AF: Where Are We Now? Part Two

We have two more important studies to address to complete our review of what’s new in atrial fibrillation (AF). The complex CASTLE-AF and the CABANA trials revealed new insights about ablation for AF and caused a lot of controversy.

Is catheter ablation better than standard treatment among patients with left ventricular dysfunction and atrial fibrillation?

CASTLE-AF supports catheter ablation for atrial fibrillation in patients with heart failure. The CASTLE-AF trial showed that catheter ablation was superior at preventing death or heart failure (HF) admissions compared to medical treatment.¹

STUDY DESIGN

Patients with left ventricular dysfunction and AF were randomized to catheter ablation (n = 179) versus conventional treatment (n = 184). Medical therapy was administered based on current guidelines, and although rhythm control was encouraged, 70 percent of patients were treated with a rate-control strategy, targeting goal resting heart rates of 60 to 80 beats per minute.

• Total number of enrollees: 363
• Duration of follow-up: median 37.8 months
• Mean age: 64 years (86 percent male)
• Mean left ventricular ejection fraction (LVEF): 35 percent

INCLUSION CRITERIA

• Symptomatic paroxysmal or persistent AF
• Intolerance or unwillingness to take an antiarrhythmic drug
• LVEF: ≤35 percent
• New York Heart Association (NYHA) Class ≥2
• Implantable cardioverter-defibrillator or cardiac resynchronization therapy-defibrillator with home monitoring capabilities

PRINCIPAL FINDINGS

The primary outcome, incidence of death or hospitalization for HF, occurred in 28.5 percent of the catheter ablation group, versus 44.6 percent of the control group (p = 0.007).

• All-cause mortality: 13.4 percent with catheter ablation versus 25.0 percent with control (p = 0.01)
• Hospitalization for HF: 20.7 percent with catheter ablation versus 35.9 percent with control (p = 0.004)

Among patients with decreased LVEF and AF, catheter ablation was associated with a reduction in deaths or hospitalizations for HF. The authors concluded that catheter ablation for AF should be strongly considered early in the management of patients with HF.

Commentary: The CASTLE-AF trial has quickly generated debate in the cardiology and electrophysiology community. Some point to the impressive improvements in outcomes.
with ablation (50 percent relative reduction in death) as a call to arms and confirmation of anecdotal experience that normal atrial contraction contributes to improved cardiac output, and decreased AF burden improves outcomes. Median absolute increase in LVEF was 8 percent in the ablation group compared with 0.2 percent in the medical therapy group. Additionally, mean AF burden (which increases AF risk—discussed in last month’s Heartbeat) was 27 percent of the time at five years in the ablation group versus 64 percent of the time in the medical therapy group.

Others have urged caution based on the relatively small number of patients, the statistical methods employed and unblinded nature of the trial. They also point out that these results alone cannot be extrapolated to older patients and women. Subgroup analysis suggested no benefit of ablation in more severe cardiomyopathy (LVEF < 25 percent) or NYHA Class III.

**Take home for the clinician:** There were no subgroups in which medical therapy was superior. The potential benefits of ablation should be strongly considered early in the management of patients with AF and HF along with optimal medical therapy—especially in younger males.

**Does ablation for AF reduce the composite endpoint of death, disabling stroke, serious bleeding or cardiac arrest compared with drug therapy?**

The CABANA trial showed that ablation is not superior to drug therapy for CV outcomes at five years among patients with new-onset or untreated AF that required therapy.\(^2\) AF is a common arrhythmia condition that affects an estimated 33 million people worldwide and has been known to increase a person’s risk of stroke and death.\(^3\) Antiarrhythmic drugs (AADs) are considered a primary strategy for treating AF. However, the application of AADs has encountered challenges due to limited efficacy and adverse side effects. Thus, catheter ablation therapy has become a generally adopted alternative technique for the treatment of AF. Limited studies have compared the therapies and much uncertainty still exists about the benefits of ablation relative to drug therapy.

The goal of the trial was to compare the safety and efficacy of catheter ablation compared with drug therapy for the treatment of patients with new-onset or untreated atrial fibrillation (AF).

**STUDY DESIGN**

Patients were randomized in a 1:1 fashion to catheter ablation (n = 1,108) or drug therapy (n = 1,096). Primary ablation was performed with standard techniques (pulmonary vein isolation/wide area circumferential ablation, ancillary ablations as needed). Drug therapy could be either for rate or rhythm control. All patients received anticoagulation.

- Total number of enrollees: 2,204
- Duration of follow-up: 5 years
- Mean patient age: 67.5 years
- Percentage female: 37 percent

**INCLUSION CRITERIA**

- Paroxysmal, persistent or longstanding persistent AF patients who warrant therapy
- ≥65 years of age
- <65 years of age with ≥1 cerebrovascular accident (CVA)/cardiovascular (CV) risk factor
- Eligible for ablation
- On ≥2 rhythm or rate control drugs

Other salient features/characteristics:

- Cardiomyopathy: 9 percent
- Chronic HF: 15 percent
- Prior CVA/transient ischemic attack (TIA): 10 percent
- Type of AF: paroxysmal: 43 percent, persistent: 47 percent
- Prior hospitalization for AF: 39 percent

Crossover: ablation to drug: 9.2 percent, drug to ablation: 27.5 percent. (This creates some challenges with strict interpretation of results based on intention to treat analysis.)
PRINCIPAL FINDINGS

The primary outcome—death, disabling stroke, serious bleeding or cardiac arrest—at 5 years for ablation versus drug therapy, was 8 percent versus 9.2 percent (hazard ratio [HR] 0.86, 95 percent confidence interval [CI] 0.65-1.15, p = 0.3) by intention to treat.

- Death: 5.2 percent versus 6.1 percent for ablation versus drug therapy, p = 0.38
- Serious stroke: 0.3 percent versus 0.6 percent for ablation versus drug therapy, p = 0.19
- Primary endpoint based on treatment received (for ablation versus drug therapy): 7.0 percent versus 10.9 percent, p = 0.006; all-cause mortality: 4.4 percent versus 7.5 percent, p = 0.005; death or CV hospitalization: 41.2 percent versus 74.9 percent, p = 0.002

Secondary outcomes:

- Death or CV hospitalization: 51.7 percent versus 58.1 percent for ablation versus drug therapy, HR 0.83, 95 percent CI 0.74-0.93, p = 0.002
- Time to first AF recurrence: HR 0.53, 95 percent CI 0.46-0.61, p < 0.0001
- Pericardial effusion with ablation: 3.0 percent; ablation-related events: 1.8 percent
- Recurrent AF for ablation versus drug therapy (HR 0.52, p < 0.001)

Commentary: Electrophysiologists and cardiologists alike continue debating the meaning and results of this first big trial of AF catheter ablation in the more-than-two-decade-long history of the procedure. Purists say the CABANA trial failed to show that catheter ablation improves hard outcomes in patients with AF, but electrophysiologists who perform the procedure see it differently, pointing to the dramatic reduction in recurrent AF in the patients randomized to ablation. They also point to the significant reduction in combined death or CV hospitalization in the ablation group, a secondary outcome. But in the setting of a negative primary endpoint, those findings are considered hypothesis generating.

A couple of caveats exist. The drug-therapy arm is very heterogeneous, and it is unclear if uniform pursuance of rhythm control in that arm would be better than the rate control arm. The included population is also somewhat unclear with respect to the patients who would most benefit with this therapy.

Electrophysiologist Faisal Siddiqi, MD, states, “Ablation is safe and treating healthier patients with ablation results in improved outcomes, but that is expected. Implicit bias results in healthier patients being selected for ablation resulting in difficulty reaching definitive conclusions.” He concludes, “It is a quality of life procedure for now (until proven otherwise) and there is no shame in that for most patients.”

Take home for the clinician: Ablation for AF is as good as medical therapy and appears safe. It is clearly more effective than medical therapy at preventing AF, decreasing symptoms in symptomatic patients and decreasing AF burden. Ablation should definitely be considered in symptomatic patients. It should be recommended early and more often in younger patients, and presented as an option in older patients with appropriate discussion.
References

