

Editorial

Atrial fibrillation ablation after the CABANA study:
beyond statistical dogmaAblación de fibrilación auricular tras el estudio CABANA:
más allá del dogmatismo estadísticoIvo Roca-Luque,^{a,b,c,*} José María Tolosana,^{a,b,c} and Josep Brugada^{a,b,c}^aInstitut Clinic Cardiovascular, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain^bInstitut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain^cCentro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain

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Atrial fibrillation is the most frequent clinically relevant rhythm disorder, with data from 2014 indicating more than 33 million people with the condition and an estimated prevalence of 10% in individuals older than 75 years.¹ Multiple lines of evidence, from classic studies in the Framingham population² to those in distinct population subgroups, have linked atrial fibrillation to a higher risk of stroke and heart failure and a 2- to 4-fold increase in the adjusted risk of death from other factors,³ even in the anticoagulation era. Nonetheless, the pharmacological arsenal for rhythm control is limited and has moderate efficacy. For these reasons, atrial fibrillation ablation has undergone technological refinements and has been implemented at an increasing rate since its introduction. Randomized studies have thus far shown a clear superiority of ablation over drugs in terms of both recurrence^{4,5} and symptoms.⁶ However, few studies have rigorously analyzed the ability of atrial fibrillation ablation to improve more ambitious cardiovascular morbidity and mortality targets, such as all-cause death and stroke.

One of the most important clinical trials in this field, the CABANA study, was published in 2019.⁷ With a mean follow-up of 4 years, this international multicenter study randomized 2204 patients with atrial fibrillation and cardiovascular risk factors to a catheter ablation strategy or antiarrhythmic drugs. The primary outcome was a composite of death, stroke, major bleeding, and sudden cardiac death. The study discussion clearly summarizes the controversy and opposing views generated by this work. Strictly speaking (from a statistical point of view), the ablation strategy had no benefit on the primary outcomes vs the antiarrhythmic drug approach (8% vs 9.2%; hazard ratio [HR], 0.86; $P = .3$). However, 27.5% of patients in the antiarrhythmic drug group finally underwent ablation and almost 10% of patients assigned to ablation ultimately did not undergo the procedure. Accordingly, the same work included an additional analysis besides the classic intention-to-treat (ITT) analysis that evaluated outcomes according to treatment received. In this per-protocol analysis (prespecified in the study design), ablation showed a clear benefit, with a 33% reduction in the primary outcome (7% vs 10.9%; HR, 0.67; $P = .006$) and a 40% reduction in all-cause death (4.4% vs

7.5%; $P = .005$). Although this analysis—based on treatment received and not that assigned—was prespecified in the study design, conceptually and from the perspective of statistical orthodoxy, ITT analysis is the only analysis that allows definitive conclusions to be drawn.

The literature contains extensive debates on the suitability of the different analytical approaches. Undoubtedly, there is general agreement that, conceptually, ITT analysis is the best method of all to reduce possible biases that may be found in more pragmatic analyses.⁸ However, this type of puristic analysis no longer reflects actual practice and is not valid for evaluating a specific treatment when a significant percentage of patients in any of the treatment strategies being compared do not ultimately receive that particular treatment.⁹ The CABANA study is a clear example of this phenomenon, with almost half of the study patients (39.5%) not receiving the assigned treatment. Randomization and ITT analysis represented a major advance in the evolution of medicine from that solely based on individual observations toward evidence-based medicine.⁸ However, scientific conclusions may be equally biased by the absolute invalidation, strict enough to be considered “dogma”, of all other types of analysis. Thus, what is the value of a conclusion based on ITT analysis of a study of ablation vs drugs when 30% of the patients of the drug treatment group ultimately undergo ablation, the very strategy with which they were being compared? In this regard, the benefits of atrial fibrillation ablation regarding morbidity and mortality have been clear in multiple observational studies, even in extensive populations analyzed with propensity scores,¹⁰ with 30% to 40% reductions in the rates of stroke¹¹ and mortality, respectively, as well as in recent studies of the generalizability of the CABANA study to real life.¹² It is true that no statistical strategy (eg, P value, propensity score, classic paired analysis) can theoretically replace randomization and ITT analysis with the same validity but, again, these formal analyses do not seem completely valid in cases such as the CABANA study with markedly low adherence to the treatment strategy.

In parallel, the CABANA study confirms 2 findings of major clinical relevance, which were even validated by the dogmatic ITT analysis: first, ablation is superior to drugs in terms of recurrence and quality of life,¹³ and, second, its safety is not inferior to that of drug therapy. The first of these findings was already known from previous⁴ and contemporaneous⁶ studies and is widely accepted by the scientific community. In fact, it has been the common thread

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in most current indications for atrial fibrillation ablation. However, the safety exhibited by ablation in the CABANA study is highly relevant, because one of the classic arguments made by the detractors of this intervention has been the very real possibility of complications. In this study, as in studies of ablation in other conditions, such as ventricular tachycardia ablation (with a higher possibility of procedural complications than with atrial fibrillation ablation),¹⁴ the safety of ablation is at least similar to that of antiarrhythmic drugs.

Finally, it should be noted that, in contrast to ablation, the use of antiarrhythmic drugs has failed to show value over atrial fibrillation ablation-mediated rate control in recent years in terms of both quality of life¹⁵ and mortality in the case of the AFFIRM study.¹⁶ In fact, that study was the first to discuss the mortality benefits of sinus rhythm maintenance vs rate control alone. Although the study results were negative, its conclusions should once again be applied with caution because, first, patients treated with antiarrhythmic drugs had higher mortality (HR, 1.49), and, second, those that maintained sinus rhythm had lower mortality (HR, 0.53). Accordingly, the AFFIRM study has probably already left us 2 conclusions beyond statistical formalism, which, despite not being widely disseminated because they were derived from a subgroup analysis, are very clear: antiarrhythmic drugs are associated with certain risks (increased mortality) and sinus rhythm is better in terms of mortality than atrial fibrillation. A less statistically puristic interpretation (with all of its limitations) of the CABANA study probably corroborates these findings: the prognosis of patients with atrial fibrillation can be improved with a more effective therapeutic tool than antiarrhythmic drugs for sinus rhythm control, without compromising safety.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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