B-LBCT03
Late-Breaking Clinical Trials Updates

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B-LBCT03-01

ORAL CONTRACEPTIVE USE AND THE RISK OF CARDIAC EVENTS IN WOMEN WITH CONGENITAL LONG QT SYNDROME

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Introduction: Women with congenital long-QT syndrome (LQTS) experience increased risk of cardiac events (CE) after the onset of adolescence, possibly due to effects of estrogen and progesterone on cardiac potassium channels. Use of oral contraceptives (OC) may modulate those effects. However, there are no data on the clinical effect of OC use by formulation type in LQTS.

Methods: Beginning in 2010, information on OC use, pregnancy and menopause were obtained from all women enrolled in the Rochester LQTS Registry for a female-specific study. Follow up is reported through March 2021. Type of OC was categorized as Progestin-only, Estrogen-only or Combined (Estrogen/Progestin). Andersen-Gill multivariate modeling was employed to evaluate the association of time-dependent OC use with the burden of CE (total number of syncope, aborted cardiac arrest, and LQTS-related sudden cardiac death events) from age 15 through 40 years. Findings were adjusted for genotype, QTc duration, and time-dependent beta-blocker therapy.

Applications: We report data on 1656 LQTS women (39% LQT1, 35% LQT2, 14% LQT3), of whom 333 (20%) were treated with an OC at any time during follow-up. During a cumulative follow-up of 35,797 years, there were a total of 1977 CE. Multivariate analysis showed that Progestin-only OC was associated with a pronounced 2.6-fold increased risk of CE among women who did not receive beta-blocker therapy (HR=2.63 [95% CI 1.19-5.78]; p=0.01), while beta-blocker therapy was highly protective during progestin-only OC treatment (HR=0.22; [95% CI 0.07-0.74]; p=0.01); p-value for beta-blocker-by-OC interaction = 0.01. Estrogen-only OC and Combined OC were not associated with increased CE rates compared to no-OC regardless of beta-blocker treatment (Figure).

Next Steps/Future: To our knowledge, this is the first study to assess the association of OC by formulation type on the risk of CE in congenital LQTS. Our findings suggest that progestin-only OC should not be administered in LQTS women without concomitant beta-blocker therapy. Future studies should focus on sex-hormones for the therapeutic modulation of arrhythmic risk in congenital and drug-induced LQTS.

B-LBCT03-02

EARLY RHYTHM CONTROL THERAPY IN PATIENTS WITH ATRIAL FIBRILLATION AND HEART FAILURE

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Introduction: While a growing body of evidence suggests that rhythm control therapy might be beneficial in patients with atrial fibrillation (AF) and heart failure (HF), further evidence illustrating these effects in different HF subgroups is needed. We studied whether the clinical benefit of early rhythm control (ERC) observed in the EAST - AFNET 4 trial is present in patients with HF.

Methods: We analysed the effect of ERC in patients with HF (defined as NYHA class II-III or left ventricular ejection fraction [LVEF] <50%) enrolled into the EAST - AFNET 4 trial. Applications: This analysis includes 798 patients with HF, 442 patients had HF with preserved LVEF (LVEF≥50%; mean LVEF 61%± 6.3), 132 HF with reduced LVEF (LVEF<40%; mean LVEF 31% ± 5.5), and 211 HF with mid-range LVEF (LVEF40-49%; mean LVEF 44% ± 2.9). Over the 5.1-year median follow-up, the composite primary outcome of cardiovascular death, stroke or hospitalization for worsening of HF or for acute coronary syndrome occurred less frequently in HF-patients randomized to ERC (94 patients with events/396 patients, 5.7/100 patient-years) than in HF-patients randomized to usual care (UC; 130 patients with...
events/402 patients, 7.9/100 patient-years, hazard ratio 0.74 [0.56-0.97], p=0.029; figure 1). ERC was safe in patients with HF. The primary safety outcome (death, stroke, or serious adverse events of rhythm control therapy) occurred in 71/396 (17.9%) HF-patients randomized to ERC and in 87/402 (21.6%) HF-patients randomized to UC (p=0.188). LV function improved in both groups (LVEF change at two years ERC 5.3%±11.6, UC 4.9%±11.6, p=0.43). ERC also improved an outcome of death or hospitalization for worsening of HF modeled after the CASTLE-AF trial (ERC 91 events, UC 123 events, p=0.036). Interactions of the intervention with baseline LVEF and AF symptoms and the impact of ERC on CABANA-like outcomes will be reported.

Next Steps/Future: Early rhythm control based on either antiarrhythmic drug therapy or catheter ablation should be offered to all patients with AF and symptoms of HF or reduced LVEF.

B-LBCT03-03

ECONOMIC OUTCOMES OF ABLATION VERSUS DRUG THERAPY IN CABANA

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Introduction: The Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial found that ablation did not significantly reduce the primary endpoint of death, disabling stroke, serious bleeding or cardiac arrest compared to drug therapy with standard rhythm and/or rate control drugs, but found clinically significant improvements in quality of life, freedom from AF recurrence and decreased AF burden. In this pre-specified economic analysis, we will report costs and cost-effectiveness of catheter ablation compared to drug therapy by using patient-level data collected prospectively during the trial.

Methods: Resource use data (including hospitalizations, procedures and emergency department visits) were reported on the case report form for all enrolled patients (n=2204). For US patients with billing data (n=1171), hospital-based costs were estimated from charges using department-level cost-to-charge ratios. Encounters without bills were valued using cost weights from generalized linear models developed with collected billing data. Resource use and costs (in 2018 USD) were estimated using inverse probability weighting to account for variable trial follow-up (median follow up 48.5 months). Extrapolated life expectancies were estimated using age-based survival models developed from the overall CABANA cohort. Quality-of-life adjustment factors were based on utilities directly measured during the trial. Cost-effectiveness was evaluated from a US health care perspective over a lifetime horizon; incremental cost-effectiveness ratios were calculated as the difference in mean lifetime cost divided by the difference in mean quality-adjusted life expectancy between intention-to-treat groups.

Applications: Patients assigned to drug therapy accrued an average of 12.5 life years (LYs) and 10.7 quality-adjusted life years (QALYs) for a total cumulative cost of $96,071 (95% CI 84,233 - 107,734). There was a significantly higher cost with catheter ablation compared to drug therapy in the first 3 months of follow up (attributed to the initial cost of ablation: mean $26,656 ± SD 9123); however, there were no significant differences in costs beyond 12 months. Consistent with the main clinical results, the age-based survival models did not find substantial LY gains (+0.08 LYs) in the ablation group relative to drug therapy. However, after accounting for quality-of-life improvements, the estimated incremental cost per QALY gained with catheter ablation fell within conventionally accepted thresholds for value, and ablation appeared to be economically attractive.

Next Steps/Future: The full cost-effectiveness results will be reported, including the estimated incremental cost effectiveness ratio for the overall trial and key patient subgroups, such as those with heart failure.

B-LBCT03-04

SAFETY AND EFFECTIVENESS OF MULTI-SITE PACING IN INITIAL NON-RESPONDERS TO CONVENTIONAL CARDIAC RESYNCHRONIZATION THERAPY

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Introduction: Previous large, randomized cardiac resynchronization therapy (CRT) trials have failed to demonstrate superiority of multi-site over single-site left ventricular (LV) pacing. Yet, multi-site pacing (MSP) has shown promise in increasing CRT response rates in targeted patients. The SMART MSP study was designed to evaluate the safety and effectiveness of MSP in non-responders to conventional CRT.

Methods: Subjects were enrolled after de novo Resonate™ CRT-defibrillator and quadripolar LV lead implantation and programmed to conventional CRT. After 6 months, subjects were evaluated via Clinical Composite Score (CCS). Responders (CCS Improved) exited the study. Non-Responders (CCS Unchanged or Worsened) had MSP enabled and were reevaluated at 12 months. Adverse events were assessed by investigators for relationship to MSP. The primary safety and effectiveness endpoints were MSP-related complication-free rate compared to a predefined goal of...
90% and 12-month CRT conversion rate (CCS Improved) compared to a predefined goal of 5%.

**Applications:** Data are presented in Table 1. Of 528 patients who completed the 6 month CCS assessment, 74.1% (391/528) responded to conventional CRT at 6 months. At 12 months, 78 patients met effectiveness endpoint analysis requirements and demonstrated a response rate to MSP of 51.3% (40/78). The MSP-related complication-free rate was 99%. Mean battery longevity projections at 12 months was 8.1±2.2 years in MSP patients. Stimulation from the most proximal LV pacing electrode (E4) was associated with greater CRT response to MSP (64% vs 38%, p=0.029).

**Next Steps/Future:** When used in non-responders to conventional CRT, MSP is safe and effective, exceeding pre-determined performance goals, and has minimal impact on battery longevity in Resonate™ CRT-D devices. Future effort should focus on examining (1) sub-populations that may further benefit from MSP, (2) optimal programming and vector selection for MSP, and (3) the impact of early MSP activation in CRT recipients.

<table>
<thead>
<tr>
<th>SMART MSP Study Outcomes</th>
<th>All (N=528)</th>
<th>MSP (N=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MSP-Related Complication-Free Rate</strong></td>
<td>N/A *</td>
<td>99% **</td>
</tr>
<tr>
<td>Clinical Composite Score (Improved)</td>
<td>391 (74.1%)</td>
<td>40 (51.3%)</td>
</tr>
<tr>
<td>Clinical Composite Score (Unchanged)</td>
<td>71 (13.5%)</td>
<td>21 (26.9%)</td>
</tr>
<tr>
<td>Clinical Composite Score (Worsened)</td>
<td>66 (12.5%)</td>
<td>17 (21.8%)</td>
</tr>
<tr>
<td>Estimated Remaining Battery Life (years) ***</td>
<td>8.9±2.1</td>
<td>8.1±2.2</td>
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<tr>
<td>Responders by LV Electrode (Proximal, E4)</td>
<td>50/67 (74.6%)</td>
<td>20/31 (64.5%)</td>
</tr>
<tr>
<td>Responders by LV Electrode (Distal, E1-E3)</td>
<td>341/461 (74.0%)</td>
<td>17/44 (38.6%)</td>
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</tbody>
</table>

*MSP not enabled; **MSP enabled in 102 subjects; ***Battery estimates are based on 82 subjects