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EDITORIAL

CABANA Trial: The Aftermath after the Negative / Neutral Results

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Abstract

The results of the CABANA trial were recently presented at the Heart Rhythm Society Meeting in May 2018, indicating that ablation in patients with atrial fibrillation (AF) did not confer a benefit over drug treatment in the intention-to treat analysis, but did so in an on-treatment analysis. The presentation stirred commotion in the medical community with fierce controversy appearing in the media, mostly related to an apparent willingness of electrophysiologists to dispel the first and accept the second type of analysis. ***Rhythmos*** 2018;13(3): 45-47.

Key Words: atrial fibrillation; catheter ablation; pulmonary vein isolation; antiarrhythmic drug therapy

Abbreviations: AF = atrial fibrillation; CT = computed tomography; CV = cardiovascular; EF = ejection fraction; ICD = implantable cardioverter defibrillator; PVI = pulmonary vein isolation; TIA = transient ischemic attack

Introduction

The CABANA (**C**atheter **AB**lation Versus **AN**ti-arrhythmic Drug Therapy for **A**trial Fibrillation) trial (NCT00911508) sponsored by the NIH with additional support from industry (including St. Jude Medical, Johnson & Johnson, Medtronic, and Boston Scientific) was designed to randomize 2200 atrial fibrillation (AF) patients to a strategy of catheter ablation versus rate or rhythm control drug therapy. [2] Inclusion criteria included ≥ 1 risk factor for stroke and eligibility for both catheter ablation and ≥ 2 anti-arrhythmic or≥ 2 rate control drugs. Patients were followed every 3 to 6 months (median 4 years) and underwent repeat trans-telephonic monitoring, Holter monitoring, and CT/MR in a subgroup of patient studies to assess the impact of treatment on AF recurrence and atrial structure. With 1100 patients in each treatment arm, CABANA was projected to have 90% power for detecting a 30% relative reduction in the primary composite endpoint of total mortality, disabling stroke, serious bleeding, or cardiac arrest. Slow enrollment and lower than expected event rates prompted a monitoring committee and the investigators to expand the primary endpoint from overall mortality to a composite of overall mortality, disabling stroke, major bleeding, and cardiac arrest.

Results of the CABANA Trial

The first results of the trial were presented at the Heart Rhythm Society Meeting in May 2018

(http://abstractsonline.com/pp8/#!/4554/presentation/7907) (Table 1). The trial finally included 2,204 patients (median age 68 years, 63% male, 81% hypertensive, 10% with prior stroke or TIA, 4% other thromboembolic events, 36% class II/III heart failure, 10% cardiomyopathies) enrolled at 126 sites from 2009 to 2016, randomized to drug therapy (n=1096, 49.7%) and catheter ablation with pulmonary vein isolation (PVI) (n=1108) (www.acc.org/latest-in-cardiology/clinical-trials/2018/05/10/15/57/cabana). Adjunctive ablative procedures were used at operator's discretion. Median ejection fraction (EF) was 58%, with 5% with an EF ≤35%. Paroxysmal AF was present in 946 (43%) and 1257 (57%) had persistent or long-standing persistent AF, all with a median of 1.1 years since AF onset prior to enrollment. Median follow-up was ~4 years.

In an intention-to-treat analysis, the primary endpoint, a composite of clinical events consisting of death, disabling stroke, serious bleeding, or cardiac arrest, occurred in 89 patients (8%) randomized to ablation and 101 patients (9.2%) randomized to drugs (hazard ratio-HR 0.86, p=NS). Also, none of the components of the primary endpoint differed significantly.

Table 1. **CABANA Trial Results**

Principal Findings:

- *Intention-to-Treat Analysis* → Primary outcome (death, disabling stroke, serious bleeding, or cardiac arrest) at 5 years for ablation vs drugs: 8% vs 9.2% (hazard ratio -HR 0.86, p=0.3)
- Death: 5.2% vs 6.1% (ablation vs drugs), p = 0.38
- Serious stroke: 0.3% vs 0.6%, p = 0.19
- *On Treatment Analysis* → Primary endpoint (ablation vs drugs): 7.0% vs 10.9%, p = 0.006; all-cause mortality: 4.4% vs 7.5%, p = 0.005; death or CV hospitalization: 41.2% vs 74.9%, p = 0.002

Secondary outcomes:

- Death or CV hospitalization: 51.7% vs 58.1% (ablation vs drugs), HR 0.83, p = 0.002
- Time to first AF recurrence: HR 0.53, p < 0.0001
- Pericardial effusion (PVI): 3%; ablation-related events: 1.8%

Controversy heightened when Douglas Packer, the presenter of the trial, presented the results of the on-treatment analysis (see discussion below). There was a large number of crossovers, and finally 1307 patients underwent ablation and 897 received drugs. In this as-treated analysis, which was prespecified as a sensitivity analysis of the primary results, ablation resulted in a 3.9% absolute risk reduction in the primary endpoint ($p = 0.006$) and a 3.1% reduction in all-cause death ($p = 0.005$). In a similar per-protocol analysis, ablation reduced the rate of the primary endpoint by 27% (HR, 0.73; $P= 0.046$).

Adverse events occurred in both groups. About 4% of the ablation group had problems related to catheter insertion, and 3.4% had complications related to catheter manipulation in the heart, including 22 (2.2%) patients having pericardial effusion. No atrio-esophageal fistulas and no deaths were incurred by the procedure.

Critique

Milton Packer, a heart failure specialist and trialist, cautioned about the per-protocol and treatment-received analyses. "This is an open-label trial, so the only valid way of analyzing is intention-to-treat." Without blinded randomization, he explains (www.medscape.com/viewarticle/896508?src=wnl_tp10n_180607_mscpedit&uac=12462FY&impID=1650872&faf=1#vp_2), knowledge of treatment assignment can influence adjudication of events. "No one does a per-protocol analysis for a drug trial anymore," as they were long ago discredited, he said, and the same standard should apply to device trials. Before CABANA, "the electrophysiology community claimed, or believed, that there was a benefit of doing ablation above and beyond making the electrocardiogram look better. This trial now provides evidence that the claim is not true."

The headings of some of the media covering the announcement of the results of the CABANA trial on May 10, 2018 are very characteristic:

- **TCTMD** the heart beat: ***CABANA Misses Primary Endpoint, but Electrophysiologists See Support for Ablation***
- **Forbes**: ***CABANA: No Outcomes Benefit In First Big Trial Of AF Ablation***
- **Medscape**: ***CABANA: Ablation Disappoints for AF vs Drugs, Questions Remain***
- **MedPage Today**: ***CABANA Misses Primary But May Spur Afib Ablation Anyway***
- **Healio**: ***CABANA: Ablation an 'acceptable treatment strategy' for AF***
- **Mass Device**: ***HRS 2018: Study questions benefit of ablation over drug therapy for atrial fibrillation***

Preliminary subgroup analysis indicated that patients younger than 65 years seemed to show a benefit from ablation, while patients older than 75 showed little benefit. Patients with heart failure seemed to particularly derive benefit, which goes along with the results of the CASTLE-AF trial.[2] It should be noted though that subgroup analyses are typically underpowered for valid conclusions and thus

everybody urges that they should be interpreted with caution.

Although we'll have to wait for the formal publication of the results of the trial and for more information from the subgroup analysis with all its inherent limitations, however, this trial was indeed a negative trial, as it did not show ablation to be superior to drugs for reducing major outcomes. Nevertheless, ablation may be a reasonable option for selected patients with AF. It should be noted that the trial was a non-blinded trial with all inherent limitations of such a trial. Thus, the next rational step may lead to a future trial designed to include a sham procedure as the placebo-controlled arm in which patients and doctors are blinded to ablation. Other recent trials that comprised a sham procedure have indicated that is the right scientific course of action, like in renal denervation and coronary revascularization. However, many electrophysiologists seem to oppose this idea as non-feasible or even unethical (www.tctmd.com/news/cabana-misses-primary-endpoint-electrophysiologists-see-support-ablation).

Quickly here the results will be refreshed of the other randomized controlled trial, CASTLE-AF, which was a positive ablation trial, albeit in a very selective patient population.[2] In CASTLE-AF, a total of 363 patients (median age 64 years) with symptomatic paroxysmal or persistent AF and NYHA II-IV heart failure (HF) with LVEF ≤35% and an ICD were randomized to catheter ablation (n=179) or medical therapy (rate or rhythm control) (n=184). Over a median of 37.8 months, the primary composite end point (death or HF hospitalization) occurred in significantly fewer patients in the ablation group than in the medical group (28.5% vs 44.6%, hazard ratio-HR 0.62, p=0.007). There were also fewer deaths (13.4% vs 25%, HR 0.53, p=0.01), and fewer HF hospitalizations (20.7% vs 35.9%; HR 0.56, p=0.004).

The trial was criticized by Milton Packer as being a small trial in a highly selected patient population with only 10% of the patients screened for the study finally enrolled. (www.medpagetoday.com/blogs/revolutionandrevelation/71006). The trial was also significantly underpowered to test its hypothesis, as it was terminated before reaching its prespecified targets, falling short of its planned enrollment targets by 32%. Furthermore, randomized patients as well as events following randomization were excluded from the analysis, which is not the right procedure for an intention-to-treat analysis. Many patients (n=33) were lost to follow-up with more patients (n=23) lost to follow-up in the intervention group than in the control group. Most importantly, the primary analysis was based on just a handful of events. Based on all these shortcomings, Packer concluded that the trial has serious flaws and it cannot provide definitive answers on the utility of ablation in the patients who were studied unless these results could be replicable in future trials.

For both studies, Milton Packer's common critique was that "For most (electrophysiologists), performing catheter ablations has become a major source of revenue" in the US, directly stating that the reasons of accepting the results of the smaller CASTLE-AF trial and denying those of the larger CABANA trial were driven by finances (www.medpagetoday.com/blogs/revolutionandrevelation/72905).

Perspective

Although ablationists may feel disappointed by the CABANA trial results and non-electrophysiologists may adopt a reprimanding attitude towards those who recommend ablation for reasons of improvement of hard endpoints, the truth probably lies somewhere in between. A selective and more critical approach to AF ablation using participatory medicine in a shared decision model between patient/patient's family and physician might be a more reasonable strategy. Improving quality of life via a reduction of AF burden and curtailing drug intake, achievable via ablation, is important to many symptomatic patients but not to all patients, especially to those with asymptomatic or silent AF, and may be a futile exercise in older patients with a lot of comorbidities. Even in patients with heart failure and AF, only a very select group appear to benefit the most. [2]

Thus, for now, let's wait for the full publication of the CABANA trial results and seriously consider the design of a future trial with a sham procedure for a more rigorous approach to the potent placebo effect that our interventions have surprisingly been shown to confer in other instances, like with renal denervation for hypertension and coronary stenting for stable angina.

Until then, let's concentrate on our individual patient and his/her needs, looking for arrhythmia triggers to take care (uncontrolled hypertension, alcohol, obesity, sleep apnea, stressful situations, extreme exercise, thyroid dysfunction, etc), and properly advise our patients about their options with drugs and availability of ablation, albeit with its potential procedural risks and inherent intricacies, so that they can reach an informed and educated decision about the desired management of their disease.

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