Optimisation of CRT using device algorithms - when should we use them and how effective are they?

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Cardiac Resynchronisation Therapy (CRT)

- Reduces heart failure (HF) mortality by 40% on top of optimal medical therapy
- Decreases HF-related hospitalisations by 52%
One-third of patients do not experience the full benefit of CRT\textsuperscript{1-6}

- MIRACLE\textsuperscript{1}: 67%
- MIRACLE ICD\textsuperscript{2}: 52%
- MIRACLE II ICD\textsuperscript{3}: 58%
- InSync III Marquis\textsuperscript{4™}: 67%
- PROSPECT\textsuperscript{5}: 69%
- FREEDOM\textsuperscript{6}: 67%


*AV optimized only
There are many drivers for CRT non responders

- Suboptimal AV Timing
- Arrhythmia
- Anemia
- Suboptimal LV Lead Position
- < 90% Biventricular Pacing
- Suboptimal Medical Therapy
- Persistent Mechanical Dyssynchrony
- Underlying Narrow QRS
- Compliance Issues
- Primary RV Dysfunction

Percentage of Nonresponder Patients with These Findings

Strategies to Improve CRT response

- Improve Patient Selection
- Device based optimisation
Multiple single centre studies have reported that echocardiographic parameters may better predict response. However, a randomised multicentre trial (Prospect) failed to show any viable echocardiographic parameter to predict response. Why?

### Table 1. Summary of Echocardiographic Predictors of Response to CRT

<table>
<thead>
<tr>
<th>Echocardiographic Predictor</th>
<th>Description of Method</th>
<th>Echocardiography Method</th>
<th>Cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPWMD$^{10}$</td>
<td>Septal-posterior wall motion delay; M mode measured by parasternal short-axis view</td>
<td>M mode</td>
<td>≥130 ms</td>
</tr>
<tr>
<td>IVMD$^{14}$</td>
<td>Interventricular mechanical delay defined as the difference between left and right ventricular preejection intervals</td>
<td>Pulsed Doppler</td>
<td>≥40 ms</td>
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<tr>
<td>LVFT/RR$^{14}$</td>
<td>Left ventricular filling time (LVFT) in relation to cardiac cycle length</td>
<td>Pulsed Doppler</td>
<td>≤40%</td>
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</table>

### Table 3. Interobserver and Intraoperator Variability Summary

<table>
<thead>
<tr>
<th>Echocardiographic Measure</th>
<th>Intraobserver CV, %</th>
<th>Interobserver CV, %</th>
<th>Interobserver $\kappa$ Coefficient*</th>
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<tbody>
<tr>
<td>LVESV</td>
<td>3.8</td>
<td>14.5</td>
<td>NA</td>
</tr>
<tr>
<td>LPEI</td>
<td>3.7</td>
<td>6.5</td>
<td>0.67</td>
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<tr>
<td>SPWMD</td>
<td>24.3</td>
<td>72.1</td>
<td>0.35</td>
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<tr>
<td>Ts-SD</td>
<td>11.4</td>
<td>33.7</td>
<td>0.15</td>
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<tr>
<td>Ts-peak (basal)</td>
<td>15.8</td>
<td>31.9</td>
<td>0.25</td>
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</table>

LPEI indicates left ventricular preejection interval.

*Segments at basal level
Strategies to Improve CRT response

- Improve Patient Selection
- Device based optimisation
Device based optimisation

- More recently focus has been shifting to device based optimisation

- Potential benefits over echo:
  - Simpler to perform
  - No inter-observer variability
  - Can optimise more frequently
Device Companies

- Biotronik: AV opt*, Multi Pole Pacing
- Boston Scientific: Smart Delay*
- Livanova: SonR, Multi Pole Pacing
- Medtronic: Adaptive CRT, Effective CRT, Multi Pole Pacing
- Abbott: Quick Opt*, Multi Pole Pacing

* Clinic visit optimisation only
Boston Scientific-Smart Delay

- Smart Delay provides both paced and sensed recommendations by accounting for three inputs:
- Optimised quarterly at clinic visits

Primary Endpoint - LVESV

Primary Results From the SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy (SMART-AV) Trial

A Randomized Trial Comparing Empirical, Echocardiography-Guided, and Algorithmic AV Delay Programming in Cardiac Resynchronization Therapy

Kenneth A. Ellenbogen, MD, Michael R. Gold, MD, PhD, Timothy E. Meyer, PhD, Ignacio Fernandez-Luizano, MD, Seshar Nidala, MD, Alan D. Wagner, MD, Brian Landis, MD, Jagmeet P. Singh, MD, PhD, Francis G. Aptaker, MD, PhD, Jennifer E. Van Eijk, PhD, Jeffrey Whitfield, MD, Stephan Weinert, MD, Manfred Brog, MD, Joshua Kaplan, MD, Kenneth M. Strum, MD

Background—Onset variables that may influence cardiac resynchronization therapy response to the programmed atrioventricular (AV) delay. The SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy (SMART-AV) Trial prospectively randomized patients to a fixed empirical AV delay (100 milliseconds), echocardiographically optimised AV delay, or AV delay optimized with SmartDelay, an algorithm-based algorithm.

Methods and Results—A total of 1014 patients (66% men; mean age, 65.7 years; mean left ventricular ejection fraction, 29.7%) who met enrollment criteria received a cardiac resynchronization therapy device, and 550 patients were randomized to a 1:1 ratio. All patients were programmed (DDDR-DD or DDDR-D) and evaluated after implantation and 3 and 6 months later. The primary end point was left ventricular end-systolic volume. Secondary end points included New York Heart Association class, quality of life score, 6-minute walk distance, left ventricular end-diastolic volume, and left ventricular ejection fraction. The median (IQR) days for change in left ventricular end-systolic volume at 6 months for the SmartDelay, echocardiography, and fixed arms were: 22 (6-45) and 64 (39-109) and 59 (40-109) and 64 (59-109) and 64 (59-109) and 13 (6.5-22), respectively. No significant improvement in left ventricular end-systolic volume at 6 months was observed between the SmartDelay and echocardiography arms (P = 0.52) or the SmartDelay and fixed arms (P = 0.68). Secondary end points, including structural (left ventricular end-diastolic volume and left ventricular ejection fraction) and functional (cardiac and functional status, quality of life, and New York Heart Association classification) measures, were not significantly different between arms.

Conclusion—These results suggest that a final AV delay of 120 milliseconds. These results have shown that the SmartDelay determined AV optimization techniques assessed in this trial is not warranted. However, future data do not exclude possible utility in selected patients who do not respond to cardiac resynchronization therapy.

Clinical Trial Registration—EURE: http://eure.clinicaltrials.gov. Unique identifier: NCT00675904

Key Words: clinical trials, randomized; echocardiography; electrophysiology; heart failure; implantable cardioverter-defibrillators
Abbott- QuickOpt

QuickOpt optimisation uses proprietary formula to suggest optimal AV an VV delays

- Performed at clinic visits
- Randomised multicentre trial
- 1647 patients
- 1:1 randomisation to QuickOpt vs Standard care

<table>
<thead>
<tr>
<th>Intention-to-Treat</th>
<th>QuickOpt Optimization Treatment group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure Clinical Composite Score</td>
<td>n (%)</td>
<td>n (%)</td>
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<tr>
<td>Improved</td>
<td>551 (67.52%)</td>
<td>559 (67.51%)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>76 (9.31%)</td>
<td>86 (10.39%)</td>
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<tr>
<td>Worsened</td>
<td>189 (23.16%)</td>
<td>183 (22.10%)</td>
</tr>
<tr>
<td>Total</td>
<td>816 (100%)</td>
<td>828 (100%)</td>
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</tbody>
</table>

p-value: 0.50
Medtronic AdaptivCRT

- Main goals are:
  - Achieve LV only pacing in patients with normal AV conduction
  - Achieve dynamic AV conduction to simulate normal AV function
  - To continually optimise AV and VV intervals to improve CRT response
- P and QRS width measurements occur every 16 hr
- AV Interval Measurements occur every minute
Adaptive CRT Trial

- 522 patients, prospective, multi-center, randomised double-blinded study
- aCRT vs Echo optimised CRT
Comparison to Echo optimisation

- Compared echo based optimisation (1 and 6 months) versus adaptive CRT.
Higher percentage Synchronized LV Pacing in the aCRT Arm had a lower rate of death and HF hospitalizations.

AdaptivCRT Arm Only
Time to Heart Failure Hospitalization or All-Cause Death
(With Number at Risk)

Logrank
p = 0.003

Improved clinical outcomes for patients with Normal AV Conduction

% Patient Improvement in Packer Clinical Composite Score

Normal AV

AdaptivCRT with Normal AV intervals
Blue
Control with Normal AV intervals
Green

p = 0.041

81% 69%

% Improved Clinical Composite Score

0% 10% 20% 30% 40% 50% 60% 70% 80% 90%

MIRACLE
Miracle ICD
Miracle II ICD
InSync III Marquis
Prospect
Freedom

67% 52% 58% 67% 69% 67%
A high percentage of BiV pacing is associated with improved CRT response.\textsuperscript{1}

However, the presence of a pacing stimulus does not imply full capture.\textsuperscript{2,3}

Traditional pacing counters only report the presence of a pacing stimulus, potentially leading to over-reporting of effective pacing.\textsuperscript{2,3}

\textsuperscript{1} Hayes DL, et al. *Heart Rhythm*. 2011;8:1469-1475.
EffectivCRT™ Diagnostic
AUTOMATIC ASSESSMENT OF EFFECTIVE PACING

Capture principle: Effective capture of tissue generates a negative deflection on the EGM measured from the pacing cathode (LV) to an indifferent electrode (RV coil)

- 98% sensitivity in determination of effective pacing versus surface ECG\(^1\)

Clinical Evidence
OLÉ Study Results

57 CRT patients post-implant with standard-of-care device programming; Ambulatory device data collected by Holters over 24 hours.

- %V pacing (94.8 ± 8%) was significantly greater than % EffectivCRT pacing (87.5 ± 23%, p<0.001)
- In 18% of patients, % V. Pacing was at least 3% greater than % EffectivCRT

3/57 patients had virtually NO effective pacing, whereas the %V pacing was >90%

1 Hernandez-Madrid A, et al. Device Pacing Diagnostics Overestimate Effective Cardiac Resynchronization Therapy Pacing Results of the hOLter for Efficacy analysis of Cardiac Resynchronization Therapy Study (OLE CRT Study).
EffectivCRT during AF algorithm

- EffectiveCRT during AF algorithm:
  - Improves percentage of time patients receive effective CRT by changing the pacing rate without substantially increasing the average heart rate
    - Increase of pacing rate if too much ineffective paced or sensed events
    - Decrease of pacing rate if sufficient effective pacing detected
  - Maximum heart rate is programmable

![Graph showing Heart Rate (bpm) during AF with and without EffectivCRT during AF]
EffectivCRT™ during AF Increases Effective CRT delivery by upto 15%\(^1\)

Prospective, randomized, multicenter crossover study to demonstrate the ability of EffectivCRT™ During AF to increase effective pacing (N = 54)

Results:

- EffectivCRT™ During AF increased effective pacing, from 81% to 88% (p < 0.001).
- Heart rate increased by 3 beats per minute, from 77 to 80 BPM (p < 0.001).
- Patients with baseline < 80% paced received the greatest benefit.

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\(^1\) Mittal S, et al. A Novel Algorithm Increases Effective Left Ventricular Pacing During Atrial Fibrillation in Patients Undergoing Cardiac Resynchronization Therapy: Primary Results of the Randomized CRTee Trial. Presented at ESC Congress 2016.
Livanova SonR

- Uses a hemodynamic sensor embedded in the atrial sense / pace lead, detects cardiac muscle vibrations that reflect the first heart sound

- The amplitude of the first heart sound reflects changes in contractility (LVdP/dtmax)

- Optimises VV & AV delays weekly
RESPOND CRT study design

**DESIGN**

RESPOND-CRT is an International, Multicenter, Randomised (2:1), Prospective, Double-blinded trial

**PATIENTS**

- LVEF ≤ 35%
- QRS ≥ 120 ms in LBBB or QRS ≥ 150 ms in non-LBBB
- NYHA III or IV
- Without permanent AF

**ENROLLMENT**

- 125 sites in Europe, USA, Australia
- Jan 2012 – Oct 2014
- Long term follow up ongoing (2 years)
Response to CRT is based on a hierarchical set of clinical criteria:

1. Death: Yes → RESPONDER
   No → HF Event
2. HF Event: Yes → RESPONDER
   No → NYHA (blinded)
3. NYHA (blinded): Worsened → WORSENED
   Improved → Equal
   Equal → RESPONDER
4. NYHA (blinded): Improved → RESPONDER
   Worsened → WORSENED
5. QoL (blinded): Worsened → WORSENED
   Improved → Equal
   Equal → RESPONDER
   Improved → RESPONDER
   Worsened → WORSENED

The decision tree includes blinded NYHA and QoL assessments.
Primary efficacy end points at 12 months

- **Improved**: 75.0% (SonR n=649), 70.4% (Echo AV & VV n=318)
- **Stable**: 4.0% (SonR), 4.4% (Echo AV & VV)
- **Worsened**: 21.0% (SonR), 25.2% (Echo AV & VV)
### 12 month Results

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>SonR (N=649)</th>
<th>Echo AV &amp; VV (N=318)</th>
<th>P value</th>
<th>Echo Better</th>
<th>SonR Better</th>
<th>Odds Ratio</th>
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<tbody>
<tr>
<td>Overall</td>
<td>75.0%</td>
<td>70.4%</td>
<td></td>
<td></td>
<td></td>
<td>1.26</td>
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<tr>
<td>&lt;68.5 years</td>
<td>72.6%</td>
<td>68.1%</td>
<td>0.99</td>
<td></td>
<td></td>
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<tr>
<td>≥68.5 years</td>
<td>77.3%</td>
<td>73.2%</td>
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<td>1.25</td>
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<td>Gender</td>
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<tr>
<td>Male</td>
<td>71.6%</td>
<td>68.6%</td>
<td>0.23</td>
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<td>1.15</td>
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<td>&lt;30 kg/m²</td>
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<td>0.74</td>
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</table>
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<td>1.26</td>
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<tr>
<td>Age</td>
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<td>&lt;68.5 years</td>
<td>73.8%</td>
<td>69.8%</td>
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<td>68.7%</td>
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<td>1.16</td>
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<td>74.7%</td>
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<tr>
<td>LBBB</td>
<td>74.9%</td>
<td>69.4%</td>
<td>0.19</td>
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<td>0.74</td>
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<tr>
<td>QRS duration</td>
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<tr>
<td>&lt;150 ms</td>
<td>66.1%</td>
<td>53.2%</td>
<td>0.13</td>
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<tr>
<td>≥150 ms</td>
<td>75.5%</td>
<td>74.9%</td>
<td></td>
<td>1.03</td>
</tr>
<tr>
<td>PR interval</td>
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<td></td>
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<tr>
<td>&lt;200 ms</td>
<td>75.8%</td>
<td>72.7%</td>
<td>0.90</td>
<td>1.17</td>
</tr>
<tr>
<td>&gt;200 ms</td>
<td>69.2%</td>
<td>66.7%</td>
<td></td>
<td>1.13</td>
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<tr>
<td>Cardiomyopathy</td>
<td></td>
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<tr>
<td>Ischemic</td>
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<td>66.9%</td>
<td>0.17</td>
<td>0.94</td>
</tr>
<tr>
<td>Non-Ischemic</td>
<td>78.4%</td>
<td>71.6%</td>
<td></td>
<td>1.44</td>
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<td>History of AF</td>
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</tr>
<tr>
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<td>64.1%</td>
<td>48.1%</td>
<td>0.11</td>
<td>1.93</td>
</tr>
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<td>No</td>
<td>74.2%</td>
<td>73.5%</td>
<td></td>
<td>1.04</td>
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<td>Renal dysfunction</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>60.3%</td>
<td>43.0%</td>
<td>0.02</td>
<td>2.01</td>
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<td>No</td>
<td>76.6%</td>
<td>78.1%</td>
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<td>65.9%</td>
<td>0.98</td>
<td>1.18</td>
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<tr>
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<td>74.8%</td>
<td>71.7%</td>
<td></td>
<td>1.17</td>
</tr>
<tr>
<td>Smoker</td>
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<tr>
<td>Yes</td>
<td>72.7%</td>
<td>73.5%</td>
<td>0.63</td>
<td>0.96</td>
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<td>No</td>
<td>72.9%</td>
<td>68.8%</td>
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<td>1.22</td>
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<td>Beta Blocker</td>
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<td>69.4%</td>
<td>0.38</td>
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<td>62.7%</td>
<td>68.0%</td>
<td></td>
<td>0.79</td>
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</table>
Aim: assess the benefit of SonR-based CRT optimization in patients with AF history (n=153), RD (GFR<60mL/min/m², n=165) and LBBB QRS<150ms (n=238)

Endpoints:

- Clinical response was defined as the percentage of patients alive, without heart failure (HF)-related events at 18 months, and with an improvement in NYHA class or quality-of-life.

- LV remodeling response (and super response): defined as the percentage of patients with DLVESV≥15% (DLVESV≥30%) between baseline and 12 months.

- Hazard ratios of all-cause death or cardiovascular (CV) / heart failure (HF) hospitalization were assessed using adjusted Cox analysis, up to 24 months.
Respond CRT sub study

Clinical response rate in patients subgroups

Significantly higher clinical response with SonR in all subgroups at high risk of non-response
Multi Point Pacing

- Pacing from two LV sites (“Multipoint LV stimulation”) and one RV
  - Capture a larger area
  - Engage areas around scar tissue
  - Improve pattern of depolarisation/repolarisation
  - Improve hemodynamics
  - Improve resynchronisation

- Using MPP does appear to reduce battery life by around 6-12 months
1 Barbieri F et al., Comparison of conventional resynchronization therapy to multipoint pacing using two separate left
Response definition:
ESV reduction ≥ 15% and Alive Status

Conventional Group (N = 21)
- 57% Responders
- 43% Non-responders

MultiPoint™ Pacing Group (N = 21)
- 76% Responders
- 24% Non-responders

19% Higher Absolute Response
44% Relative Reduction in Non-responder
MPP IDE Study

Safety and Efficacy of MultiPoint Pacing in Cardiac Resynchronization Therapy: The MultiPoint Pacing (MPP) IDE Trial

*Gery Tomassoni¹, James Baker II², Raffaele Corbisiero³, Charles Love⁴, David Martin⁵, Robert Sheppard⁶, Seth J. Worley⁷, Niraj Varma⁸, and Imran Niazi⁹ on behalf of the MPP IDE Investigators

¹Lexington Cardiology at Central Baptist, Lexington, KY, USA, ²Saint Thomas Research Institute, Nashville, TN, USA, ³Deborah Heart and Lung, Browns Mills, NJ, USA, ⁴NYU Langone Medical Center, New York, NY, USA, ⁵Lahey Clinic Medical Center - Cardiology, Burlington, MA, USA, ⁶The Heart Institute, St. Petersburg, FL, USA, ⁷Lancaster Heart Foundation, Lancaster, PA, USA, ⁸Cleveland Clinic Foundation, Cleveland, OH, USA, ⁹Aurora Cardiovascular Services, Milwaukee, WI, USA

*Advisor, Speaker, Medical Device Board: SJ Medical, Biosense Webster, Medtronic, Boston Scientific, Biotronics, Siemens, STXS, Topera, Atricure & Pfizer
SJM MPP IDE Study design

Study Detail:

Objective:
- Assess safety and efficacy of MPP technology in heart failure (HF) patients indicated for a CRT-D

Design:
- Prospective, Multi-center, Randomized, Double-blinded non-inferiority trial
- 506 patients, 49 centers
- Responder status assessed at 3 & 9 mo. using Clinical Composite Score (CCS).
- CCS includes: NYHA, Patient Global Assessment (PGA), HF events, and cardiovascular death.

Study enrollment (n=506)

CRT Implants (n=506)
(Trad BiV for 3mths)

Acute Echo Test (VTI)
(MPP ≥ BiV)

Randomization 1:1 (n=381)

- Traditional BiV
  N=180
- MPP
  N=201

Assess Response

Remain on BiV
(n=30)

22 Patients not randomized (PNS, Lead displacement, medically unstable etc)

Assess Response

3mths

9mths

Responder Rate

- < 30 mm Spatial Separation (n=115): 40% Super-responder*, 23% Responder, 37% Non-responder
- ≥ 30 mm Spatial Separation & > 5 ms Timing Delay (n=32): 47% Super-responder*, 22% Responder, 31% Non-responder
- ≥ 30 mm Spatial Separation & 5 ms Timing Delay (n=52): 54% Super-responder*, 33% Responder, 13% Non-responder

Comparison:
- p=0.007
- p=0.817
- p=0.153
Converting Non Responders To responders

- 100% of patients who were non-responders at Randomization were converted to responders when programmed to “Optimal MPP”

- 65% of non-responders randomized to continued Bi-V pacing became responders
Conclusions

- Echo based optimisation has very little evidence base for routine clinical work.
- Device based algorithms are becoming more common and in initial trials do appear to confer some increased benefit.
- Multi point LV pacing may also improve response but does have effect on battery life.
- No head to head data across the different companies.
Thank You..