Stroke and mortality risk after atrial fibrillation ablation: lesson from the CABANA trial

Cristina Balla¹ and Riccardo Cappato²*

¹Cardiovascular Center, University of Ferrara, Ferrara, Italy
²Department of Biomedical Sciences, Humanitas Clinical & Research Center & Humanitas University, Milan, Italy

KEYWORDS
Atrial fibrillation; Risk of stroke; Ablation therapy

The CABANA trial is a randomized controlled study comparing catheter ablation vs. conventional medical therapy in atrial fibrillation (AF) patients. The results of the study showed that catheter ablation did not have a significant reduction of strokes, deaths, serious bleeding, or cardiac arrest compared to medical therapy. However, a significant improvement in AF recurrences, quality of life, and symptom relief has been shown after catheter ablation compared to drug therapy. The mixed results of the study emphasized an active controversy in the cardiology community on the interpretation of the data and their use in current clinical practice. In this review, we summarized the principal controversy points of the trial describing the strengths and weaknesses of the study design and analysis.

Introduction

Atrial fibrillation (AF) is the most common tachyarrhythmia affecting more than 6 million patients throughout Europe. The prevalence ranges between 0.5 and 1%, increasing with age and comorbidities.¹ Reduced quality of life due to bothersome symptoms is not the only adverse outcome in these patients; AF has also been associated with an increased risk of death, stroke, and heart failure.² Therefore, AF is becoming an important public health issue in western countries.

Medical therapy has been the only treatment option for decades with limited effectiveness, in part due to the lack of compliance for adverse drug effects and organ toxicity. The proarrhythmic propensity of antiarrhythmic therapy further limits its use. Surgical procedure to treat AF was developed in the late 1980s with efficacy to maintain sinus rhythm.³ Subsequently, a percutaneous approach has been developed based on the concept of isolation of pulmonary veins as treatment of AF.⁴ Catheter ablation of AF has been defined as a well-established therapy to relieve AF associated symptoms and improve quality of life.⁵ However, no clear evidences were available regarding the ability to protect from major adverse cardiovascular outcomes such as mortality, stroke, or bleeding. In 2005, the AF work group of the National Heart, Lung and Blood Institute (NHLBI) assessed the need for a clinical trial to compare catheter ablation vs. drug therapy to treat AF for the hardest endpoint of mortality. Therefore, the Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial was conceived by the investigators. The CABANA pilot study showed the feasibility of the study and its results were used to design the CABANA trial.⁶

The CABANA trial design

The CABANA trial is an investigator-initiated, open-label, multicentre, randomized study funded by NHLBI and industry partners, involving 126 centres in 10 countries. It was designed to determine whether catheter ablation is more effective than state-of-the-art medical therapy to improve cardiovascular outcomes in AF patients.⁷ Eligible patients were required to have new-onset or undertreated paroxysmal persistent or longstanding AF that need additional therapy. All patients older than 65 years were included. For patients younger than 65 years, an additional risk factor was required such as hypertension, diabetes, congestive heart failure, prior stroke, TIA.
or systemic emboli, atherosclerotic vascular disease, left atrium (LA) >5.0 cm, and ejection fraction <35%. The more relevant exclusion criteria were previous LA catheter ablation or AV nodal ablation, failure of >2 membrane active antiarrhythmic drugs at therapeutic dose due to inefficacy or side effects or amiodarone’s failure after 8 weeks of treatment.

Eligible patients were randomized in 1:1 ratio between catheter ablation and drug therapy. Pulmonary vein isolation was required by the protocol. Additional lesions were left to the physician’s discretion. In patients randomized to conventional medical therapy, rate control medication was recommended first. After the failure of rate control therapy, a rhythm control strategy could be initiated according to physician preference.

The trial design planned to enrol 3000 patients followed for 3 years with a mortality rate projection of 12%. Therefore, based on previous data, a 30% reduction of relative risk was hypothesized in patients treated with catheter ablation compared to patients treated with conventional medical therapy.

The modified trial design

The initial trial was based on the hypothesis that catheter ablation would be superior to medical therapy (rate or rhythm control strategy) to reduce the primary endpoint of all-cause mortality and the secondary composite endpoint of mortality, disabling stroke, serious bleeding, or cardiac arrest in AF patients. However, in early 2013, an interim analysis of the trial recommended a modification of the trial design due to slow enrolment and lower than expected aggregated event rates. Therefore, in 2013, the leadership group promoted a revision of the trial design:

- The primary endpoint became the composite of death, disabling score, serious bleeding, and cardiac arrest
- All-cause mortality was downgraded to the secondary endpoint
- The average follow-up time was extended with a subsequent reduction in the sample size of the study.

The steering committee of the study justified this unusual on-going modification of the study endpoints by the need to have adequate power of the study with reasonable sample size.

However, several issues may be posed by the use of a composite endpoint in terms of results interpretation and value. Classic challenges of using mixed composite endpoints in RCTs include clinical equipoise of distinct components (such as death vs. major bleeding), differential risk of severe vs. less severe events, and individual effect of treatment on relative risk reduction. In addition, endpoint occurrence is usually assessed using a time-to-event approach. In composite endpoints (that are not mutually exclusive), the individual occurrence of a single endpoint component may be misinterpreted as the occurrence of multiple events over follow-up. Accordingly, hierarchical and pre-specified analysis of the endpoint component is strongly advised in such cases, but this analysis is lacking in the CABANA trial.8

CABANA trial: how to interpret the results

According to the intention-to-treat analysis in which patients were analysed on the assigned group after randomization, the study showed neutral results. A primary composite outcome event occurred in 89 patients in the catheter ablation group and in 101 patients in the drug therapy group with no significant difference [hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.65-1.15; P = 0.30]. Similar results were found for the secondary endpoint of all-cause mortality (5.2% vs. 6.1%, HR 0.85, 95% CI 0.60-1.21; P = 0.38). A significant benefit was demonstrated in the secondary composite endpoint of death or cardiovascular hospitalization (HR 0.83, 95% CI 0.74-0.93; P = 0.001).

However, an important issue regarding the analysis and interpretation of the results was due to the number of treatment crossovers observed between the two groups: 9.2% of the patients in the ablation group did not receive ablation and 27.5% those in the drug therapy group crossed over to receive ablation.

Moreover, the event rate for mortality and disabling stroke was much lower than expected based on historical controls.

Although during the design of the study, the power projections considered an allowance of up to 30% of crossovers from drug to ablation therapy, the 9.2% of patients that did not receive ablation in the ablation group and the lower than expected event rate were unexpected and underpowered the study. With the intent to overcome the crossover issue and to estimate the effect of the two treatments, the investigators performed also a sensitivity analysis using as-treated and per-protocol analysis. Using both analyses, a significantly decreased incidence of the primary and secondary endpoints was observed in the catheter ablation group compared to medical therapy. With this analysis, patients were counted and analysed based on the real treatment that they performed. So, patients that crossed over from the medical therapy group to the ablation group were counted only in the ablation group.

Considering that the fundamental principle to compare treatment effects is that the two groups are similarly based on the randomization and differ only in the treatment received, the per-protocol analysis has to be considered potentially biased due to the lack of randomization.

CABANA trial: quality of life, atrial fibrillation recurrence, low incidence of ablation related complication

For many patients, AF has a detrimental impact on the quality of life and symptoms, such as palpitations, dyspnoea, and exercise intolerance are the main reason to seek for medical advice.

Previous studies, limited by small sample size and short follow-up in very selected AF patients (mostly paroxysmal AF), suggested an improved quality of life (QOL) after catheter ablation compared to drug therapy.9,10

Concordant with previous smaller studies, the CABANA trial showed a lower AF recurrence rate, measured after
3 months blanking period following ablation or initiation of drug therapy, with catheter ablation compared to drug therapy (50% vs. 69% at 3 years)\textsuperscript{7,9,11} The long-term follow-up of this study confirmed the idea that AF ablation is not curative since many (17.1%) patients required a second ablation during follow-up, mainly to improve symptoms.

Regarding quality of life, the CABANA trial analysed two different QOL scores demonstrating an improvement in the quality of life at 12 months follow-up in the catheter ablation group compared to drug therapy. Interestingly, there was a benefit in AF symptoms and QOL scores in both groups compared to baseline highlighting the importance of treatment in symptomatic patients.\textsuperscript{12} The improvement was more evident in the catheter ablation group compared to drug therapy. A potential bias of QOL results is due to the knowledge of the on-going treatment by the patients that may respond to the questionnaires biased on their own hopes and expectations on the treatment.

Regarding ablation related complications, the CABANA trial showed that catheter ablation is rather a safe procedure with a relatively low rate of severe complications if performed by experienced operators. Pericardial effusion with tamponade, while infrequent, was the most frequent complication occurring in 2.2% of patients. Also in the medical therapy group, drug-related adverse events were relatively low: thyroid disorders were reported in 1.6% of the patients.

Conclusions

Although the findings on major cardiovascular outcomes were inconclusive, the CABANA trial demonstrated the efficacy and safety of catheter ablation and highlighted the importance of performing catheter ablation in symptomatic patients with atrial fibrillation as suggested by current guidelines.

Conflict of interest: none declared.

References

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed AF in adults. National implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in AF (ATRIA). JAMA 2001;285:2370-2375.
2. Benjamin EJ, Wolf PA, D’Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946-952.
3. Cox J, Boineau J, Schuessler R, et al. Five year experience with the Cox-Maze procedure for mitral regurgitation and associated atrial fibrillation. Ann Thorac Surg 1993;56:814-823.
4. Haissaguerre M, Jais P, Shad D, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. New Engl J Med 1998;339:659-666.
5. Ganesan AN, Shipp NJ, Brooks AG, et al. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. J Am Heart Assoc 2013;2:45-49.
6. Packer DL, Mark DB, Robb RA, et al. Catheter ablation vs Antiarrhythmic Drug Therapy for Atrial fibrillation (CABANA) trial: study rationale and design. Am Heart J 2018;199:192-199.
7. Packer DL, Mark DB, Robb RA, et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding and cardiac arrest among patients with atrial fibrillation. JAMA 2019;321:1261-1274.
8. Briceno D, Mohanty P, Di Biase L, et al. CABANA trial: ‘beauty is in the eye of the beholder. Interv Card Electrophysiol 2020;57:1-3.
9. Cosedis NJ, Johannessen A, Raatikainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. N Eng J Med 2012;367:1587-1595.
10. Morillo CA, Verma A, Connolly SJ, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2) a randomized trial. JAMA 2014;311:692-700.
11. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 2018;378:417-427.
12. Mark DB, Anstrom KJ, Shen S, et al. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation The CABANA randomized trial. JAMA 2019;321:1275-1285.