S-LBCT01
Late-Breaking Clinical Trials
Session I
Thursday, May 9, 2019
8:00 - 9:30 a.m.

CHAIRS:
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S-LBCT01-01
TRANSCUTANEOUS ELECTRICAL VAGUS NERVE STIMULATION TO SUPPRESS ATRIAL FIBRILLATION (TREAT AF): A RANDOMIZED CLINICAL TRIAL
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Introduction: Low-level transcutaneous electrical stimulation of the auricular branch of the vagus nerve at the tragus (LLTS) acutely suppresses atrial fibrillation (AF) in humans, but the chronic effects remain unknown.

Methods: We conducted a sham-controlled, double-blind, randomized clinical trial to examine the effect of chronic LLTS on AF burden in 53 patients with paroxysmal AF over a 6-month period. LLTS (20Hz, 1mA below the discomfort threshold) was delivered using an ear clip attached to either the tragus (active; n=26) or the ear lobe (sham; n=27) for 1 hour daily over 6 months by the patients themselves after individual training. AF burden over 2-week periods was assessed by noninvasive continuous ECG monitoring at baseline, 3 and 6 months. Heart rate variability (HRV) based on 5 min ECG and serum cytokines were measured at the respective time points. A Generalized Estimating Equations modeling approach was used to compare the outcomes over time between the 2 arms, after adjusting for the respective baseline values.

Applications: Baseline characteristics were similar between the 2 arms (active vs. sham: mean age 65.2±14.5 vs. 68.0±10.0, female 54% vs. 56%, mean CHADS2-VASc score 2.9±2.1 vs. 3.0±1.4). During follow up, 3 patients (2 sham, 1 active) died of noncardiac causes, 1 patient (active) was lost to follow up and 2 patients (both sham) withdrew consent. Adherence to the stimulation protocol (<5 sessions lost per month), was 75% in the active and 83% in the sham arm (p>0.05). At 6 months, the median AF burden was reduced by 85% in the active compared to the sham arm (ratio of medians: 0.15, 95% CI: 0.03 to 0.65, p=0.011; Figure). After combining across the 3- and 6-month time points, the median AF burden was reduced by 75% in the active compared to the sham arm (ratio of medians: 0.25, 95% CI: 0.08 to 0.77, p=0.016). Frequency domain indices of HRV were significantly altered with active vs. sham stimulation (p<0.01). No device-related side effects were observed. Serum cytokine analysis is currently underway.

Next Steps/Future: Our results support the emerging paradigm of noninvasive neuromodulation to treat AF. Further studies to optimize patient selection and maximize efficacy are warranted.

S-LBCT01-02
PROSPECTIVE RANDOMIZED COMPARISON OF ROTOR ABLATION VS CONVENTIONAL ABLATION FOR TREATMENT OF PERSISTENT ATRIAL FIBRILLATION - THE REAFFIRM TRIAL
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Introduction: Catheter ablation is the cornerstone of therapy for drug refractory symptomatic persistent atrial fibrillation (PersAF). The exact pathophysiology of how pulmonary vein (PV) triggers initiate and/or maintain episodes of AF has been elusive. Previous work has shown higher acute and long-term efficacy with the addition of Focal Impulse and Rotor Modulated (FIRM)-guided ablation in AF patients.

Methods: REAFFIRM (NCT02274857) is the first prospective, multicenter, randomized, controlled trial comparing conventional pulmonary vein isolation (PVI) to FIRM-guided ablation followed by PVI in PersAF patients. The intention was to compare PVI only vs FIRM-guided + PVI only; though other ablation strategies were not prohibited. 375 patients were enrolled and randomized at 18 centers. The Intent to Treat (ITT) population consisted of 350 patients (25 patients with no catheter inserted were excluded), 171 in the FIRM arm and 179 in the conventional arm. Patients were followed for 12 months. Primary effectiveness was defined using dual endpoints: Single procedure freedom from AF/AT recurrence at 3 months or single procedure freedom from AF/AT recurrence from 3-12 months, after the initial ablation procedure.
Applications: A total of 324 patients (165 FIRM, 159 conventional) completed the 12-month follow-up. All baseline parameters were equally distributed except for a small, but significantly (P < 0.01) larger LA diameter in the FIRM arm. Ablation was limited to PVI only in 51% (91/177) of conventional patients and 59% (96/164) of FIRM-guided +PVI patients. Primary effectiveness (ITT population) showed no significant difference between arms. Single procedure freedom of AF/AT recurrence from 3-12 months was 69.3% (115/166) in the FIRM group and 67.5% (110/163) in the conventional group (P = 0.96). There was no significant difference at either the 7-day or 12-month safety endpoints. Ablation procedure time was comparable and the percentage of repeat procedures did not differ significantly. Additional analysis on subgroups will be provided.

Next Steps/Future: This study failed to provide evidence for FIRM+PVI superiority at 3-12 months in PersAF patients. Additional ablation beyond PVI was at physician discretion, not controlled for and represented nearly half of patients in the study. Effectiveness in both arms was higher than historically reported success rates. This improvement may be related to higher operator experience, new technologies and different patient populations. This requires further analysis and may warrant additional clinical trials. Safety and efficacy of catheter ablation in the study proved the excellent performance of catheter ablation in this patient population.

S-LBCT01-03

EVALUATE RENAL ARTERY DENERVATION IN ADDITION TO CATHETER ABLATION TO ELIMINATE ATRIAL FIBRILLATION (ERADICATE-AF) TRIAL

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Introduction: Activation of the sympathetic nervous system plays an important role in the development and perpetuation of atrial fibrillation (AF). Renal artery denervation (RDN) can produce significant sympatholysis and a small randomized clinical trial has demonstrated enhanced efficacy when RDN is added to pulmonary vein isolation (PVI) for patients with AF and hypertension (HTN). The ERADICATE-AF Trial was designed to assess the safety and efficacy of RDN on long-term arrhythmic outcomes in a large single-blind longitudinal randomized clinical trial (NCT 01873352).

Methods: Patients with a history of HTN (defined as SBP ≥ 130 and/or DBP ≥ 80 mmHg) despite ≥ 1 anti-hypertensive medication, and paroxysmal (P) AF and plans for a guide-line-supported catheter ablation, were eligible. Subjects were randomized 1:1 to PVI alone or PVI+RDN at 5 centers and were blinded to treatment assignment. Complete PVI was performed in all patients, and RDN by RF delivery via approved catheters within each renal artery. The primary study endpoint was antiarrhythmic drug freedom from AF recurrence at 12 months (not including a 3 month blanking period). A sample size of 300 was calculated to provide 80% power to detect a relative 40% decrease in the one-year incidence of AF in patients treated with PVI+RDN compared to PVI alone.

Applications: The target sample size of randomized patients was met in March 2019: age 60.2 ± 6.4 years, 40% female; baseline BP 150.2±8.7/89.8±8.9 mm Hg. Patients were well matched between groups. Periprocedural complications occurred in 13 (4.4%), not different between groups; all resolved prior to discharge. At the end of 12 months, the PVI+RDN group had significantly greater freedom of AF than the PVI only group: 71.4% vs 57.8% (HR = 0.61 [95%CI = 0.41-0.90], p = 0.011, Figure).

Next Steps/Future: RDN was safe when employed with PVI to patients with PAF and HTN, and significantly increased the likelihood of freedom from AF in this single-blind randomized clinical trial. Additional prespecified secondary endpoints, including BP control, will be analyzed in the future. Consideration of adjunctive RDN is reasonable to increase the success rate of AF ablation in patients with HTN.

S-LBCT01-04

BAROREFLEX ACTIVATION THERAPY IN PATIENTS WITH HEART FAILURE WITH A REDUCED EJECTION FRACTION

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Introduction: Heart failure with a reduced ejection fraction (HFrEF) is associated with poor life expectancy, frequent
heart failure hospitalizations, lower quality of life, and substantial limitation in exercise capacity. We hypothesized that HF symptoms will improve by increasing parasympathetic and decreasing sympathetic activity by using Baroreflex Activation Therapy (BAT).

**Methods:** A novel prospective two-phase randomized controlled trial (BeAT-HF; ClinicalTrials.gov Identifier: NCT02627196), part of the FDA Breakthrough Devices Program, randomized subjects with an unmet clinical need to ongoing guideline-directed medical and device therapy (GDMT) or ongoing GDMT plus BAT. Patients with New York Heart Association (NYHA) Class III HFrEF (≤35%) despite being treated with the appropriate heart failure GDMT and not eligible for cardiac resynchronization therapy were enrolled. The safety endpoint was device- or procedure-related major adverse neurological and cardiovascular events (MANCE), while the first phase effectiveness endpoints included six-month changes in 6-min hall walk distance (6MHWD), Minnesota Living with Heart Failure Quality of Life (MLWHF QoL) score, and N-terminal pro-brain natriuretic peptide (NT-proBNP). Data collection also includes recurrent heart failure hospitalizations and cardiovascular mortality for the extended outcome (second) phase of the study (ongoing).

**Applications:** A total of 408 subjects were randomized, 209 to GDMT and 199 to GDMT + BAT, with 184 successfully implanted with the BAT device. Patient characteristics are shown in Table 1. The following data will be provided in the Late Breaking Clinical trial presentation: MANCE and changes in 6MHWD, MLWHF QoL score, and NT-proBNP levels.

**Next Steps/Future:** BeAT-HF will determine whether BAT is safe and improves symptoms in GDMT treated NYHA Class III patients with HFrEF.

### Table 1: Baseline Characteristics (Mean ± SD or %)

| Age (years) | 63 ± 11 | MLWHF QoL | 53 ± 25 |
| Male / Female | 80% / 20% | eGFR (mL/min/1.73m²) | 61 ± 23 |
| White / Black or African American | 72% / 18% | History of Atrial Fibrillation | 39% |
| BMI (kg/m²) | 30 ± 5 | History of Diabetes | 45% |
| SBP / DBP (mmHg) | 119±18 / 73±11 | HF Hospitalization in past 12 months | 49% |
| HR (bpm) | 75 ± 11 | Beta-Blocker | 95% |
| LVEF (%) | 26 ± 7 | ACE / ARB / ARNI | 83% |
| NT-proBNP (pg/mL) Median (Q1, Q3) | 1058 (594, 2424) | Diuretics | 89% |
| NYHA Class III (%) | 94% | MRA | 41% |
| 6MHWD (m) | 295 ± 72 | ICD | 78% |

**S-LBCT01-05**

**HIS CORRECTIVE PACING OR BIVENTRICULAR PACING FOR CARDIAC RESYNCHRONIZATION IN HEART FAILURE: A RANDOMIZED PILOT TRIAL (HIS SYNC)**

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**Introduction:** His pacing has been shown to circumvent proximal left bundle branch block and restore electrical resynchronization. The aim of this pilot trial was to compare His pacing versus biventricular pacing (BiV) as a first-line strategy for cardiac resynchronization therapy (CRT) in patients with heart failure.

**Methods:** The HIS SYNC trial was a prospective, multicenter, single-blinded, randomized, controlled pilot trial with 1:1 allocation to His-CRT versus BiV (NCT02700425). Patients with standard indications for CRT were enrolled at 7 centers. Crossovers were permitted if QRS correction could not be achieved with His CRT or if coronary venous anatomy was unfavorable. The primary endpoints were improvement in QRS duration, LVEF, and freedom from cardiovascular hospitalization or mortality. Echocardiographic response was defined as a >5% improvement in LVEF.

**Applications:** 41 patients were enrolled over a 2-year period (1 withdrawal, 1 lost to follow-up). 21 patients were randomized to His-CRT and 19 to BiV. No differences in baseline characteristics were observed between groups. The median age was 67.5 yrs (54-75.5 yrs), 38% female, and 45% had NICM, with median LVEF of 28% (24-31%) and median QRS duration of 167 ms (155-180 ms) (88% LBBB). The rate of crossover was 48% in the His-CRT arm and 26% in the BiV arm. By intention to treat analysis, a significant reduction in QRS duration was observed with His-CRT (median 167 ms to 140 ms; p=0.001), but not with BiV (162 ms to 153 ms; p=0.13). The median improvement in EF was 9.1% (3.8-14.4%) with His-CRT vs. 5.2% (1.5-11.3%) with BiV (p=0.33) at 6 months, with higher rates of echocardiographic response (67% vs 53%, p=0.40). No differences were seen in freedom from cardiovascular hospitalization (n=5) and mortality (n=1) with low event rates.

**Next Steps/Future:** His corrective pacing was effective as an initial strategy for CRT with a significant reduction in QRS duration. Improvement in EF with His-CRT was greater than with BiV, but the difference was not statistically significant in this pilot study with high crossover rates. Larger prospective studies are justifiable to test for a smaller difference in effect size between CRT modalities.