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Impact of atrial fibrillation catheter ablation on mortality, stroke and heart failure hospitalizations: a meta-analysis.

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Prof. Anselmino is consultant for Biosense Webster and has received lecture fees from Biosense Webster and Abbott; Prof. De Ponti has received lecture fees from Biosense Webster and Biotronik; Prof. Di Biase is a consultant for Stereoaxis Biosense Webster, Boston Scientific, and St. Jude Medical and has received speaker honoraria/travel support from Medtronic, Atricure, EPiEP, and Biotronik.

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Abstract

Background The impact of atrial fibrillation (AF) catheter ablation (CA) on hard clinical endpoints remains controversial.

Objective Our aim was to conduct a random effect model meta-analysis on efficacy data from high-quality large matched database/registry studies and randomized clinical trials. We compared long-term all-cause mortality, stroke and hospitalization for heart failure in patients undergoing AFCA *vs* patients treated with medical therapy alone (rhythm and/or rate control medications) in a general AF population.

Methods and Results PubMed/MEDLINE and Embase databases were screened and a total of nine studies were selected (one randomized clinical trial – CABANA – and eight large matched population studies). A total of 241,372 patients (27,711 in the ablation group, 213,661 in the non-ablation group) were included. After a median follow-up of 3.5 years, AFCA decreased the risk of mortality (HR 0.62, 95% CI 0.54-0.72; I^2 = 54%; number needed to treat – NNT = 28), stroke (HR 0.63, 95% CI 0.56-0.70; I2 = 23%; NNT 59) and hospitalization for heart failure (HR 0.64, 95% CI 0.51-0.80; I^2 = 28%; NNT = 33) compared with AF patients treated with medical therapy alone.

Conclusion Based on the currently available efficacy and effectiveness evidence, AFCA significantly reduces the risk of death, stroke and hospitalization compared to medical therapy alone.

Keywords: atrial fibrillation; catheter ablation; all-cause mortality, stroke, hard clinical outcomes.

Abbreviations and acronyms

AADs = anti-arrhythmic drugs

ACR = assumed control risk

AF = atrial fibrillation

AFCA = atrial fibrillation catheter ablation

ARR = absolute risk reduction

CI = confidence interval

HR = hazard ratio

NNT = number needed to treat

RCT = randomized clinical trial

TIA = transient ischemic attack

Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, with a progressively growing burden due to population aging. Sinus rhythm maintenance (rhythm control), reflecting the native heart rhythm, may be perceived as the most natural solution compared to just controlling ventricular rate (rate control). However, in terms of prevention of death, stroke and heart failure, rate control has been proven to be non-inferior to rhythm control with anti-arrhythmic drugs (AADs) in pivotal clinical trials [1, 2]. This is most likely explained by the side effects and pro-arrhythmic effects related to AADs, together with a relatively low efficacy of these agents in maintaining sinus rhythm.

Atrial fibrillation catheter ablation (AFCA) has emerged in clinical practice; although few randomized clinical studies [3, 4] have reported promising outcomes in terms of sinus rhythm maintenance and safety when compared to AADs, they have singularly failed to demonstrate a statistically significant impact of the procedure on hard outcomes (mortality, stroke or HF hospitalization). These studies have however been widely debated, being generally underpowered to reveal a possible impact on the aforementioned outcomes in patients undergoing AFCA [5] or affected by crossovers between the study arms [6]. On the contrary, evidence from observational matched databases/registry studies suggest a net benefit of AFCA in terms of hard clinical endpoint reductions [7, 8].

The present meta-analysis aimed to determine whether AFCA is effective and safe in the general AF population by assessing its long-term impact on mortality, stroke and hospitalization due to heart failure decompensation.

Methods

The present systematic review and meta-analysis were performed in accordance to PRISMA [9] and MOOSE guidelines [10].

Search strategy

We screened PubMed/MEDLINE and Embase databases from their inceptions to April 30th 2019, using the following search terms: (atrial fibrillation OR AF) AND (catheter ablation OR AFCA OR ablation) AND (Mortality OR death OR stroke OR CVA OR hospitalization) AND (database OR registry OR registries OR databases OR RCT).

Study selection and quality assessment

Two investigators (A.S., M.A.) independently reviewed the titles/abstracts and studies to determine their eligibility based on the inclusion criteria and extracted all the relevant outcomes of interest. Randomized and non-randomized studies were eligible for inclusion if they (a) compared at least one hard clinical outcome (mortality, stroke and, since AF is known to mimic heart failure symptoms and/or trigger heart failure episodes, hospitalization for heart failure) between cohorts of ablated and non-ablated AF patients (in case of registry studies, only if they provided adjusted risk estimates); (b) reported risk estimates for the investigated outcomes based on *time-to-event* data (hazard ratio – HR); (c) had a median follow-up of at least 2 years, thus focusing on studies evaluating long-term impact of AFCA on hard clinical outcomes; (d) did not exclusively include patients with impaired left ventricular ejection fraction.

Risk of bias assessment was performed at the study level using the Cochrane bias risk assessment tool for RCT and the Newcastle-Ottawa Scale (NOS) for observational studies (Appendix).

Statistical analysis

Baseline characteristics of pooled study populations were reported as median values between the included studies, along with their interquartile range.

Due to the observational nature of most of the studies, a random effect model (inverse-variance weighting) was adopted. Random effect model meta-analysis gives more conservative estimates with respect to fixed effect model meta-analysis, since, differently from fixed effect model, it takes into account the estimated between-study heterogeneity when pooling individual study results.

Meta-analysis of hazard ratio (HR) was performed after logarithmic transformation. The results with the corresponding 95% confidence interval (CI) were back-transformed and forest plots for the different outcomes were generated. To investigate potential publication bias, Egger test was used to identify asymmetry of funnel plot. Heterogeneity across studies was assessed using the Cochran Q test. Higgins I^2 statistics was used to determine the degree of between-study heterogeneity ($I^2 < 25\%$—low, 25–50%—moderate, and >50%—high degree of heterogeneity). In case of high degree of heterogeneity, meta-regression analysis was performed to assess potential source of heterogeneity.

For each outcome, absolute risk reduction was calculated by multiplying the meta-analytic HR (with the corresponding CI) by the assumed control risk (ACR) obtained from the meta-analysis of the incidence rate of the outcome (expressed as events/person years) in non-ablation cohorts (Appendix, Figure 1). Number needed to treat (NNT) was derived by dividing 1 by the calculated absolute risk reduction (ARR), and the resulting number was finally divided by the meta-analytic median follow-up in order to obtain an estimate normalized to follow-up duration.

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).

Results

The initial search, by the specified search criteria, identified 1,187 potential studies (Figure 1). After detailed evaluation, 19 publications were eligible for possible inclusion and, therefore, full texts reviewed. Four RCTs were excluded since they were specifically conducted in the setting of heart failure [11-14]. Four RCTs were excluded since they did not provide *time-to-event* risk estimates (hazard ratio) for the investigated outcomes [15-18]. One large registry study was excluded due to the indirect nature of the comparison between the ablation and non-ablation cohort [19], while a second was discarded since it did not provide confidence intervals for the adjusted risk estimates of mortality and stroke [20].

Finally, 9 studies (one RCT – CABANA – and eight large matched population databases/registries) were included in the analysis [6, 8, 21-28], encompassing 241,372 patients (27,711 in the ablation group, 213,661 in the non ablation-group), with a median follow-up of 3.5 years (Table 1). The baseline clinical features of the resulting meta-analytic population are summarized in Table 2. Median age was 64.1 years, with nearly 2:1 male-to-female ratio. The most frequent concurrent comorbid conditions were hypertension (55.0%), diabetes (17.0%) and coronary artery disease (19.2%). Baseline heart failure was present in a low percentage of patients (15.3%). A median of 5.2% patients suffered previous stroke/TIA and 69.8% had high thromboembolic risk (CHA_2DS_2-VASc score ≥ 2). CABANA population, with respect to the pooled population derived from non-randomized matched databases, resulted slightly older, with more comorbid conditions and a higher baseline thromboembolic risk (Table 2). The statistical methods to control confounding in non-randomized matched database are reported in Table 1: 5 studies used propensity score matching, 2 other propensity score techniques (adjustment and weighting) and 1 study used multivariate regression analysis.

By random effect model meta-analysis, AFCA decreased the risk of mortality (HR 0.62, 95% CI 0.54-0.72; I2 = 54%; NNT 28), stroke (HR 0.63, 95% CI 0.56-0.70; I2 = 23%; NNT 59) and hospitalization for heart failure (HR 0.64, 95% CI 0.51-0.80; I2 = 28%; NNT 33) compared with medically-treated AF patients. One-year estimated absolute risk reduction in mortality, stroke and hospitalization for heart failure were 1%, 0.5% and 0.8%, respectively.

There was no evidence of publication bias for the outcomes of interest (Egger's test p value 0.28, 0.65 and 0.46, respectively; funnel plots are reported in the Appendix, Figures 3-5). Significant heterogeneity was only present in the mortality estimate. Meta-regression analyses excluded baseline heart failure (p=0.316) as potential source of heterogeneity, while increased age was significantly associated with a reduced benefit from ablation (p=0.004, Appendix Figure 2).

Considering "treatment received" rather than "intention to treat" analysis from CABANA data, catheter ablation decreased the risk of mortality by a greater extent (HR 0.60, 95% CI 0.53-0.67; I2 = 29%), with a decrease in the estimated heterogeneity (Figure 4).

Discussion

In the present meta-analysis, AFCA was more effective than medical therapy in reducing hard clinical endpoints, providing a 38% decrease in mortality, 37% decrease in stroke and 36% reduction in heart failure hospitalization over a median follow-up of 3.5 years.

AFCA is currently a rhythm control option in AF patients who remain symptomatic on adequate rate control therapy. Conversely, the proven increased efficacy in maintaining sinus rhythm and safety of AFCA compared to AADs prompts questions regarding a possible favorable prognostic impact of modern rhythm control strategy, either with AFCA alone or with an hybrid approach (AFCA+AADs). The Catheter Ablation for Atrial Fibrillation with Heart Failure (CASTLE-AF) Trial [11] confirmed previous meta-analytic impressions [29], showing that in patients with heart failure, AFCA reduced the primary endpoint of all-cause-death or hospitalization compared with medical therapy. Differently, in patients without heart failure, a meta-analysis comparing AFCA vs medical therapy on published RCTs apparently found no difference in survival between these two strategies [5]. However, it should be noted that, in the latter analysis, the included studies were only four, underpowered for detecting differences in survival (low number of enrolled patients), the follow-up duration was short (9 to 24 months, median 12 months) and, most importantly, the number of events investigated extremely low (6 and 7, in the pooled ablation and medical therapy cohorts, respectively). Recently, Barra et al. [30] also investigated the topic either in RCTs and observational studies. In their analysis, the authors found a survival benefit of AFCA, but the randomized evidence was driven by studies performed specifically in the HF setting, concluding that more data are needed to draw conclusions in the general AF population. More specifically regarding risk of stroke, a benefit was only seen within the observational studies, while no benefit emerged considering randomized evidences (however, only 32 stroke events in the pooled cohorts were seen during the follow-up).

In addition, inclusion of the latest, widest randomized clinical trial surely increases available knowledge. The CABANA trial [6], in the "intention to treat" analysis, reported no significant differences neither in the primary outcome (composite of death, disabling stroke, serious bleeding, or cardiac arrest), nor in mortality between AFCA and medical therapy groups. This result, however, was likely affected by a significant lower-than-expected overall mortality rate (from the expected 12% after 3 years to the actual 5% after 4 year) and high treatment crossover (27.5% from drug therapy to ablation). Moreover, the composite primary outcome of CABANA trial included bleeding and stroke, which AFCA has no impact on. In fact, as stated by the authors, definitive conclusions cannot be drawn, especially considering that, on the other side, "treatment received" analysis suggested a significant reduction in mortality in the AFCA group of 40% (HR 0.60, 95% CI 0.42-0.80).

Given these premises, our aim was to synthetize high-quality RCT data of AFCA *efficacy* (deriving from CABANA) with real-life evidence of AFCA *effectiveness* (provided by large registry studies), in terms of hard clinical endpoints (mortality, stroke and hospitalization for heart failure) in a general AF population. In this sense, our meta-analysis is different from the meta-analysis of Barra et al. [30] since (1) it excludes studies exclusively enrolling HF patients, in order to draw general conclusions in the general AF population; (2) it includes the greatest randomized evidence published so far in the context of AF (CABANA trial [6]); (3) it includes recently released observational data not included in the previous meta-analysis [27, 28].

The meta-analytic estimates indicate that AFCA significantly reduces all three hard clinical endpoints by nearly 40%. The heterogeneity of the data was high only for mortality ($I^2 = 63\%$). Interestingly, older age was associated with a decrease in AFCA benefit and thus could explain, at least partly, the increased heterogeneity of the data. Considering "treatment received" instead of "intention to treat" analysis from CABANA, we appreciated a drop in the total heterogeneity of mortality data and an increase in the benefit of AFCA. Of note, the *efficacy* estimate deriving from patients that actually underwent ablation in CABANA (HR 0.60, 95% CI 0.42-0.80) is highly comparable to the meta-analytic *effectiveness* pooled estimate of mortality reduction in AFCA group for the registry studies (HR 0.60, 95% CI 0.53-0.68; $I^2 = 43\%$).

Additional information is conveyed by the calculated NNTs for each outcome of interest, which not only take into account the magnitude of the benefit of the intervention, but also depend on the rate of the specific endpoint in the study population. Despite a similar HR for the three outcomes, NNTs differed between stroke (NNT 59) and the other two endpoints (NNT 28 for mortality, NNT 33 for hospitalization), reflecting the different pooled incidence rates in the medically treated group (mortality: 2.70 events/100 person-years; stroke: 1.32 events/100 person-years; hospitalization for heart failure: 2.41 events/100 person-years) (Figure 4). In this sense, considering the high proportion of patients in the included meta-analysis at high thromboembolic risk (CHA_2DS_2-VASc score > 2: 69.8%), the relatively more limited impact of AFCA on incidence rate of stroke, compared to the other outcomes, probably reflects the effective anticoagulation strategy of the medical arm.

In this context, awaiting publication of the Early treatment of Atrial fibrillation for Stroke prevention (EAST) Trial (ClinicalTrial.gov Identifier: NCT01288352), the present meta-analyses summarizes the latest *efficacy* evidence from CABANA and real-world *effectiveness* data derived from observational registries comparing AFCA with medical therapy, suggesting promising effects of the electrophysiological procedure not only in preventing AF recurrences but also in improving long-term prognosis of AF patients.

Limitations

First, this study is limited by the heterogeneity of study participants and outcome definitions between different studies. Moreover, retrospective registry data should be interpreted with caution, due to their observational nature. Even though matching and multivariable analysis can control known confounders, residual confounding attributable to unmeasured factors remains a concern. In addition, retrospective registry data often lacked information regarding the type of AF (paroxysmal vs persistent) and arrhythmia duration of the included patients, thus precluding possible subgroup meta-analyses. Finally, it is possible that studies shorter than two years, excluded since the focus of the present analysis on long-term outcomes, may have contributed additional patients and power to detect differences in investigated outcomes that may manifest within the first two post-procedural years.

Conclusion

In the present meta-analysis, based on the CABANA trial and data form eight large matched registries, AFCA significantly reduces the risk of death, stroke and hospitalization for heart failure compared to medical therapy alone (AADs and/or rate control drugs).

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Figure legends

Figure 1. Flow-chart of the search strategy following PRISMA guidelines. LVEF: left ventricular ejection fraction; HR: hazard ratio.

Figure 2. Meta-analysis forest plots. Shown are random-effect hazard ratios for mortality (a), stroke (b) and hospitalization for heart failure (c) in the included studies.

Figure 3. Meta-analysis forest plot of mortality (considering treatment received analysis of CABANA data).

Figure 4. Impact of atrial fibrillation catheter ablation on hard clinical outcomes. PY: person-years; NNT: number needed to treat.