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 Atrioventricular Delay Programming in Cardiac Resynchronization Therapy

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Background—One variable that may influence cardiac resynchronization therapy response is 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 (120 milliseconds), echocardiographically optimized AV delay, or AV delay optimized with SmartDelay, an electrogram-based algorithm.

Methods and Results—A total of 1014 patients (68% men; mean age, 66 ±11 years; mean left ventricular ejection fraction, 25 ±7%) who met enrollment criteria received a cardiac resynchronization therapy defibrillator, and 980 patients were randomized in a 1:1:1 ratio. All patients were programmed (DDD-60 or DDDR-60) 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 medians (quartiles 1 and 3) for change in left ventricular end-systolic volume at 6 months for the SmartDelay, echocardiography, and fixed arms were −21 mL (−45 and 6 mL), −19 mL (−45 and 6 mL), and −15 mL (−41 and 6 mL), respectively. No difference in 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 =0.66). Secondary end points, including structural (left ventricular end-diastolic volume and left ventricular ejection fraction) and functional (6-minute walk, quality of life, and New York Heart Association classification) measures, were not significantly different between arms.

Conclusions—Neither SmartDelay nor echocardiography was superior to a fixed AV delay of 120 milliseconds. The routine use of AV optimization techniques assessed in this trial is not warranted. However, these data do not exclude possible utility in selected patients who do not respond to cardiac resynchronization therapy.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00677014.

Key Words: clinical trials, randomized ■ echocardiography ■ electrophysiology ■ heart failure ■ implantable cardioverter-defibrillators
In patients with heart failure (HF) with left ventricular dysfunction and prolonged QRS duration, cardiac resynchronization therapy (CRT) with or without an implantable cardioverter-defibrillator reduces HF hospitalizations and prolongs survival compared with optimal medical therapy alone.1,2 Moreover, CRT improves symptoms and quality of life (QOL), increases exercise tolerance, and reduces left ventricular dilatation.3–8 Recent studies also suggest that CRT results in decreased neurohormonal and proinflammatory biomarkers.9–12

Clinical Perspective on p 2

Achieving the optimal outcome from CRT may be dependent on proper programming of the optimal atrioventricular (AV) delay.13,14 Suboptimal AV delay programming can result in as much as a 10% to 15% decline in cardiac output.15,16 However, the large-scale randomized clinical trials establishing the overall efficacy of CRT have differed widely in their approach to AV optimization. In the CONTAK CD trial, there was no AV optimization.6 In contrast, the Cardiac Resynchronization–Heart Failure (CARE-HF) and Multicenter InSync Randomized Clinical Evaluation (MIRACLE) investigators used Doppler echocardiography of transmitral flow to select the optimal AV delay,13,14,17 an approach endorsed by the American Society of Echocardiography.18 In further contrast, the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) investigators used an algorithm based on the intrinsic AV interval and baseline QRS width to determine a predicted optimal programmed sensed AV delay; a modified version of this algorithm known as SmartDelay™ (SD) is available in the current Boston Scientific CRT devices.1,19 The SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy (SMART-AV) study was designed to compare 3 alternative techniques and to assess the hypotheses that systematic AV delay optimization with echocardiography and/or the SD algorithm is superior to a fixed nominal AV delay as demonstrated by improved left ventricular (LV) geometry after 6 months and that programming according to SD is noninferior to using echocardiography-determined AV delay optimization.

Methods

Study Design

Details of the study design have previously been published.20 Briefly, patients who met standard criteria for implantation of a CRT defibrillator and could undergo all testing and follow-up for a minimum of 6 months after implantation were eligible for the SMART-AV Trial. Patients were randomly assigned to 1 of 3 treatment arms at the postimplantation (1 to 14 days after implantation) visit using randomly permuted blocks within each center: AV delay set at 120 milliseconds (Fixed), AV delay programmed with the echocardiography-determined mitral inflow method, aka iterative technique (Echo), or AV delay programmed with the SD algorithm (SD).18 Patients were implanted with a commercially available Boston Scientific CRT defibrillator device with the SD algorithm (models H220, H225, H227, H229, N119, and N118). Any compatible right atrial lead, right ventricular defibrillation lead, and LV lead could be implanted. The devices were programmed at the discretion of the implanting physician to either DDDR or DDDR with a lower rate of 60 bpm, rate hysteresis turned off, dynamic AV delay turned off, and atrial tachycardia response turned on at 170 bpm.

During the enrollment period, indications for CRT defibrillator implantation were New York Heart Association (NYHA) class III or IV despite optimal medical therapy, an LV ejection fraction (LVEF) ≤35%, and QRS duration ≥120 milliseconds. Optimal medical therapy of congestive HF, including diuretics, β-blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, was strongly encouraged, and medication changes during the study were strongly discouraged. Patients who were in complete heart block or were unable to tolerate ventricular pacing at 40 bpm for up to 14 days were excluded.

After randomization, patients underwent echocardiographic imaging at 3 and 6 months after implantation. Patients allocated to the SD arm underwent optimization reprogramming with the SD algorithm at 3 months. All patients were blinded to their treatment assignment, and all underwent the same measurement protocols at each visit. The primary end point was LV end-systolic volume (LVESV). Secondary end points included NYHA class, QOL score as assessed by the Minnesota Living With Heart Failure Questionnaire, 6-minute walk distance, LV end-diastolic volume (LVEDV), and LVEF. The end point measurements were made at the 3- and 6-month visits. The echocardiographic end points were done in blinded fashion by a single core laboratory. Other data collected at these visits included ECG and electrogram measurements, current clinical status, current cardiovascualr medications, echocardiogram with tissue Doppler imaging measurements, AV delay setting, QOL questionnaire, and 6-minute walk test. HF-related adverse events and HF hospitalizations, clinical status changes, development of atrial fibrillation, changes in cardiovascular medications, and other clinical variables were also obtained at all visits (scheduled and unscheduled).

The trial was conducted in accordance with the Helsinki Declaration and the ethics or regulatory committee of each individual institution. All patients gave written informed consent to participate in this trial.

Sample Size and Statistical Analysis

The required sample size was based on the primary end point of the study, change in LVESV at 6 months after CRT. With the use of a clinically meaningful difference and standard deviation of 15 and 60 mL, respectively, between the fixed and optimized groups, a total of 759 patients (253 per group) were required to obtain at least 80% power. The sample size was calculated with a 2-sample t test at a significance level of 5%. For analysis, a sequential ordering of comparisons (gate-keeping) was used to control the type I error. A superiority comparison of the primary end point was run, SD versus Fixed. Only after successfully rejecting the null hypothesis for the comparison of SD versus Fixed would further noninferiority and/or superiority comparisons of this end point and possibly secondary end points be run in the ordering specified by the study protocol for the purpose of claims.

Mean, standard deviations, counts, and percentages were calculated for baseline demographics. P values were calculated with F tests and χ² tests for continuous and categorical variables, respectively. Medians (quartiles 1 and 3) are reported for continuous end-point data with bootstrap 95% confidence intervals estimated for the median. Counts and percents are reported for categorical data. General linear models were used to compare the pairwise changes in LVESV, 6-minute walk, LVEF, LVEDV, and QOL score from baseline to 6 months. A Shapiro-Wilk test of normality was used to evaluate residuals for normality in this patient cohort. Because of nonnormality of the data, a square root transformation of the continuous measures listed above was used. Only patients with available data at both enrollment and 6 months were included in end-point analysis models, and no adjustment was made for missing data. NYHA classification was calculated using a risk difference of improvement of >1 NYHA class from baseline to 6 months stratified by baseline NYHA classification. A test for homogeneity was
Table 1. Patient Demographics and Clinical History at Implantation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SD (n=332)</th>
<th>Echo (n=323)</th>
<th>Fixed (n=325)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.4±10.6</td>
<td>65.8±11.2</td>
<td>66.1±11.3</td>
<td>0.79</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>235 (71)</td>
<td>220 (68)</td>
<td>211 (65)</td>
<td>0.27</td>
</tr>
<tr>
<td>Height, cm</td>
<td>173±10</td>
<td>171±10</td>
<td>170±10</td>
<td>0.007*</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>89±23</td>
<td>87±20</td>
<td>86±20</td>
<td>0.12</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.7±6.6</td>
<td>29.4±6.0</td>
<td>29.6±6.3</td>
<td>0.83</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>125±20</td>
<td>121±21</td>
<td>124±20</td>
<td>0.02*</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>72±14</td>
<td>70±13</td>
<td>71±12</td>
<td>0.16</td>
</tr>
<tr>
<td>Systemic HTN, n (%)</td>
<td>238 (72)</td>
<td>217 (67)</td>
<td>224 (69)</td>
<td>0.45</td>
</tr>
<tr>
<td>Pulmonary HTN, n (%)</td>
<td>11 (3)</td>
<td>16 (5)</td>
<td>17 (5)</td>
<td>0.44</td>
</tr>
<tr>
<td>Resting heart rate, bpm</td>
<td>71±12</td>
<td>72±13</td>
<td>71±13</td>
<td>0.49</td>
</tr>
<tr>
<td>LBBB, n (%)</td>
<td>263 (79)</td>
<td>233 (72)</td>
<td>256 (79)</td>
<td>0.07</td>
</tr>
<tr>
<td>Ischemic origin, n (%)</td>
<td>190 (57)</td>
<td>182 (57)</td>
<td>183 (56)</td>
<td>0.97</td>
</tr>
<tr>
<td>Nonischemic origin, n (%)</td>
<td>142 (43)</td>
<td>140 (43)</td>
<td>142 (44)</td>
<td>0.97</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation, n (%)</td>
<td>37 (11)</td>
<td>37 (11)</td>
<td>46 (14)</td>
<td>0.62</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>133 (40)</td>
<td>109 (34)</td>
<td>128 (39)</td>
<td>0.19</td>
</tr>
<tr>
<td>Renal disease, n (%)</td>
<td>48 (14)</td>
<td>59 (18)</td>
<td>51 (16)</td>
<td>0.40</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>55 (17)</td>
<td>47 (15)</td>
<td>49 (15)</td>
<td>0.76</td>
</tr>
<tr>
<td>CABG, n (%)</td>
<td>104 (31)</td>
<td>107 (32)</td>
<td>110 (34)</td>
<td>0.76</td>
</tr>
<tr>
<td>Heart valve repair/replacement, n (%)</td>
<td>17 (5)</td>
<td>20 (6)</td>
<td>17 (5)</td>
<td>0.80</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td>0 (0)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>0.25</td>
</tr>
<tr>
<td>I</td>
<td>12 (4)</td>
<td>6 (2)</td>
<td>6 (2)</td>
<td>0.7</td>
</tr>
<tr>
<td>II</td>
<td>307 (93)</td>
<td>311 (96)</td>
<td>307 (95)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>12 (4)</td>
<td>5 (2)</td>
<td>10 (3)</td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>24.5±6.7</td>
<td>23.9±6.8</td>
<td>24.9±7.0</td>
<td>0.24</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>152±21</td>
<td>153±20</td>
<td>153±20</td>
<td>0.74</td>
</tr>
<tr>
<td>6-min walk, m</td>
<td>272±124</td>
<td>277±127</td>
<td>264±124</td>
<td>0.40</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; LBBB, left bundle-branch block; COPD, chronic obstructive pulmonary disease; and CABG, coronary artery bypass surgery. See text for a description of the 3 treatment groups.

*p<0.05 for differences between groups.

Table 2. Patient Medications and Laboratory Values

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SD (n=332)</th>
<th>Echo (n=323)</th>
<th>Fixed (n=325)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications at enrollment, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>64</td>
<td>64</td>
<td>69</td>
<td>0.28</td>
</tr>
<tr>
<td>ARBs</td>
<td>23</td>
<td>23</td>
<td>17</td>
<td>0.09</td>
</tr>
<tr>
<td>Diuretics</td>
<td>82</td>
<td>80</td>
<td>82</td>
<td>0.84</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>9</td>
<td>7</td>
<td>6</td>
<td>0.32</td>
</tr>
<tr>
<td>ß-blockers</td>
<td>92</td>
<td>91</td>
<td>93</td>
<td>0.58</td>
</tr>
<tr>
<td>ACE inhibitors or ARBs</td>
<td>86</td>
<td>84</td>
<td>85</td>
<td>0.79</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>32</td>
<td>30</td>
<td>30</td>
<td>0.80</td>
</tr>
<tr>
<td>Digoxin</td>
<td>19</td>
<td>24</td>
<td>23</td>
<td>0.30</td>
</tr>
<tr>
<td>Laboratory values, mean±SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>24.2±12.5</td>
<td>25.3±14.7</td>
<td>23.7±12.1</td>
<td>0.31</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.3±0.7</td>
<td>1.3±0.8</td>
<td>1.2±0.5</td>
<td>0.27</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; and ARB, angiotensin receptor blocker. Data are expressed as mean±SD when appropriate. See text for a description of the 3 treatment groups.

who were enrolled, implanted, and randomized in the trial are shown in Table 1. Baseline demographic characteristics were similar between patients in all 3 arms except height and systolic blood pressure, which were slightly higher in the SD group. It is not unexpected that with 24 demographic characteristic comparisons, some are statistically significant at the 0.05 level owing to chance alone. The use of various cardiac medications at enrollment and baseline blood laboratory values were similar between the 3 arms and are described in Table 2. After implantation, a total of 980 patients were randomized to 1 of 3 AV delay arms: Fixed, Echo, or SD. The study flow chart is shown in Figure 1. Programming mode (DDD versus DDDR) was similar between treatment arms, with ≈80% of patients in the DDD mode and the remaining patients programmed to the DDDR mode. Overall, the median percent of atrial pacing was 9.5% with ≈75% of patients having <30% atrial pacing. The median percent of right ventricular pacing was 97.8% and median percent LV pacing was 98.2%.

The mean follow-up was 5.8±1.6 months. Patient response to CRT in the SMART-AV trial was defined for each of the end points as follows: improvement in LVEF threshold of 15 mL, improvement of LVEDV threshold of 15 mL, improvement in LVEF threshold of 5%, reduction in QOL score of 10 points, 25-m improvement in 6-minute walk, and improvement by at least 1 NYHA classification from baseline to 6 months. Seventy-five percent of patients responded by NYHA definition, and 48% to 61% of patients responded to all other end-point definitions. No significant difference in deaths by group existed (P=0.06).

HF-Related Events

A total of 91 HF-related adverse events were collected during the course of the SMART-AV Trial. No significant difference existed between treatment groups, with patients randomized to the SD, Echo, and Fixed arms having 31, 37, and 23 patients with HF-related adverse events, respectively (P=0.16).

Results

Study Population

A total of 1060 patients signed an informed consent form and were enrolled from 100 centers in the United States and Europe between May 2008 and December 2009. Of the 1060 enrolled patients, 1014 subsequently met all inclusion criteria and were implanted with a Boston Scientific CRT defibrillator device. Demographic characteristics of the 980 patients performed with a Cochran-Mantel-Haenszel test, and results were pooled if the test statistic was not significant at an α level of 0.05. Superiority comparisons were performed at a 2-sided α level of 0.05. A serial gate-keeping strategy was used to control the type I error rate given the number of multiple comparisons. Analysis was performed with SAS 9.1 (SAS Institute Inc, Cary, NC) and R version 2.10.1 (R Foundation for Statistical Computing, Vienna, Austria).
Comparison of AV Delays by Treatment Group

The differences between AV delays recommended by SD during atrial sense and atrial pace modes and the AV delays recommended by the echocardiographic iterative method (Echo) in all patients at postimplantation (top) and at 6 months (bottom) are shown in Figure 2 and Figure I in the online-only Data Supplement. The average atrial sense-atrial pace offset as determined by the SD algorithm was 48 ± 27 milliseconds. A sensed AV delay recommended by SD or Echo (iterative method) differing by at least 30 milliseconds from the Fixed AV delay setting of 120 milliseconds was recommended in 69% and 57% of patients, respectively.

Primary End Point

The change in LVESV for the SD arm was no different from either the Echo or Fixed arm (P=0.52 and P=0.66 respectively; Figure 2). The median changes (quartiles 1 and 3) in LVESV from postimplantation to 6 months for patients in the SD, Echo, and Fixed arms were −21 mL (−45 and 6 mL), −19 mL (−45 and 6 mL), and −15 mL (−41 and 6 mL), respectively. Median LVESV values were similar across all time points for the SD, Echo, and Fixed arms with baseline values of 119, 117, and 115 mL; 3-month values of 101, 105, and 98 mL; and 6-month values of 93, 97, and 99 mL, respectively. No differences between groups at individual time points were noted (Table I in the online-only Data Supplement). Importantly, =14% of randomized patients did not undergo assessment of the primary end point (Figure 1).

Secondary End Points

Because the primary end point showed no significant difference between the SD and Fixed groups, no other end points...
are considered statistically significant according to the gatekeeping strategy. Reported P values are therefore nominal values without adjustment for multiplicity and should be interpreted as exploratory, hypothesis-generating analysis. Secondary end points included structural (LVEDV and LVEF) and functional (6-minute walk, QOL, and NYHA classification) measures. There were no significant differences in the structural or functional end points by group (Figure 3). The median changes (quartiles 1 and 3) in LVEDV from postimplantation to 6 months for patients in the SD, Echo, and Fixed arms were 13 mL (42 and 12 mL), 16 mL (41 and 17 mL), and 12 mL (42 and 10 mL), respectively. The median changes (quartiles 1 and 3) in LVEF for patients in the SD, Echo, and Fixed arms at 6 months were 6.0% (0.5% and 14.7%), 6.0% (1.4% and 13.3%), and 5.1% (1.0% and 13.1%), respectively.

The median changes (quartiles 1 and 3) in 6-minute hall walk in the SD, Echo, and Fixed arms were 55 m (5 and 123 m), 39 m (13 and 107 m), and 58 m (0 and 115 m), respectively. The median changes (quartiles 1 and 3) in QOL for patients in the SD, Echo, and Fixed arms were 21 (37 and −4), 12 (28 and 2), and 17 (36 and −3) points, respectively. Because NYHA classification improvement is an ordinal variable, the data are reported as the difference in percentage of patients with an NYHA classification change of at least 1 NYHA class. The percentage reductions of at least 1 NYHA class for patients in the SD, Echo, and Fixed arms were 77%, 71%, and 77%, respectively. With the QOL and NYHA functional secondary end points, no significant differences were observed by treatment group (Figure 3). Median values for LVEDV, EF%, QOL, 6-minute walk, and percentage NYHA class change were similar across all time points for the SD, Echo, and Fixed arms (Table I in the online-only Data Supplement). No between-group differences at individual time points existed.

Subgroup Analysis

The effects of CRT and optimization method on the primary end point in 1 prespecified subgroup (QRS duration >150 versus 120 to 150 milliseconds) and 4 other subgroups analyzed posthoc (ischemic versus nonischemic, men versus women, left bundle-branch block versus non–left bundle-branch block, and atrial pacing >30% versus <30%) are presented in Figures II and III in the online-only Data Supplement. Overall, patients with a wide QRS duration, left bundle-branch block, ischemic cardiomyopathy, and female gender responded more favorably to CRT therapy. However, the only significant optimization treatment-subgroup interaction was for gender (Figure III in the online-only Data Supplement). Women optimized with SD and Echo responded more favorably than women randomized
to the Fixed arm ($P<0.02$ for gender-treatment interaction, $P=0.02$ for optimized versus fixed in women). Although patients with $>30\%$ atrial pacing optimized with SD and Echo trended toward greater reductions in LVESV compared with Fixed, this interaction did not reach statistical significance, in part because of the limited number of patients with $>30\%$ atrial pacing ($P=0.4$).

**Discussion**

The clinical benefit of CRT for patients with moderate to severe symptomatic HF, severe LV systolic dysfunction, and intraventricular conduction delay is firmly established.\(^1\)\(\text{-}8\) Nonetheless, a significant number of patients derive limited benefit from this therapy.\(^24\) One possibility is that systematic optimization of the programmed AV delay might improve overall outcomes. However, even though many trials have shown acute benefits of AV optimization,\(^3\)\(^4\)\(^6\)\(^13\)\(^12\)\(^22\) only limited data exist to suggest that systematic AV interval optimization results in long-term improvement in clinical outcomes.\(^20\)\(^23\)\(^27\)

On the other hand, AV optimization by echocardiography is time-consuming and costly, and it would be desirable to avoid the procedure or, at the very least, to replace it with a simpler yet equally effective technique.\(^28\)

Previous large-scale, multicenter, randomized clinical trials of CRT have been inconsistent in their approach to AV optimization. MIRACLE and CARE-HF used the American Society of Echocardiography–endorsed approach of using echocardiographically measured transmural flow to determine optimal AV delay; COMPANION used an algorithm based on the intrinsic AV interval and baseline QRS width; there was no AV optimization in the CONTAK CD trial; and other techniques have been proposed.\(^1\)\(^3\)\(^8\)\(^13\)\(^14\)\(^19\)\(^20\)\(^23\)\(^27\)

A few studies have compared whether acute benefits attributed to CRT are different, depending on which method of AV delay optimization is used.\(^20\)\(^24\)\(^22\)\(^24\)\(^32\)\(^34\) For example, the CRT-AVO Study by Gold et al\(^19\) studied the acute effects of an electrogram-based algorithm, now known as SD, against other commonly used AV delay optimization methods such as aortic velocity-time integral and the Ritter method, as well as various fixed AV delays. The development of SD was based on studies in which hemodynamic changes (as measured by LV $\text{dP/dtmax}$ and pulse pressure) were recorded during CRT at different stimulation sites and AV delays.\(^13\)\(^35\)\(^36\) This method calculates sensed and paced AV delays that provide maximum hemodynamic response based on the measurement of electric conduction delays (ie, AV intervals and QRS duration).\(^19\)\(^20\) The algorithm further accounts for LV lead location, which is generally considered an important variable in ensuring optimal patient response.\(^19\)\(^20\)

The results from the CRT-AVO study demonstrated that the SD algorithm recommended a customized AV delay that increased the acute hemodynamic response in terms of percent change in LV $\text{dP/dtmax}$ compared with fixed nominal AV delays of 100, 120, 140, or 160 milliseconds as well as the Ritter method and aortic velocity-time integral.\(^19\) Thus far, however, no large-scale clinical study has directly compared different methods of AV delay optimization to determine whether there are LV reverse remodeling benefits.

Some investigators have suggested that optimization of the interventricular (VV) delay may also play a role in improving the outcomes of CRT.\(^37\)\(^38\) However, in 2 randomized trials, VV optimization yielded no additional long-term benefit in patients who had also undergone AV optimization.\(^39\)\(^40\) Optimization of the VV timing was optional in patients randomized to the Echo arm only, to be consistent with current clinical practice, but was not permitted in the other 2 randomized arms of the trial.

It is unlikely there is such a thing as a static or unchanging “optimum” AV delay in individual patients. Rather, it is likely that as hemodynamic conditions change, the “optimum” AV delay may change as well.\(^41\)\(^42\) In SMART-AV, the AV delay was reoptimized after 3 months of follow-up in the SD arm only to take advantage of the speed and relative simplicity of this technique. In the FREEDOM Trial, the AV and VV intervals were optimized frequently.\(^43\) In contrast, the complexity and length of time required to perform echocardiographic AV optimization limit the ability to routinely reoptimize patients, and to be consistent with current clinical practice, patients in the Echo arm were not reoptimized.

Thus, a variety of methods are used clinically for programming the AV delay, with no current consensus as to best practice. As a result, many implanters do not use either echocardiographic or ECG methods to optimize the AV interval but instead empirically program devices to a fixed AV delay interval and optimize only those patients who fail to respond to therapy. The clinical implications of these findings are substantial. Routine echocardiographic optimization with the American Society of Echocardiography–recommended method is no better than nominal settings. The American Society of Echocardiography–recommended method of AV optimization for patients with CRT devices should thus be abandoned as a routine measure. Routine AV delay optimization by SD is also neither inferior nor superior to nominal settings. This study, along with the results from the FREEDOM trial reported at the Heart Rhythm Society meeting in May 2010, show that to date routine methods of any type to optimize AV intervals do not have a benefit in terms of QOL, LVEF, or changes in LV volumes.\(^44\)

There is a disparity between our findings and the results from prior acute studies that demonstrate that AV optimization acutely improves resting supine hemodynamics. A potential explanation for these findings is that optimization in the supine position may yield a suboptimal result while patients are upright. This is supported by recent preliminary data showing that, in general, the acute change in supine LV $\text{dP/dt}$ with CRT was poorly correlated with long-term clinical improvement.\(^45\) If so, then fundamentally different approaches to AV optimization may be necessary. Another potential explanation is that insufficient hemodynamic improvement above the baseline benefit from CRT exists in many patient groups to be reliably detected. A third possibility is that even if there is a hemodynamic benefit, it may be too small to result in meaningful clinical improvement in these long-term end points. If any of these 3 explanations is correct, then it may be time for us to abandon the notion that
we should “optimize” the AV interval and instead invoke the notion of “satisficing,” as defined by the economist Herbert Simon, and conclude that for sufficiently complex problems, a satisfactory (good enough) solution should suffice and that true optimization may not be practical.46 For the broad population undergoing CRT, a nominal AV interval of 120 milliseconds appears to fulfill this criterion and to be a satisfactory solution. The results from this trial emphasize the notion of “satisficing,” as defined by the economist Herbert Simon, and conclude that for sufficiently complex problems, a satisfactory (good enough) solution should suffice and that true optimization may not be practical.46 For the broad population undergoing CRT, a nominal AV interval of 120 milliseconds appears to fulfill this criterion and to be a satisfactory solution. The results from this trial emphasize the

Conclusion and Clinical Implications

Systematic AV delay optimization with the SD algorithm was not different from echocardiographically determined AV interval optimization or a fixed AV delay of 120 milliseconds. The routine use of AV optimization techniques assessed in this trial is not warranted. However, these data do not exclude possible utility in selected patients who do not respond to CRT.

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Disclosures

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References


43. Abraham WT, Gras D, Yu CM, Guzzo L, Gupta MS; FREEDOM Steering Committee. Rationale and design of a randomized clinical trial to assess the safety and efficacy of frequent optimization of cardiac resynchronization therapy: the FREEDOM Trial to assess the safety and efficacy of frequent optimization of cardiac resynchronization therapy. Am J Cardiol. 2010;106:1127–1128.
The clinical benefit of cardiac resynchronization therapy for patients with moderate to severe symptomatic heart failure, severe left ventricular systolic dysfunction, and intraventricular conduction delay is firmly established. Nonetheless, a significant number of patients derive limited benefit from cardiac resynchronization therapy. One possibility is that systematic optimization of the programmed atrioventricular (AV) delay might improve overall outcomes. A variety of methods are used clinically for programming the AV delay, with no current consensus on the best practice. The SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy (SMART-AV) delay trial prospectively randomized patients to a fixed empirical AV delay (120 milliseconds), echocardiographically optimized AV delay, or AV delay optimized with SmartDelay, an empirically derived electrogram-based algorithm. A total of 980 patients were randomized and followed up for 6 months. At the end of the trial, there was no difference in the primary end point, left ventricular end-systolic volume, or any of the secondary end points: left ventricular end-diastolic volume, ejection fraction, New York Heart Association class, quality of life, and 6-minute walk distance. The routine use of echocardiographic optimization and algorithm-based AV interval optimization is not clinically warranted. However, these data do not exclude possible utility in selected patients who do not respond to cardiac resynchronization therapy.
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 Atrioventricular Delay Programming in Cardiac Resynchronization Therapy


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SUPPLEMENTAL MATERIAL

MS ID#: CIRCULATIONAHA/2010/992552

MS TITLE: Primary Results from the SMART-AV Trial: A Randomized Trial Comparing Empiric, Echocardiographic Guided and Algorithmic AV Delay Programming in Cardiac Resynchronization Therapy (CRT)
SUPPLEMENTAL FIGURE LEGENDS

Supplemental Figure 1. Distribution of AV Delays Recommended in All Patients with SD During AS (black bars), AP (gray bars) and Echo (open bars) at post-implant (top panel) and at 6-months post-implant (bottom panel).

Supplemental Figure 2. Median and 95% confidence intervals for the Primary Endpoint of Echocardiographic Left Ventricular Systolic Volume change between Baseline and 6-Month Follow-up in the Following Sub Groups: LBBB vs. non LBBB, QRS <150 ms vs. QRS > 150 ms, ischemic vs. non-ischemic, and Right Atrial Pacing >30% vs. Right Atrial Pacing <30%.

Supplemental Figure 3. Median and 95% confidence intervals for the Primary Endpoint of Echocardiographic Left Ventricular End Systolic Volume change between Baseline and 6-Month Follow-up by gender.
SUPPLEMENTAL FIGURES

Supplemental Figure 1.
Supplemental Figure 2.
Supplemental Figure 3.

Primary Endpoint by Gender

![Bar chart showing change in volume (ml) by gender and method.

Female:
- Smart Delay (n=85)
- Echo (n=95)
- Fixed (n=97)

Male:
- Smart Delay (n=198)
- Echo (n=187)
- Fixed (n=184)
Supplemental Table 1. Endpoints by visit.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>Post-Implant</th>
<th>3-Month</th>
<th>6-Month</th>
<th>Difference Between Post-Implant and 6-Month</th>
<th>95% CI for median difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVESV (ml)</td>
<td>SD</td>
<td>283</td>
<td>119 (86,156)</td>
<td>101 (69,140)</td>
<td>93 (66,139)</td>
<td>-21 (-45,6)</td>
</tr>
<tr>
<td></td>
<td>Echo</td>
<td>282</td>
<td>117 (83,157)</td>
<td>105 (73,139)</td>
<td>97 (66,147)</td>
<td>-19 (-45,6)</td>
</tr>
<tr>
<td></td>
<td>Fixed</td>
<td>281</td>
<td>115 (83,154)</td>
<td>98 (70,149)</td>
<td>99 (64,145)</td>
<td>-15 (-41,6)</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>SD</td>
<td>283</td>
<td>164 (126,209)</td>
<td>146 (116,189)</td>
<td>143 (114,191)</td>
<td>-13 (-42,12)</td>
</tr>
<tr>
<td></td>
<td>Echo</td>
<td>282</td>
<td>164 (128,204)</td>
<td>150 (119,191)</td>
<td>149 (105,200)</td>
<td>-16 (-41,17)</td>
</tr>
<tr>
<td></td>
<td>Fixed</td>
<td>282</td>
<td>163 (128,201)</td>
<td>142 (118,197)</td>
<td>148 (109,193)</td>
<td>-12 (-42,10)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>SD</td>
<td>283</td>
<td>26.1 (21.8,33.0)</td>
<td>31.9 (25.0,41.4)</td>
<td>34.0 (25.3,43.4)</td>
<td>6.0 (0.5,14.7)</td>
</tr>
<tr>
<td></td>
<td>Echo</td>
<td>282</td>
<td>28.1 (20.6,34.1)</td>
<td>31.9 (24.6,39.6)</td>
<td>33.0 (25.6,41.5)</td>
<td>6.0 (-1.4,13.3)</td>
</tr>
<tr>
<td></td>
<td>Fixed</td>
<td>281</td>
<td>27.0 (20.9,34.3)</td>
<td>31.9 (23.4,42.0)</td>
<td>33.5 (23.4,43.3)</td>
<td>5.1 (-1.0,13.1)</td>
</tr>
<tr>
<td>QOL Score</td>
<td>SD</td>
<td>289</td>
<td>48 (32.65)</td>
<td>22 (9.40)</td>
<td>21 (8.45)</td>
<td>-21 (-37,-4)</td>
</tr>
<tr>
<td></td>
<td>Echo</td>
<td>283</td>
<td>42 (26.64)</td>
<td>26 (11.45)</td>
<td>24 (9.49)</td>
<td>-12 (-28,2)</td>
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<tr>
<td></td>
<td>Fixed</td>
<td>286</td>
<td>47 (26.66)</td>
<td>24 (9.41)</td>
<td>21 (9.40)</td>
<td>-17 (-36,-3)</td>
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<tr>
<td>Six-Minute Walk (meter)</td>
<td>SD</td>
<td>277</td>
<td>285 (198,356)</td>
<td>338 (244,415)</td>
<td>350 (256,422)</td>
<td>55 (-5,123)</td>
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<tr>
<td></td>
<td>Echo</td>
<td>264</td>
<td>294 (201,366)</td>
<td>336 (244,403)</td>
<td>346 (251,421)</td>
<td>39 (-13,107)</td>
</tr>
<tr>
<td></td>
<td>Fixed</td>
<td>274</td>
<td>290 (182,361)</td>
<td>330 (260,403)</td>
<td>343 (251,419)</td>
<td>58 (0,115)</td>
</tr>
</tbody>
</table>
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