolic complications after acute cardioversion of early-onset AFib in patients at low-moderate risk of stroke (CHA_2DS_2-VASc 0-1) not assuming OAT in the 4 weeks post-CV.

Methods

The present meta-analysis was performed in accordance to PRISMA guidelines [6].

PubMed/MEDLINE and Embase databases were searched for from their inceptions to 31st January 2020, using the following string: "anticoagulation AND (acute OR early OR recent) AND cardioversion AND atrial fibrillation". Two investigators (AS, MA) independently reviewed the titles/abstracts and studies to determine their eligibility based on the inclusion criteria and extracted all relevant outcomes of interest. Studies were eligible for inclusion if they reported the 30-day incidence of thromboembolic complications after acute CV (both pharmacological or electrical) of early-onset (< 48 hours) AFib in patients at low-moderate thromboembolic risk (CHA_2DS_2-VASc 0-1) not assuming OAT in the 4 weeks following CV. Each CV performed during study-specific enrolling period was considered as an index observation, thus the number of CV may outweigh the number of patients included (each patient may have performed more than one CV during the investigated period).

Random-effect meta-analysis (inverse variance weighting) of 30-day incidence of thromboembolic complications (please refer to Supplementary Table 1 for study-specific definition) was performed using Freeman-Tukey double arcsine transformation and the results with the corresponding 95% confidence interval (CI) were reported after back-transformation. Cochran I^2 test was used to investigate heterogeneity. To deal with possible bias induced by the low number of studies included and preponderance of a single study, sensitivity analyses using inverse variance meta-analysis with different proportion transformation (logit transformation, arcsine transformation), as well as a generalized linear mixed model (GLMM) meta-analysis, were also performed.

P values < 0.05 were considered statistically significant. Statistical analyses were performed with R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria), using the package *meta* [7].

Results

Initial search yielded 276 results. According to the inclusion criteria, 4 studies reporting 30-day incidence of thromboembolic complications in a cohort of AFib patients with CHA_2DS_2-VASc 0-1 who underwent CV without anticoagulation in the 4 weeks following the procedure were finally included in the present meta-analysis [3, 8-10] (Figure 1). Table 1 summarizes main study characteristics. Meta-analytic population mainly included young men (male sex percentage range: 55-65%; age range: 55-65 years), most often undergoing electrical CV (range 39-100%). In two of the included studies [3, 8], no periprocedural anticoagulation was adopted, differently from the other two studies [9, 10], where sole periprocedural anticoagulation with low molecular weight heparin (LMWH) was established in 100% and 62% of the patients, respectively.

Meta-analysis of 30-day incidence of thromboembolic complications revealed a pooled estimate of 0.10% (95% CI, 0.00-0.30%, I^2: 0%), without significant heterogeneity. Funnel plot is reported in Figure 2. Sensitivity analyses using different meta-analytic approaches consistently produced similar results (Supplementary Figures 1-3).

Discussion

Current guidelines are contradictory in the recommendations regarding oral anticoagulation in patients at low-moderate risk of stroke (CHA_2DS_2-VASc 0-1) undergoing acute CV for early-onset (< 48 hours) AFib [4, 5]. In particular, the role of short-term OAT (4 weeks post-CV) in patients without indication of long-term OAT is controversial.

The present analysis indicates that 30-day risk of thromboembolic complications after CV in this subset of patients (CHA_2DS_2-VASc 0-1, no short-term OAT) is as low as 0.1% (95% CI 0.0%-0.3%). In addition, it is known that also just one month of OAT exposes the patient to an increased risk of major bleedings.

Unfortunately, no specific data on 30-day major bleeding risk in this population exist, precluding direct risk-to-benefit assessment of short-term anticoagulation. However, an indirect comparison with other randomized or observational studies provides interesting insights. For example, three randomized clinical trials have recently compared direct oral anticoagulants (rivaroxaban[11], edoxaban[12], apixaban[13]) to heparin/vitamin K antagonist (VKA) in the setting of scheduled AFib cardioversion, reporting major bleeding, following cardioversion, in the range of 0.3%-0.8%. In particular, the EMANATE trial[13], which compared apixaban to heparin/warfarin in AFib patients with less than 48 h anticoagulation prior to randomization, describes a clinical setting and population somewhat similar to the one investigated in this meta-analysis. Despite a slightly higher thromboembolic risk (mean CHA_2DS_2-VASc 2.2), 62% of the enrolled patients were naïve to OAT, and had a mean age of 64 years. In this trial, major bleeding following cardioversion occurred in 0.4% of patients treated with apixaban and 0.8% of those on heparin/VKA. In addition, recent real-world data from a Danish national registry [14] encompassing 54,321 patients with non-valvular AFib who initiated OAT treatment (mean CHA_2DS_2-VASc 2.9; mean HAS-BLED 2.2) showed that major bleeding incidence in the first 30 days of treatment was 0.82% (448 events/54,321 patients), with nearly one fifth being intracranial bleeding (17%). If we compare the 30-day (0.82%) with the

1-year incidence (4.4%) of major bleedings in the latter real-world study, it is evident that the first 30 days after OAT initiation are the most vulnerable period in terms of major bleedings, thus the 4 week short-term anticoagulation following cardioversion in OAC-naïve patients seems a susceptible period in terms of safety events.

To understand what these real-life bleeding data can imply in our meta-analytic population, should this population be anticoagulated for 30 days after the cardioversion, some assumptions need to be taken. First, due to the correlation between CHA_2DS_2-VASc and HAS-BLED [15], we can assume that HAS-BLED would range between 0-1 in the examined population. Second, based on the estimation of bleeding risk in the original validation cohort of HAS-BLED score across the different categories [16], bleeding risk of patients with HAS-BLED 0-1 is reduced by 43% compared to the risk of patients with HAS-BLED 2. Given these postulations, in case of short-term OAT, the expected 30-day incidence of major bleedings in the present population, assuming low HAS-BLED score (0-1), could be supposed 0.46%.

This means that, in order to reduce a 30-day 0.1% risk of a thromboembolic complication, initiation of a short-term OAT might expose the patient to a 0.46% risk of experiencing a major bleeding during the 4 weeks of therapy, with the risk of a potentially fatal intracranial bleeding projected at 0.08% (17% of major bleedings were intracranial bleedings in the study from Danish national registry [14]) (Figure 3).

Although to be confirmed in large-scale studies, in our opinion, these data, together with those of randomized and real-world data concerning the bleeding risk conferred by OAT, suggest that a strategy of short-term anticoagulation after acute CV of early-onset AFib, in this specific setting of patients, should be discouraged. The therapeutic choice following CV should be between no-OAT strategy and initiation of a long-term OAT. A no-OAT strategy appears a reasonable choice, at least in patients with CHA_2DS_2-VASc 0, possibly coupled with a timely cardioversion. In fact, based on the Finnish Cardioversion registry (FinCV) data, if the cardioversion is performed by 12 hours after symptoms onset a nearly four-fold reduction in thromboembolic risk at 30-days is reported in non-

anticoagulated patients [17].

Limitations

First, lack of complete sex subgroup data in the included studies precluded the possibility to specifically analyze thromboembolic incidence in females without (CHA_2DS_2-VASc 1) and with a single stroke risk factor other than gender (CHA_2DS_2-VASc 2), [18]. Second, additional stroke risk factors accounted for in the CHA_2DS_2-VASc score (other than gender) may have different impact in terms of increased thromboembolic risk [19]. The impossibility of performing meta-regression analyses, due to low number of studies included (< 5) and the lack of complete baseline characteristics of the subgroup of CHA_2DS_2-VASc 0-1 patients in most of the studies, unfortunately limits the possibility to account for single variables. Finally, the fact that some patients in the included studies received more than one cardioversion should be regarded as a possible confounder.

Conclusion

Thromboembolic complications following acute CV of early-onset AFib (< 48 hours) in patients not assuming OAT and having low-moderate thromboembolic risk (CHA_2DS_2-VASc 0-1) are rare (30-day incidence: 0.10%, 95% CI 0.00-0.30%). Given this, and the knowledge that the OAT-associated major bleeding risk is higher in the first 30 days after treatment initiation, short-term anticoagulation (4 weeks) following acute CV of early-onset AFib should be discouraged. At index presentation the focus should be on a careful patient assessment in order to establish whether long-term OAT is, instead, indicated.

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None.

Figure Legends

Figure 1. Study flow diagram.

Figure 2. Forest plot of 30-day incidence of thromboembolic complication following cardioversion.

Figure 3. 30-day incidence of thromboembolic events and expected major bleedings following cardioversion of early onset atrial fibrillation in patients with low-moderate thromboembolic risk (a), with distribution of major bleeding subtypes (b). *Expected major bleeding incidence and major bleeding subtype distribution are based on data by Lamberts [14]. AFib: atrial fibrillation; TE: thromboembolic.

Tables

Table 1. Main characteristics of the included studies.

First author, year	Study population	Total number of patients	Patients included (number of cardioversions)	Mean Age (years)	Heart failure (%)	Type of cardioversion	Periprocedural anticoagulation
Gronberg 2016	Finnish CardioVersion (FinCV) registry	3143	nr (2772)	62.2 (CHA2DS2-VASc 0-1 patients: 54.3)	5%	Electrical 89.1%***; Pharmacological 10.9%***	None
Garg 2016	Cleveland Clinic Cardiac Electrophysiology Laboratory database	484	188 (220*)	62.8	27	Electrical 100%	None****
Tampieri 2018	Italian Emergency Department patients undergoing acute CV	157	157 (218)	55.2**	0**	Pharmacological 61%; Electrical 39%	LMWH 100%
Bonfanti 2018	Italian Emergency Department patients undergoing acute CV	490	66 (66)	61	nr	Electrical 100%	LMWH 81%

LMWH, Low Molecular Weight Heparin; nr, not reported

*Estimation based on the cardioversion-to-patient ratio in the entire cohort (1.17 cardioversions per patient)

** This study only included patients at low cardio-embolic risk

***Referred to CHA_2DS_2-VASc 0-1 patients, irrespective of anticoagulation status

****Comprised cardioversions performed either without anticoagulation or on warfarin with INR<1.5.

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