CABANA Trial Results Announced at Heart Rhythm Society Scientific Sessions: The Neutral Trial That Wasn’t Neutral

The recently completed Catheter Ablation Versus Anti-Arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) Trial was designed to help answer questions about the relative efficacy of ablative versus drug therapy in decreasing the primary endpoint, which is the composite of death, disabling stroke, serious bleeding, or cardiac arrest in individuals with AF. Secondary endpoints included all-cause mortality; mortality or cardiovascular hospitalization; mortality, stroke, or hospitalization for heart failure or an ischemic event; cardiovascular death; freedom from recurrent AF; and composite adverse events. Additionally, medical costs and quality of life in each arm were evaluated.

2204 patients were enrolled at 126 study sites in the U.S., Australia, Canada, China, Czech Republic, Germany, Italy, South Korea, Russian Federation, and the United Kingdom. CABANA aimed to study individuals over the age of 65 or less than age 65 with one or more risk factors for stroke, two or more episodes of paroxysmal atrial fibrillation (PAF) or one episode of persistent AF in the prior six months, and who are suitable for drug- (rhythm or rate control) or catheter-based treatment. Patients were randomized in a 1:1 fashion into PVI (1108 patients), or drug therapy (1096 patients). (The specific pharmacologic agents utilized were left to the discretion of the treating provider, although providers were encouraged to follow ACC/ESC/AHA treatment guidelines.) The mean patient age was 67.5 years, and 37% were female. The mean duration of follow-up was 48 months. All patients were to receive anticoagulation based on current guidelines.

Douglas L. Packer, MD, former Director of the Division of Heart Rhythm Services at Mayo Clinic in Rochester, Minnesota and past president of Heart Rhythm Society, was the principal investi-
The primary endpoint (the composite of death, disabling stroke, serious bleeding, or cardiac arrest) based on intention-to-treat (ITT) analysis at 48 months for PVI vs drug therapy was 8% vs 9.2% (HR 0.86, 95% CI 0.65–1.15; p=0.303 NS) (Figure 1). However, 9.2% of patients randomized to PVI did not undergo ablation, while 27.5% of patients randomized to drug therapy actually crossed over to PVI. By ITT analyses, the endpoint of mortality or cardiovascular hospitalization showed a 17% reduction, and the recurrence of AF was reduced by 47% (Figure 2). The primary endpoint based on actual-treatment-received analysis for PVI vs drug therapy was 7.0% vs 10.9%, (HR 0.67, 95% CI 0.50–0.89; p=0.006) (Figure 3).

Dr. Packer notes that CABANA is a complicated study, so it is important to avoid over-inter-pretation of the CABANA data. Intention-to-treat analysis preserves the randomization and if appropriately designed and powered will factor out selection bias; it is generally regarded as the “gold standard” measure in clinical trials. However, where there are a significant number of crossovers, or patients don’t receive the randomized therapy, ITT may fail to clearly establish anticipated outcome. In certain interventional trials, on-treatment analysis may better reflect actual treatment outcomes. “You can’t benefit from a therapy if you don’t receive the therapy,” said Dr. Packer. The data indicated a 33% reduction in the primary endpoint and a 40% reduction in mortality in patients who actually received ablation compared to those individuals who received drug treatment. Furthermore, even in the intention-to-treat analysis, the two secondary endpoints of total mortality or cardiovascular hospitalization and recurrent atrial fibrillation were significantly better in the ablation arm. He also pointed out that by design the drug treatment arm included a heterogeneous group of rate control or anti-arrhythmic drugs selected by the patient’s primary cardiologist. It is unclear whether or not the choice of treatment drug affected outcomes or adverse events.

Dr. Packer pointed out during his presentation that one of the findings of the trial is that ablation is a safe option for individuals with symptomatic atrial fibrillation. “There was a low rate of adverse events, even in the higher-risk patients who underwent ablation,” said Dr. Packer. The most common findings were vascular injury at catheter insertion sites (2.3%) and cardiac perforation (0.8%) in the PVI arm, and thyroid abnormalities (1.6%) and proarrhythmic events (0.8%) in the drug therapy arm.

In the CABANA Trial, ablation did not produce a significant reduction in either the primary endpoint or the secondary endpoint of all-cause mortality, according to an intention-to-treat analysis. The results were affected by crossovers in both directions and lower-than-expected event rates. Ablation did significantly reduce the secondary endpoint of mortality or CV hospitalization by 17% compared to drug therapy. There also was a significant 47% reduction in recurrent AF with ablation compared to drug therapy.

As such, CABANA demonstrated that ablation is an acceptable treatment strategy with low procedural risks even in treating AF patients with higher underlying risk. The challenge is to identify those individuals most likely to benefit from ablation. For the most part, these will be the patients with symptomatic AF. “Further subgroup analysis of trial data will provide information about the economics of each approach and quality-of-life measures which will help us better identify those individuals most likely to benefit from ablative therapy,” says Dr. Packer.

![Figure 1. The primary endpoint (the composite of death, disabling stroke, serious bleeding, or cardiac arrest) based on intention-to-treat at 48 months for PVI vs drug therapy was 8% vs 9.2% (HR 0.86, 95% CI 0.65–1.15; P=0.303 NS).](image-url)
Roger S. Blumenthal, MD presented the 12th Annual Gerald T. Gau Lectureship entitled “Is Traditional ASCVD Risk Estimation More Predictive Than a Coin Flip?” at Mayo Clinic in Rochester, Minnesota. Dr. Blumenthal (right), the Kenneth Jay Pollin Professor of Cardiology and the Director of the Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, is pictured with Dr. Gau (left) at the event.

The American Heart Association awarded Margaret Fuchs, MD the AHA Women in Cardiology Trainee Award of Excellence during the 2017 Scientific Sessions. Dr. Fuchs, a cardiology fellow at Mayo Clinic in Rochester, Minnesota, was one of nine women trainees to receive the award.

Allan S. Jaffe, MD, cardiologist at Mayo Clinic in Rochester, Minnesota, received the 2018 Distinguished Teacher Award from the American College of Cardiology. The award was presented in recognition of Dr. Jaffe’s outstanding teaching and innovative, compassionate educational efforts throughout his career.

### Figure 2. AF recurrence reduced by 47% based on intention-to-treat at 48 months for PVI vs drug therapy (HR 0.53, 95% CI 0.46–0.61; P<0.0001).

### Figure 3. The primary endpoint based on actual treatment received for PVI vs drug therapy was 7.0% vs 10.9%, (HR 0.67, 95% CI 0.50 – 0.89; p=0.006).

### Primary and Secondary Outcomes (Treatment Received)*

<table>
<thead>
<tr>
<th></th>
<th>Ablation (N = 1307)</th>
<th>Drug (N = 897)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>92 (7.0%)</td>
<td>98 (10.9%)</td>
<td>0.67 (0.50, 0.89)</td>
<td>0.006</td>
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<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
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<tr>
<td>All-cause mortality</td>
<td>58 (4.4%)</td>
<td>67 (7.5%)</td>
<td>0.60 (0.42, 0.86)</td>
<td>0.005</td>
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<tr>
<td>Death or CV hospitalization</td>
<td>538 (41.2%)</td>
<td>672 (74.9%)</td>
<td>0.83 (0.74, 0.94)</td>
<td>0.002</td>
</tr>
<tr>
<td>Death, disabling stroke, hospitalization for HF or ACS</td>
<td>150 (15.2%)</td>
<td>164 (15.0%)</td>
<td>0.79 (0.64, 0.99)</td>
<td>0.044</td>
</tr>
</tbody>
</table>

*pre-specified
Sarcoïdose is a multisystem inflammatory disorder of unknown origin that is characterized by noncaseating granulomas in involved tissues. It most commonly affects young and middle-aged adults. Sarcoïdose frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltrates, uveitis, or skin lesions, but any organ, including the heart, may be involved. Only a small minority of patients with sarcoïdose are diagnosed with cardiac involvement. According to autopsies of a series of patients with systemic sarcoïdose, however, the rate of cardiac sarcoïdose (CS) is approximately 25%, indicating that CS is underdiagnosed in this population.

**Diagnosing CS**

Diagnosing CS remains challenging. Definite CS can only be established by the presence of noncaseating granulomas on endomyocardial biopsy (EMB) (Figure 1).

Due to the patchy nature of granulomatous deposition in the myocardium, the diagnostic yield of EMB has been reported to be only about 20%. Using electrogram guidance, as is commonly performed during EMB for suspected CS at Mayo Clinic, increases the diagnostic yield up to 50%. Suraj Kapa, MD, electrophysiologist at Mayo Clinic in Rochester, and his colleagues are continuing to work on optimizing where, when, and how biopsies should be performed to confirm cases of CS.

Cardiac involvement may precede, occur concurrently with, or follow lung or other organ involvement. Clinicians should thus consider the possibility of CS in patients with known extracardiac sarcoïdose who develop cardiac symptoms, ECG changes, or abnormal findings on cardiac imaging. Clinicians should also consider the diagnosis of CS in otherwise healthy young or middle-aged persons who present with cardiac symptoms, arrhythmias or heart failure without a preceding diagnosis of extracardiac sarcoïdose. A high index of suspicion is thus required to consider the diagnosis of CS, and expert evaluation is essential to confirm the diagnosis and provide appropriate recommendations regarding therapy.

Echocardiography is often the first imaging screening test for CS and is extremely useful for assessing left and right ventricular systolic and diastolic function and estimating pulmonary artery pressures (Figure 2). Echocardiography, however, has low sensitivity for detecting early CS. Newer echo technologies, including speckle tracking imaging, show promise in the early diagnosis of CS and may predict clinical outcomes.

Cardiac magnetic resonance (CMR) has also emerged as a useful tool in the diagnosis of CS. Although CMR images may show thinned walls, aneurysms, and segmental wall motion abnormalities in a noncoronary distribution, the principle method for detecting CS by CMR relies on identifying areas of late gadolinium enhancement, usually in a subepicardial or transmural distribution (Figure 3).

Cardiac FDG-PET has increasingly been utilized for the diagnosis and management of CS due to its high spatial resolution. Cardiac PET imaging for CS involves two different scans: one scan to assess resting myocardial perfusion and areas of fibrosis or scar using 82Rubidium or 13N-Ammonia, and another scan to detect inflammation using FDG (Figure 4). In early stages of the disease, focal areas of increased FDG uptake are present and resting perfusion defects may be seen. In advanced CS, resting perfusion defects may be seen in the absence of FDG uptake, indicating the presence of scar without inflammation. Resting perfusion defects and areas of inflammation may either coincide with or occur in different locations of the myocardium. Whole-body FDG imaging, typically from the orbits to the mid-thigh level, is increasingly being used to evaluate for extracardiac sarcoïdose during the same PET session at...
which dedicated cardiac perfusion and FDG imaging occurs. Clinicians may find this useful for identifying extracardiac metabolically active areas that may be amenable to biopsy and to help discern whether or not immunosuppressive therapy is indicated.

**Management**

There currently are no FDA approved therapies for sarcoidosis in general or CS in particular. Although corticosteroids are the mainstay treatment for patients with CS, there is a paucity of data to support the effectiveness of this therapy,” according to Lori A. Blauwet, MD, Director of the Cardiac Sarcoidosis Clinic at Mayo Clinic in Rochester. “Optimal doses and duration of corticosteroid therapy have not been systematically studied.” Although there are no clear guidelines regarding when to initiate corticosteroid therapy, most experts agree immunosuppression should be considered in symptomatic CS patients with evidence of active myocardial inflammation and any of the following: 1) reduced LVEF, 2) high-grade AV block, 3) frequent PVCs or frequent non-sustained VT, or 4) sustained VT or VF. It remains uncertain whether or not asymptomatic patients with CS benefit from treatment.

Dr. Blauwet is engaged in setting up clinical teams and trials to better track and assess outcomes in CS patients receiving a variety of treatment options. Steroid-sparing agents are often used for refractory cases or when patients experience adverse effects from steroid therapy. Anti-metabolites such as methotrexate, azathioprine, leflunomide, mycophenolate, motefil and cyclophosphamide have been used as second-line agents. If the disease progresses despite use of glucocorticoids and/or a second-line agent, TNF-inhibition with either infliximab or adalimumab should be considered. Physicians at Mayo Clinic have used rituximab, a monoclonal antibody directed against the CD20 antigen on the surface of B-lymphocytes, to treat patients with refractory CS, with some success.

Some centers, including Mayo Clinic, have routinely introduced a steroid-sparing agent when corticosteroid therapy is initiated rather than waiting to determine responsiveness to steroid therapy before adding a second agent, allowing a more rapid steroid taper so as to minimize the potential for steroid-induced weight gain, diabetes, osteoporosis and other complications. The steroid-sparing agent is typically continued for at least 6 to 12 months after prednisone has been discontinued.

“Granulomatous lesions and active inflammation are substrates for ventricular arrhythmias in patients with CS. Amiodarone may be useful, but long-term use is typically avoided due to potential lung toxicity,” says Dr. Kapa. Catheter radiofrequency ablation may be useful in some CS patients with VT, but results have been mixed. Current guidelines provided by the Heart Rhythm Society state that catheter ablation can be useful in patients with CS and ventricular arrhythmias that are refractory to immunosuppressive and antiarrhythmic therapy. VT recurrences are common, however. Repeat ablation with concomitant antiarrhythmic therapy in these patients may be useful.

As many patients with CS present with high grade AV block, pacemaker implantation is frequently indicated per standard device guidelines. Device implantation can also be useful for patients with CS with an indication for pacing even if the AV block is transient. ICD implantation can be considered in patients with CS who have an indication for permanent pacing even in the absence of ventricular arrhythmias. ICD implantation is indicated in patients who have a history of spontaneous sustained ventricular arrhythmias or who have LVEF ≤35% despite optimal medical therapy and a period of immunosuppression, if inflammation is present. ICD implantation may be useful for patients with CS with unexplained syncope or near syncope and inducible sustained ventricular arrhythmias.

**Prognosis**

The natural history and prognosis of patients with CS remains uncertain. Symptomatic patients seem to have a poorer outcome than asymptomatic patients. The extent of LV dysfunction tends to be the most important predictor of survival. Several studies have examined the prognosis of clinically silent CS with varying results. Many patients with clinically silent CS have a benign clinical course,
but some of these patients present with sudden cardiac death. Clinicians are advised to closely monitor patients with CS for disease progression and development of symptoms so as to optimize management in order to prevent potentially devastating complications.

Mayo Clinic in Rochester, Minnesota launched the Cardiac Sarcoidosis Clinic earlier this year in order to optimize the diagnosis and treatment of patients with this disease. The clinic is staffed by specialists from the Department of Cardiovascular Medicine with expertise in myocardial diseases and heart failure. These specialists collaborate with specialists from other disciplines, including electrophysiology, cardiac imaging, pathology, rheumatology, pulmonary, ophthalmology, and neurology to provide multidisciplinary assessment and coordination of care of patients with cardiac sarcoidosis. The clinic is one of only a handful of clinics in the world specifically dedicated to the care and treatment of patients with CS.

**Innovation in Cardiac Sarcoidosis Care at Mayo Clinic**

The team at the Mayo Clinic Sarcoidosis Clinic is involved in innovating approaches to diagnosis and treatment of patients with suspected or clinically definite cardiac sarcoidosis. These efforts have included development of a unique agent for PET scanning to hopefully improve diagnostic accuracy, development of new tools and techniques for biventricular biopsy, and engagement with colleagues in genetics and pathology to better understand the potential pathophysiologic causes of CS and to help identify potential new therapeutic targets. Epidemiologic efforts are also underway to help clinicians understand treatment effects, elucidate patients who most benefit with specific interventions such as ablations or defibrillators, and help guide patients on the prognosis related to their specific disease.

For more information about the Cardiac Sarcoidosis Clinic at Mayo Clinic in Rochester, Minnesota, please call 507-284-3687.

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**Figure 3.** Cardiac magnetic resonance imaging of patient with cardiac sarcoidosis. A, Noncontrast image shows left ventricular chamber dilatation with marked thinning of the interventricular septum (arrows). B, Postcontrast image shows focal transmural late gadolinium enhancement involving the entire interventricular septum (arrows).

**Figure 4.** Fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography imaging in a patient with cardiac and extracardiac sarcoidosis (maximum intensity projection). Multiple focal sites of increased FDG activity in the heart, lungs, pleura, liver, spleen, bones and multiple lymph nodes are evident.
New Chair of Cardiovascular Medicine at Mayo Clinic in Rochester

The Rochester and Midwest Department of Cardiovascular Medicine recently announced the selection of a new chair, Paul A. Friedman, MD. Dr. Friedman succeeds Charanjit S. Rihal, MD, MBA, who led the department for the past 8 years.

Dr. Friedman grew up in Texas and attended the University of Texas at Austin, where he received a Bachelor of Science degree in electrical engineering and a Bachelor of Arts degree in the honors liberal arts program. He then attended medical school at Stanford University in California and subsequently went to the University of Washington in Seattle for an internship in internal medicine. Following that he returned to Stanford where he completed his internal medicine residency. Dr. Friedman then came to Mayo Clinic in Rochester, Minnesota, where he trained in cardiovascular medicine and electrophysiology. Upon completion of training he joined the staff, working in the Invasive Electrophysiology Laboratory performing catheter ablation and device implantation procedures. He has served as the Director of the Cardiovascular Fellowship Training Program and the Mayo Clinic Cardiac Implantable Device Lab. Dr. Friedman has previously served as Vice Chair for Academic Affairs and Faculty Development and Vice Chair for the Department of Cardiovascular Medicine, and assisted on the team that worked on enterprise-wide department integration.

His primary interest has been non-pharmacologic therapy for the treatment of arrhythmias. He has been energetic in bringing new procedures and techniques into practice, in collaboration with colleagues in cardiovascular medicine and surgery. Dr. Friedman has had a strong interest in innovation with over 40 patents pertaining to medical devices, signal processing, remote monitoring, valvular heart disease, ablation, pacing, defibrillation, epilepsy treatment, and the application of artificial intelligence to medicine. He was named a Minnesota Top Inventor in 2013, and he has been the recipient of multiple NIH grants.

Dr. Friedman says that he is inspired by the core value of the Mayo Clinic, the power of the simple idea that the needs of the patient come first. That concept of service to others and a team-based approach to achieve excellence uniquely permits Mayo Clinic to manage complex medical challenges. It is the core idea that brings people from around the world -- scientists, physicians, and other talented providers, administrators, and health professionals -- to Mayo Clinic campuses to advance the human condition.

RECOGNITION

Joseph A. Dearani, MD, chair of cardiovascular surgery at Mayo Clinic in Rochester, Minnesota, was elected second vice-president of The Society of Thoracic Surgeons at the annual meeting in January 2018. The Society of Thoracic Surgeons represents more than 7,300 surgeons, researchers, and allied health care professionals worldwide who are dedicated to ensuring the highest quality outcomes for surgeries of the heart and lungs and other surgical procedures within the chest.

The Council on Clinical Cardiology has selected Sharonne Hayes, MD, cardiologist at Mayo Clinic in Rochester, Minnesota, as the winner of the 2017 Women in Cardiology Mentoring Award. This award, initiated by the Women in Cardiology Committee, was designed to recognize individuals who have an outstanding record of effectively mentoring women cardiologists and to underscore the importance of mentoring in the professional development of women.
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August 25-30, 2018

Interventional Cardiology Board Review
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Challenges in Clinical Cardiology: A Case-Based Update
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Advanced Ablation Course
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October 24-27, 2018

Coronary Artery Disease: Case-Based Learning
Dana Point, CA
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Echo on Marco Island: Case-Based Approach
Marco Island, FL
December 17-20, 2018

Cardiology Update at Puerto Vallarta: A Focus on Prevention
Puerto Vallarta, Mexico
January 7-11, 2019

Arrhythmias & the Heart: A Cardiovascular Update
Maui, HI
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Hawaii Heart: Echocardiography & Multimodality Imaging Case-Based Clinical Decision Making
Big Island, HI
February 4-8, 2019

Cardiovascular Conference at Snowbird
Snowbird, UT
February 6-9, 2019

Updates in Cardio-Oncology: Challenges and New Frontiers
Scottsdale, AZ
February 7-9, 2019

Cardiology at Cancun: Topics in Clinical Cardiology
Cancun, Mexico
February 25-March 1, 2019

Echocardiographic Workshop on 2-D and Doppler Echocardiography at Vail
Vail, CO
March 3-7, 2019

Heart Failure Management for NP’s, PA’s and Primary Care Providers
Lake Buena Vista, FL
March 21-23, 2019

Mayo Clinic Vascular Symposium
Jacksonville, FL
March 28-30, 2019