EDITORIAL

# Catheter Ablation for Atrial Fibrillation
## Lessons Learned From CABANA

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**Atrial fibrillation (AF)** is the most common heart rhythm disturbance, with an estimated 33.5 million people affected worldwide.[1] By age 75 years, more than 10% of the population will have developed AF.[2] It is well recognized that AF increases the risk of thromboembolic stroke[3]; however, AF also increases the risk of other highly morbid conditions such as heart failure (HF).[4] As a result, even in the modern era of anticoagulation, mortality rates among patients with AF remain up to 2-fold higher than mortality rates among individuals without AF.[4,5] For many patients, AF also has a major detrimental effect on quality of life, similar to that observed in patients with coronary artery disease requiring percutaneous coronary intervention (PCI) or after a myocardial infarction.[6] Symptoms from AF, which include, but are not limited to, palpitations, dyspnea, and exercise intolerance, are the primary reason that patients seek medical treatment, and physicians treat AF-related symptoms with a therapeutic armamentarium that includes rate control agents, antiarrhythmic drugs, and catheter ablation. Therefore, clinicians hope to achieve 2 potential goals with current therapies directed at AF: to improve quality of life and to decrease AF-related morbidity and mortality.

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In this issue of *JAMA*, the CABANA trial investigators present their pivotal results on these dual outcomes for AF ablation.[7,8] The multicenter, international CABANA trial randomized 2204 patients with AF to a strategy of catheter ablation or drug therapy, and then followed patients longitudinally for an average of 4 years for mortality and a comprehensive series of clinically relevant cardiovascular outcomes, quality of life, and AF recurrence.[7] The patients' conditions had to warrant active therapy per guidelines, and thus asymptomatic patients comprised only 10% of the study population. Enrollment criteria included electrocardiographic documentation of 2 or more episodes of paroxysmal AF or 1 episode of persistent AF in the past 6 months. Most patients (58%) had persistent or long-standing AF, and 80% had previously been treated with a rhythm control agent. Physicians performing catheter ablations were required to be experienced with the procedure, and recommended medical therapy in the drug and catheter ablation treatment groups was consistent with contemporary guidelines, such that long-term oral anticoagulation was maintained in patients with a $CHA_2DS_2$-VASc score of 2 or above regardless of perceived success of therapy.[9] Although previous randomized trials have evaluated catheter ablation vs drug therapy, none of these trials was powered to examine the effect of catheter ablation on morbidity or mortality, nor did they enroll or follow such a diverse AF population for so wide a variety of end points, such that efficacy and safety could be simultaneously assessed. Much can be learned from the results of this important study.

The first CABANA article, by Packer and colleagues,[7] presents the primary results on cardiovascular outcomes and mortality. In the intention-to-treat analysis, patients randomized to receive catheter ablation (n = 1108) did not experience a significant decrease (or increase) in the primary composite end point of death, disabling stroke, serious bleeding, or cardiac arrest compared with patients randomized to receive drug therapy (n = 1096), with rates of the composite outcome of 8.0% vs 9.2%, respectively (hazard ratio, 0.86 [95% CI, 0.65-1.15]; $P = .30$). As seen in prior smaller trials, primarily performed in patients with paroxysmal AF,[10,11] patients randomized to ablation had a significantly lower rate of AF recurrence (49.9% vs 69.5%) after a prespecified 3-month blanking period following ablation or initiation of drug therapy, as measured by monitoring in a subset of 1240 patients. Of the patients randomized to catheter ablation, 19.4% underwent repeat procedures. The secondary end point of death and cardiovascular hospitalization, although not centrally adjudicated, was also significantly reduced in the catheter ablation group (51.7% vs 58.1%), primarily due to a lower incidence of hospitalizations for antiarrhythmic drug titration, toxicity, and pacemaker implantations. In many HF trials, a reduction in cardiovascular hospitalizations would be viewed as a successful result. Rates of individual serious adverse events were low in both treatment groups, although a composite adverse event rate was not reported.

The second CABANA article, by Mark and colleagues,[8] reports the results for the important secondary end point of quality of life using several scales validated in patients with AF. In the intention-to-treat analysis, patients in both treatment groups of the trial had significant improvements in their quality of life over the course of the study, based on the co-primary end points of the Atrial Fibrillation Effect on Quality of Life (AFEQT) summary score and the Mayo AF-Specific Symptom Inventory (MAFSI); however, the improvement in the catheter ablation group was significantly greater. The mean AFEQT score increased (higher scores signify better quality of life, scale from 0-100) from a mean of 62.9 to 86.4 in the catheter ablation group vs 63.1 to 80.9 in the drug therapy group at 12 months, for a mean difference of 5.3 points (clinically important difference >5.0 points)

in favor of the catheter ablation group. The mean frequency and severity scores of the MAFSI were reduced in both treatment groups (lower scores signify improved symptoms), but again to a greater extent in the catheter ablation vs drug therapy group. These findings appeared durable over the extended period of the trial. In post hoc analyses, the benefit was greatest among patients with the most symptomatic impairment (*P* for interaction = .02).

In another clinical trial recently published in *JAMA* (the CAPTAF trial), Blomström-Lundqvist and colleagues[12] also examined the effect of catheter ablation vs antiarrhythmic drug therapy on quality of life in 155 patients with AF. The authors similarly found a significant, clinically relevant improvement in quality of life at 12 months after randomization to catheter ablation compared with medical therapy, with a mean treatment group difference of 8.9 points as assessed by the 36-Item Short Form Health Survey.[12] These 2 separate quality-of-life trials with consistent findings make this a robust observation.[8,12]

The lack of blinding does introduce potential bias, although any positive effect on quality of life soon after the procedure due to a placebo effect would be expected to begin to dissipate by a year. The quality-of-life data in CABANA are analogous to randomized trials of PCI for stable angina, which in appropriate patients improves quality of life, although the effect on "hard" end points (ie, myocardial infarction and mortality) outside of the setting of acute coronary syndromes is less certain.[13] Furthermore, improvements in quality of life with PCI were also observed largely in the context of unblinded trials. Blinding of procedural trials is possible and ideal but drives up the cost and complexity substantially.[14]

Randomized clinical trials of therapeutic strategies, in particular those involving invasive procedures, are among the most challenging to design and execute. Patients who seek care at experienced catheter ablation centers, such as those participating in CABANA, are often referred for the procedure and might not want to be randomized to drug therapy. Thus, it took more than 6 years to enroll the patient population. In addition, as in many strategy trials, particularly those testing interventional procedures, a percentage of patients randomized to catheter ablation did not undergo the procedure (9%), which dilutes the intervention effect and would be expected to bias the results toward the null. In addition, as is often seen in clinical practice, 27.5% of patients randomized to drug therapy eventually crossed over to catheter ablation.

Because protocol adherence and crossover are not random, there is no ideal way to determine the effect that these occurrences might have had on the results.[15] Excluding, censoring, or reassigning these patients—as was done in the per-protocol or on-treatment analyses—may lead to biases that could potentially favor catheter ablation. In general, nonadherent patients tend to do worse, and the patients in the drug therapy group who crossed over to catheter ablation had, for the most part, lower-risk features. It is, however, reassuring that the intention-to-treat analyses and these secondary analyses did not demonstrate a signal for an increase in mortality, with all the hazard ratios suggesting potential benefit associated with catheter ablation. Complication rates with catheter ablation were also very low, with the most common serious adverse event being cardiac tamponade, which occurred at a rate of 0.8%; less serious local vascular complications, such as hematomas and pseudoaneurysms, occurred at a rate of 3.4%.[7]

While it is true that the CABANA trial did not meet its primary end point in the intention-to-treat analyses (and this is the most rigorous way to evaluate trial results), this study provides important, clinically relevant insights regarding current treatment options for AF management. In experienced centers, when performed by skilled operators with low procedural complication rates as achieved in CABANA, catheter ablation can be performed successfully and safely in most patients. For patients with symptoms, in whom quality of life is impaired by AF, catheter ablation can improve quality of life to a greater extent than drug therapy. However, patients who choose drug therapy will also likely experience significant improvements in quality of life and have no worse risk for the most concerning complications of AF, stroke and death. Thus, there is no mandate for these patients to undergo catheter ablation at this time. Catheter ablation may also have the added benefits of reducing AF burden and cardiovascular hospitalizations. However, it is important to note that more than 50% of patients randomized to ablation had a recurrence of AF over 4 years, and some of these patients may require repeat ablations in the future. Also, because patients with stroke risk factors continued to receive anticoagulation therapy as per guidelines, it remains unknown whether anticoagulation can be safely stopped in such patients even in the setting of a successful ablation. This latter hypothesis is being tested in the ongoing Optimal Anticoagulation for Higher Risk Patients Post-Catheter Ablation for Atrial Fibrillation Trial (OCEAN) (NCT02168829).

Although CABANA is the largest trial to date, it is still conceivable that catheter ablation may have more modest benefits on morbidity and mortality than were able to be detected even in a trial of this size. The mortality rate in the medication treatment group (5.3% at 4 years)[7] was much lower than what was expected based on historical controls (12.0% at 3 years), and the incidence of disabling stroke over 4 years was exceedingly low (0.7%) in the current era of anticoagulation and guideline-based management of AF. Overall, this is excellent news for patients with AF, but also results in the need for a much larger sample of patients than that enrolled in CABANA to be able to detect benefits on mortality and stroke. It is also still possible that there are subgroups of patients for whom the relative benefits of catheter ablation may differ. For example, patients with AF with systolic dysfunction and HF who have failed antiarrhythmic drugs have been found to experience a mortality benefit in prior smaller trials.[16,17] Of note, subgroup treatment interactions, including in those with HF (n = 337), were not significant in CABANA; however, the trial was not adequately powered to detect such interactions.

Where does this leave the patient with AF? Shared decision making between the cardiologist and the patient is the

best answer and is critical in determining treatment. The CABANA trial provides a wealth of additional data regarding the comparative benefits and risks of catheter ablation vs drug therapy to inform this process. This approach may be well positioned to occur in comprehensive AF management centers that offer the full range of anticoagulation options, antiarrhythmic drug therapy, and percutaneous and surgical procedures, coupled with lifestyle modification, such as weight loss, that may further augment the success of ablation,[18] medical therapies,[19] or both. Thus, the CABANA trial provides essential information to optimize the care of patients with AF in a very patient-centric way.

## ARTICLE INFORMATION

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## REFERENCES

1. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;129(8):837-847. doi:10.1161/CIRCULATIONAHA.113.005119

2. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114(2):119-125. doi:10.1161/CIRCULATIONAHA.105.595140

3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22(8):983-988. doi:10.1161/01.STR.22.8.983

4. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *BMJ*. 2016;354:i4482. doi:10.1136/bmj.i4482

5. Conen D, Chae CU, Glynn RJ, et al. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. *JAMA*. 2011;305(20):2080-2087. doi:10.1001/jama.2011.659

6. Dorian P, Jung W, Newman D, et al. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *J Am Coll Cardiol*. 2000;36(4):1303-1309. doi:10.1016/S0735-1097(00)00886-X

7. Packer DL, Mark DB, Robb RA, et al; CABANA Investigators. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial [published March 15, 2019]. *JAMA*. doi:10.1001/jama.2019.0693

8. Mark DB, Anstrom KJ, Sheng S, et al; CABANA Investigators. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial [published March 15, 2019]. *JAMA*. doi:10.1001/jama.2019.0692

9. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm*. 2017;14(10):e275-e444. doi:10.1016/j.hrthm.2017.05.012

10. Cosedis Nielsen J, Johannessen A, Raatikainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med*. 2012;367(17):1587-1595. doi:10.1056/NEJMoa1113566

11. Morillo CA, Verma A, Connolly SJ, et al; RAAFT-2 Investigators. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA*. 2014;311(7):692-700. doi:10.1001/jama.2014.467

12. Blomström-Lundqvist C, Gizurarson S, Schwieler J, et al. Effect of catheter ablation vs antiarrhythmic medication on quality of life in patients with atrial fibrillation: the CAPTAF randomized clinical trial [published March 15, 2019]. *JAMA*. doi:10.1001/jama.2019.0335

13. Bhatt DL. Percutaneous coronary intervention in 2018. *JAMA*. 2018;319(20):2127-2128. doi:10.1001/jama.2018.5281

14. Bhatt DL, Kandzari DE, O'Neill WW, et al; SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med*. 2014;370(15):1393-1401. doi:10.1056/NEJMoa1402670

15. DeMets DL, Cook T. Challenges of non-intention-to-treat analyses. *JAMA*. 2019;321(2):145-146. doi:10.1001/jama.2018.19192

16. Marrouche NF, Brachmann J, Andresen D, et al; CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med*. 2018;378(5):417-427. doi:10.1056/NEJMoa1707855

17. Kheiri B, Osman M, Abdalla A, et al. Catheter ablation of atrial fibrillation with heart failure: an updated meta-analysis of randomized trials. *Int J Cardiol*. 2018;269:170-173. doi:10.1016/j.ijcard.2018.07.024

18. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol*. 2014;64(21):2222-2231. doi:10.1016/j.jacc.2014.09.028

19. Chatterjee NA, Albert CM. Risk factor modification in atrial fibrillation: saving dollars and making sense. *JACC Clin Electrophysiol*. 2017;3(5):448-450. doi:10.1016/j.jacep.2017.03.007