International Journal of Cardiology 203 (2016) 269–273

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Strokes after cardioversion of atrial fibrillation — The FibStroke study☆

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ARTICLE INFO

Article history:
Received 16 July 2015
Received in revised form 1 October 2015
Accepted 19 October 2015
Available online 20 October 2015

Keywords:
Atrial fibrillation
Cardioversion
Stroke
Transient ischemic attack

ABSTRACT

Background: Cardioversion of atrial fibrillation (AF) is associated with an increased risk for stroke. We identified all cardioversions during the 30 days preceding stroke or transient ischemic attack (TIA) in patients with a previously diagnosed AF, and sought to assess the characteristics of cardioversions leading to stroke or TIA.
Methods: FibStroke is a cross-sectional observational multicenter registry that included AF patients with an ischemic stroke or intracranial bleed identified from a discharge registry of four Finnish hospitals. In total 3677 consecutive AF patients suffered 3252 strokes and 956 TIA episodes during 2003–2012. This pre-specified analysis focused on the 1644 events that occurred to patients with paroxysmal or persistent AF at the time of stroke/TIA.
Results: A total of 78 strokes and 22 TIA episodes were preceded by a cardioversion. Post-cardioversion strokes accounted for 6.4% of strokes in patients with paroxysmal/persistent AF. Of the 100 cardioversions leading to an ischemic event, 77 were acute and 23 were elective, 63 events occurred in patients not using anticoagulation, and 5 patients had periprocedural INR < 2. Importantly, 21 patients were in low risk of stroke, i.e. CHA_2DS_2-VASc score < 2. The median delay from cardioversion to event was 2 days. All nine patients who after an unsuccessful cardioversion developed a stroke had a spontaneous cardioversion prior to stroke.
Conclusions: Every sixteenth stroke of patients with paroxysmal/persistent AF is preceded by a cardioversion. Most post-cardioversion strokes occur in patients not using oral anticoagulation before cardioversion of acute AF.

1. Introduction

Cardioversions are an essential part of rhythm-control strategy in the treatment of atrial fibrillation (AF). Every cardioversion is, however, associated with a temporary increase in stroke risk, although the risk has been less than 1% in patients with adequate anticoagulation or after cardioversion of acute AF [1–4]. Although rhythm control is a tempting primary treatment option, this strategy has offered no mortality benefit compared to rate-control in randomized trials [5,6]. Majority of strokes occurred in these trials in patients with subtherapeutic anticoagulation or in whom warfarin had been stopped after restoring the sinus rhythm. These results highlight the importance of long-term therapeutic anticoagulation in patients with paroxysmal and persistent AF in whom sinus rhythm is pursued.

In this pre-specified analysis of the FibStroke study, we sought to assess the clinical characteristics and significance of cardioversion as a risk factor for cerebral thromboembolism in a large population of AF patients who suffered an ischemic stroke or transient ischemic attack (TIA).

We hypothesized that cardioversion is a common risk factor for thromboembolic complications in patients with AF and that antithrombotic medication is underused in this population. The main objective of the study was to assess the typical characteristics of cardioversions leading to thromboembolic complication, with the ultimate goal of identifying potential targets for improving clinical practice and increasing patient safety.

Abbreviations: AF, atrial fibrillation; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes mellitus, and prior Stroke, transient ischemic attack or thromboembolism (doubled), vascular disease, Age 65 to 74, sex category (female, unless <65 years and no other risk factors); INR, international normalized ratio; IQR, inter-quartile range; TIA, transient ischemic attack.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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http://dx.doi.org/10.1016/j.ijcard.2015.10.168
0167-5273/

2. Methods

2.1. Study population

The FibStroke study (www.ClinicalTrials.gov, identifier NCT02146040) is part of a wider protocol in progress to assess thrombotic and bleeding complications of AF in Finland [7–9].

The FibStroke registry included all consecutive patients with a previously diagnosed AF who suffered a stroke or intracranial bleeding during the study period. Data for the study was collected from two university hospitals and two central hospitals in Finland. The initial screening was conducted by identifying all patients from the hospital discharge records with the following criteria: 1) The patient had been diagnosed with AF or atrial flutter and 2) the patient had been diagnosed with ischemic stroke, TIA or intracranial bleed between the years 2003–2012 (in one central hospital 2006–2012). A comprehensive list of the ICD 10 codes used for the screening is provided in the Supplementary methods. After the initial screening, all patient files were reviewed individually, and all procedures and cardioversions performed during the 30 days preceding the stroke, TIA or intracranial bleeding were identified. Detailed information about the cardioversion and the patient characteristics at the time of cardioversion and at the time of the stroke, TIA or intracranial bleeding was recorded. Data was collected in a structured electronic case report form.

There were a total 3677 patients with a history of AF and who after the diagnosis of AF developed a total of 3252 ischemic strokes and 956 TIA episodes. For this pre-specified analysis we focused on patients in whom an elective or acute cardioversion for paroxysmal or persistent AF was performed during the 30 days preceding the stroke or TIA.

As a control for the ischemic events, we also identified 767 patients with a previously diagnosed AF who suffered 794 intracranial bleeds during the study period, and preceding cardioversions for AF were recorded similarly in this subgroup.

2.2. Exclusion

We excluded one patient who underwent cardioversion of AF during coronary artery bypass operation. The stroke was discovered on the first postoperative day. One of the included patients developed two strokes after a single cardioversion. The first stroke was hemorrhagic and warfarin was stopped followed by another ischemic stroke 12 days later. The second stroke was excluded from this analysis.

2.3. Ethical issues

The study protocol was approved by the Medical Ethics Committee of the Hospital District of Southwest Finland and the ethics committee of the National Institute for Health and Welfare. Informed consent was not required because of the registry nature of the study. The study conforms to the Declaration of Helsinki.

2.4. Definitions

Diagnosis of AF was confirmed by 12-lead electrocardiogram according to the standard criteria. Cardioversion was considered successful if sinus rhythm was obtained and the patient was discharged in sinus rhythm. The diagnosis of stroke and TIA were confirmed from the patient records, as diagnosed by the treating neurologist. Only strokes and TIAs considered as definite by the treating physician were included in our study. All patients were imaged by computed tomography or magnetic resonance imaging.

2.5. Statistical analysis

Continuous variables were reported as mean ± standard deviation if they were normally distributed, and as median [inter-quartile range (IQR)] if they were skewed unless stated otherwise. Categorical variables were described with absolute and relative (percentage) frequencies. Comparisons between study subgroups were performed with Mann–Whitney test for continuous and Chi-square test or Fisher's exact test as appropriate for categorical variables. All tests were two-sided and statistical significance was set at 5%. Statistical analysis was performed using IBM SPSS Statistics software version 22.0 and SAS version 9.3.

This manuscript was written following STROBE guidelines for the reporting of observational studies [10].

3. Results

3.1. Characteristics of the patients and the ischemic events

A total of 3252 ischemic strokes and 956 TIA episodes occurred during the study period. The type of AF was permanent in 2188, paroxysmal or persistent in 1644, and undefined in 376 at the time of the event. We identified a total of 78 ischemic strokes and 22 TIAs in 99 patients that were preceded by a cardioversion of AF. One patient had two ischemic events that were both preceded by a cardioversion. The first was a TIA and second was an ischemic stroke which occurred over two years after the first episode. Clinical characteristics of the patients are depicted in Table 1. Since cardioversions were only performed in patients with paroxysmal or persistent AF, post-cardioversion events accounted for 6.1% of all ischemic events and 6.4% of strokes in this patient group at risk, while 2.4% of all events and 2.4% of all strokes were preceded by a cardioversion.

3.2. Characteristics of the cardioversions

Of the 100 cardioversions leading to an ischemic event, 77 were acute and 23 were elective, and 63 of the events occurred to patients not using anticoagulation (Table 2). Similarly, of the 78 cardioversions complicated by a stroke, 61 (78.2%) were acute and 17 (21.8%) were elective, and 51 (65.4%) of the strokes occurred to patients not using anticoagulation. Of the 10 patients who had been using warfarin prior to cardioversion of acute AF leading to stroke, 4 had INR less than 2.

The majority of the cardioversions leading to cerebral thromboembolism were successful in terms of restoring sinus rhythm. All nine patients who after an unsuccessful cardioversion developed a stroke had a spontaneous cardioversion before the onset of stroke. Seven of these

Table 1
Clinical characteristics of 99 patients who suffered 78 ischemic strokes and 22 transient ischemic attacks in 30 days after cardioversion of atrial fibrillation or atrial flutter.

	N (%)
N	99
Female	53 (53.5)
Age, median (range)	71.1 (47.0–91.8)
Hypertension	66 (66.7)
Diabetes	14 (14.1)
Coronary artery disease	29 (29.3)
Previous myocardial infarction	17 (17.2)
Heart failure	9 (9.1)
Previous stroke or TIA	8 (8.1)
HAS-BLED-score, median [IQR][a]	2 [1–3]
0–2	65 (65.7)
>2	34 (34.3)
Mechanical heart valve	3 (3.0)
Pacemaker	6 (6.1)

In the one patient suffering two events (one TIA and one stroke over two years apart), characteristics at the time of the first event are depicted.
HAS-BLED = hypertension, abnormal renal or liver function (1 point each), stroke, bleeding, labile INRs, elderly (age > 65 years), drugs or alcohol (1 point each); IQR = inter-quartile range; TIA = transient ischemic attack.
[a] Modified HAS-BLED calculated without labile international normalized ratio (INR).