https://doi.org/10.24207/jca.v32i2.989_IN

Reflections on CABANA Trial (Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial)

Reflexões sobre o Estudo CABANA (*Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial*)

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Atrial fibrillation has been consolidated in recent decades as a serious public health problem, considering its notorious increase in prevalence with aging combined with increased population survival. Data from the Framingham Heart Study indicate that, even in an optimal scenario of absence of classic risk factors for its occurrences, such as smoking, alcohol abuse, obesity, hypertension, diabetes, and heart disease, about 10% of individuals aged 80 or over and about 25% of those aged 90 or over will have atrial fibrillation[1]. These rates substantially increase when added to single or combined risk factors. Despite its already well-known association with the occurrence of thromboembolic stroke[2], the presence of atrial fibrillation has been identified as an independent mortality risk factor in large population studies[3].

In September 2005, the National Heart, Lung and Blood Institute of the United States, considering the epidemiological importance of atrial fibrillation and the increase in the number of patients submitted to treatment by percutaneous ablation, convened a task force responsible for evaluating the role of ablation in the treatment of this arrhythmia. As the role of ablation in maintaining sinus rhythm has been defined in several studies[4], this task force recommended a large study to establish its impact on mortality reduction.

After the implementation of a pilot study (CABANA Pilot Study) that in fact endorsed the superiority of ablation in maintaining sinus rhythm compared to pharmacological treatment, the National Institute for Health approved the funding of the Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA Trial), with the support of the catheter, devices and mapping systems industry. The results of this study were eagerly awaited by the community of atrial fibrillation researchers from all over the world, considering the types of outcomes evaluated and the reliability of results that would be brought by a potentially correct design under the methodological aspect. This reflection is essential since, over the years, several studies have been carried out on the subject, but most of them have a great weakness of scientific credibility, given

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their design characteristics, such as retrospective character, lack of comparison to control groups, small samples, endpoints based on so-called "soft" outcomes, etc.

In March 2019, the results of the CABANA Trial were finally published[5]. CABANA was a multicenter, prospective, randomized, open, intent-to-treat study, involving 126 centers in 10 countries, aiming to compare percutaneous ablation to conventional drug therapy in the occurrence of a composite outcome that included death, disabling stroke, major bleeding, and cardiac arrest. *Patients with paroxysmal or persistent atrial fibrillation, aged 65 years or older, were included in the study. Patients under 65 years of age could be included, as long as they presented one or more risk factors for thromboembolism.* All patients had to be potentially eligible for ablation or drug therapy, which could be by controlling the rhythm and/or heart rate. The use of oral anticoagulation was recommended in both groups of patients, according to the guidelines of the American Heart Association, American College of Cardiology and European Society of Cardiology. About 2,200 patients were included.

Concisely, the final results of the study after about four years of *follow-up could not demonstrate the superiority of ablation over drug therapy concerning the composite endpoint*. The number of patients in the randomized group for a drug therapy that was crossed for ablation was high (≅ 27%), in a *crossover* not considered for the evaluation of final results, *since it was an intent-to-treat study.*

The feeling of disappointment and nonconformity with the demonstrated results was generalized in the community of electrophysiologists. One of the basic principles of the scientific method that gives credibility to the study design is the intention to treat, which was criticized based on the assumption that, in a *per-protocol* evaluation, the results would favor the ablation treatment. The perception of the disguised desire for a change of method to achieve the desired effect, something incompatible with science, remained.

Randomized studies are designed to promote a balance of the participants' characteristics at the beginning, and the *intention-to-treat* principle is fundamental for the maintenance of this balance. The removal of patients from a group to be included in the comparison group potentially promotes a rupture of this balance and creates uncertainties that significantly compromise the reliability of the study results. However, the famous statement attributed to the astronomer Carl Sagan must always be kept in mind: "absence of evidence is not evidence of absence."

Many methodological variables are capable of interfering with the search for an evidence-based truth in a study, even though it is a randomized controlled trial. In a close look at the CABANA Trial design, some overlooked aspects are too intriguing. The initial hypothesis of the study was that percutaneous ablation *primarily* would reduce total mortality in comparison to conventional drug therapy. In 2013, an essential primary endpoint change was established: it went from a single endpoint (overall mortality) to a composite endpoint, which included death, disabling stroke, major bleeding, and cardiac arrest. This change was induced by a lower-than-expected rate of events and a slower inclusion of patients. In a thorough verification of the studied primary composite endpoint components, it is possible to identify an apparent plausibility of only one of the four established endpoints: stroke. In other words, it is rational to suppose that patients submitted to ablation for treatment of atrial fibrillation, when compared to those treated by medication, will have a lower rate of occurrence of strokes, as a result of a supposed superiority of ablation rhythm control. However, why assume that the highest bleeding rates would be lower in the ablation-treated group, considering the recommendation of permanent use of anticoagulant therapy in patients *of both groups* based on their higher risk chance?

Regarding the "cardiac arrest" component, why infer that this outcome is expected in patients with atrial fibrillation and, consequently, of a lower probability of occurrence in the group treated by ablation, which supposedly would have a more dynamic rhythm control? Is cardiac arrest relevant to atrial fibrillation patients? Finally, the composite outcome component *mortality* is no less problematic for valuation of importance in patients with atrial fibrillation.

Atrial fibrillation has been identified in population studies as an independent predictor of total mortality[3], as previously mentioned. However, it is important to emphasize that atrial fibrillation is an arrhythmia that accompanies several different clinical conditions, each of them conferring its particularities under the aspect of prognostic significance. For example, a 66-year-old male patient, with paroxysmal atrial fibrillation, without other comorbidities, anticoagulated, would be eligible for CABANA Trial. Would we expect in this patient a significant mortality risk conferred by arrhythmia that could be modified by percutaneous ablation? Apparently not. On the other hand, a 66-year-old patient with ischemic heart disease, heart failure, and persistent atrial fibrillation, anticoagulated, would also be eligible for CABANA Trial. It is quite reasonable to infer that atrial fibrillation in this patient is an increasing risk factor for mortality, considering wall stress and increased myocardial oxygen consumption generated by arrhythmia in a heart with fibrosis and ischemia, and that the recovery and maintenance of a stable sinus rhythm have a significant prognostic impact in terms of hard outcomes.

It is, therefore, understandable that CASTLE-AF Trial (Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation Trial), which compared ablation and medication in patients with heart failure, has demonstrated a reduction in mortality provided by ablation, related to a higher chance of rhythm control determined by this therapy[6].

It is thus reasonable to deduce that CABANA Trial is a fragile study under the methodological aspect *primarily in its essence*, based on a debatable hypothesis, applied in a heterogeneous, broad, and nonspecific population. No results other than those found could be expected. It is back to square one. Doubts and dilemmas persist. Fundamental random criteria defined by Bradford Hill in the evaluation of this problem, such as the strength of association, biological gradient, biological plausibility, and experimental evidence[7] did not consistently support the construction of the CABANA Trial hypothesis. That is the biggest problem.

Since atrial fibrillation is such a multifaceted problem, the question to be formulated for structuring a study hypothesis that aims to evaluate mortality when talking about ablation should be: *which category of patients should be assessed in this study?*

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