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Incidence of thromboembolic events following atrial fibrillation catheter ablation and rate control strategies according to the kind of oral anticoagulation: A systematic review and meta-analysis

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ABSTRACT

Introduction: Anticoagulantion therapy (OAT) represents the cornerstone to reduce thromboembolic events for atrial fibrillation (AF). Recent studies suggest that AF catheter ablation on top of OAT may be useful to further reduce the thromboembolic risk in AF patients. The aim of the present study is to compare the long-term risk of thromboembolic events and treatment-related complications in patients with AF treated by OAT strategies and catheter ablation.

Methods: Pubmed, Cochrane and Google Scholar were searched for studies including >500 patients evaluating AF patients treated with OAT (VKA: vitamin K antagonist or DOAC: Direct oral anticoagulants) and/or AF ablation. Pooled incidence of stroke/year was the primary end point, while that of stroke, of all cause bleeding and of major bleeding the secondary ones. All the analyses were stratified according to the $CHADS_2$ score of included patients.

Results: Overall, 27 studies were selected, including 50,973 patients in the AF catheter ablation group; 281,595 patients in the VKA group; 54,811 patients in the DOAC group. After a mean follow-up of 2.4 (1.5–3.8) years, the overall incidence of stroke and thromboembolic events was 0.63 per 100 patients/year in AF ablation group, 2.09 per 100 patients/year in VKA group and 1.24 per 100 patients/year in DOAC group ($p < 0.001$). After stratification in 4 groups according to $CHADS_2$ score, the incidence of thromboembolic events remained lower in patients included in the AF ablation, followed by DOAC and VKA respectively ($p < 0.001$), for each $CHADS_2$ cluster. Both the incidence of all cause bleedings and major bleedings resulted lower in AF ablation group ($p < 0.001$). The incidence of all-cause mortality in the AF ablation group was significant lower than in the group of OAT ($p < 0.0001$).

Conclusion: AF catheter ablation significantly reduces the incidence of long-term thromboembolic events compared to both VKA and DOAC. This reduction is maintained in all $CHADS_2$ score clusters and is strengthened by the concomitant reduction in hemorrhagic complications provided by AF ablation.

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia observed in general population [1]. AF relates to a higher incidence of stroke and thromboembolic events compared to patients in sinus rhythm (SR) [2]. Oral anticoagulation therapy (OAT) is recommended for AF patients with intermediate or high annual thromboembolic risk, ranging from 3 to 18% according to the $CHADS_2$ score, or from 2 to 23% according to the CHA_2DS_2-VASc score [3,4]. In particular, OAT can be established with vitamin K antagonists (VKA) or direct oral anticoagulants (DOAC), that have demonstrated a significant reduction in the risk of thromboembolic events, respectively by two thirds compared to placebo for VKA [5] and at least the same or even more than VKA for DOAC [6–9].

However, most of the AF patients included in the studies that evaluated DOAC efficacy were treated by rate control strategies [10], while rhythm control strategies were rarely pursued, resulting in a high incidence of persistent AF or high burden paroxysmal AF patients. In this setting, the bleeding risk conferred by OAT should be considered,

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balanced with the benefits in stroke prevention, when deciding to undertake OAT [11], especially for patients with low/intermediate thromboembolic risk.

Recent evidences suggest that effective rhythm control strategies, in particular AF catheter ablation, on top of OAT when recommended, may be useful to further reduce the risk of thromboembolic events [12,13].

We performed this systematic review and meta-analysis aiming to compare the long-term incidence of thromboembolic events and hemorrhagic complications in patients with AF treated by OAT strategies (VKA or DOAC), and in patients with AF candidate to catheter ablation.

2. Methods

The present study was performed according to current guidelines, including the recent Preferred Reporting Items for Systematic reviews and Meta-Analyses amendment to the Quality of Reporting of Meta-analyses (PRISMA) statement and recommendations from The Cochrane Collaboration and Meta-analysis of Observational Studies in Epidemiology (MOSE) [14–16].

Four Authors, independently from each other (FDA, ET, MP, MM), searched Pubmed, Cochrane and Google Scholar for the following terms: "atrial fibrillation" AND "stroke" AND "ablation", searching for studies published in English between January 2004 and March 2017. Title and abstract of the retrieved citations were first independently screened. Selected reports were appraised in the full text version with respect to the following inclusion criteria: [1] human studies, [2] studies evaluating therapy with OAT in patients treated with AF ablation and patients without, and [3] online full-text available publication. Exclusion criteria were: [1] duplicate reporting and [2] study population < 500 patients. In the case of duplicate reporting, the manuscript with the largest sample of patients was selected.

2.1. Data extraction

The following data were independently extracted by 4 Authors (FDA, ET, MP, MM) on pre-specified electronic forms: authors, journal, year of publication, location of the study group, baseline features (in particular age, thromboembolic risk, bleeding risk). Encountered bias were further subdivided into analytical, selection, adjudication, and attrition bias. Relevant study data were extracted independently by 3 Authors (MP, ET, FDA). The corresponding Authors of the relevant studies were queried for required quantitative details not available from the published manuscripts.

2.2. End points

The primary efficacy endpoint was ischemic stroke incidence per 100 patients/year, while the secondary endpoints were stroke at median follow up, and major and all-cause bleeding, considered as the safety endpoint.

2.3. Evaluation of the quality of the studies

The quality of the included studies was independently appraised by 4 Authors (FDA, ET, MP, DE), with disagreements resolved by consensus. Design of the study (multicenter or single-center, randomized, prospective or retrospective), area of enrollment and type of multivariate analysis performed were collected.

2.4. Statistical analysis

Continuous variables are reported as mean (standard deviation) or median (first and third quartile). Categorical variables are expressed as counts (percentage). Statistical pooling for incidence estimates was performed according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals (CI), using the software RevMan 5.2 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Hypothesis testing for superiority was set at the 2-tailed 0.05 level. Hypothesis testing for statistical homogeneity was set at the 2-tailed 0.10 level and based on the Cochran Q test, with I2 values of 25%, 50%, and 75% representing mild, moderate, and severe heterogeneity, respectively. Meta-regression analysis was performed with random effect with Comprehensive meta-analysis.

3. Results

3.1. Search results

After the first Pubmed and Cochrane Database search, 340 titles and abstracts were identified and preliminary evaluated. Following the application of inclusion and exclusion criteria, i.e. appropriate data, complete full data and exclusion of duplicate reporting, 27 studies including one or more arms (AF ablation, VKA and/or DOAC) were finally selected and included in the systematic review and meta-analysis (Supplemental Fig. 1) [7–9,13,17–39]. The full text was carefully read, and the relevant data were extracted and included in the analysis.

3.2. Baseline population

The overall population was divided in 3 groups, according to the strategy selected: 50,973 patients from 16 arms in the AF catheter ablation group; 281,595 patients from 21 arms in the VKA group; 54,811 patients from 9 arms in the DOAC group. Baseline characteristics of the overall population are reported in Table 1. In particular, mean age was 58 years for AF ablation group, 61 and 65 years for DOAC and VKA groups. The majority of patients were men, and paroxysmal AF was more common in the AF ablation group, while the prevalence of persistent or permanent AF was higher in DOAC and VKA groups. The prevalence of comorbidities such as hypertension, diabetes and heart failure was lower in the AF ablation group, and mean $CHADS_2$ score was 1 (0.7–1.1) in the AF ablation, 2 (1.3–2.1) in the VKA and 2 (1.1–2.5) in the DOAC groups, respectively.

Due to the presence of studies published before the introduction of CHA_2DS_2-VASc score, the $CHADS_2$ score, available from all the included studies, was used throughout the analysis. In the AF ablation group the choice of the appropriate anticoagulant therapy was based on current guidelines and on the physician preferences.

3.3. Endpoints of the study

After a mean follow-up of 2.4 (1.5–3.8) years, the overall incidence of stroke and thromboembolic events was 0.63 per 100 patients/year in the AF ablation group, 2.09 per 100 patients/year in the VKA group and 1.24 per 100 patients/year in the DOAC group ($p < 0.001$), as reported in Fig. 1. Additionally, stratification was performed dividing the population in 4 groups according to $CHADS_2$ score, respectively characterized by a $CHADS_2$ score of 0, 1, 2 and 3 or more. The incidence of thromboembolic events resulted significantly lower in patients included in the AF ablation, followed by the DOAC, and higher for the VKA group, even after stratification by $CHADS_2$ score value ($p < 0.001$ for each $CHADS_2$ cluster) (Figs. 1b and 3a–d).

Concerning the incidence of bleedings, both all cause bleedings and major bleedings, defined as life-threatening or requiring blood cell transfusion, resulted lower in the AF ablation group, followed by DOAC, and higher for VKA ($p < 0.001$), as represented in Fig. 2.

Table 1
Baseline features of the overall population.

	AF ablation (16 studies, 50,973 patients)	VKA (21 studies, 281,595 patients)	DOAC[a] (9 studies, 54,811 patients)
Age (years old)	58 (57–63)	65 (61–80)	61 (60–78)
Male gender (%)	74 (63–77)	57 (45–60)	61 (56–70)
Paroxysmal AF (%)	62 (58–63)	45 (40–56)	50 (40–61)
Hypertension (%)	48 (45–50)	67 (56–71)	86 (45–78)
Diabetes (%)	10 (7–15)	22 (13–36)	24 (8–34)
Heart failure (%)	12 (7–22)	20 (17–40)	37 (20–46)
Renal failure (%)	8 (6–9)	11 (6–13)	10 (7–11)
CAD (%)	12 (8–5)	12 (9–15)	14 (11–17)
Mean CHADS score	1 (0.7–1.1)	2 (1.3–2.1)	2 (1.1–2.5)
Patients on antiarrthymic drug at follow up (%)	58 (33–65)	42 (40–67)	43 (23–56)
Anticoagulation at follow up (%)	58 (45–81)	–	–
Sinus rhythm after ablation (%)	79 (72–85)	–	–

AF atrial fibrillation, CAD coronary artery disease, VKA vitamin K antagonists, DOAC direct oral anticoagulants.
[a] 3 studies with apixaban, 2 with edoxaban, 2 with dabigatran and 2 with rivaroxaban.

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