Left Ventricular Reverse Remodeling With Biventricular Versus Right Ventricular Pacing in Patients With Atrioventricular Block and Heart Failure in the BLOCK HF Trial

St. John Sutton et al: Reverse Remodeling with Biventricular Pacing

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DOI: 10.1161/CIRCHEARTFAILURE.114.001626

Abstract

Background—Biventricular (BIV) pacing in heart failure (HF) improves survival, relieves symptoms and attenuates left ventricular remodeling. However, little is known about BIV in HF patients with atrioventricular block (AVB) because they are typically excluded from BIV trials.

Methods and Results—The BLOCK HF trial randomized patients with AVB, NYHA symptom class I-III HF, and left ventricular ejection fraction (LVEF) ≤50% to BIV or right ventricular (RV) pacing. Doppler echocardiograms (DE) were obtained at randomization (following 30-60 days of RV pacing post-implant) and every 6 months through 24 months. Data analysis comparing changes in 10 pre-specified echo parameters over time was conducted using a Bayesian design. Left ventricular end systolic volume index (LVESVI) was also evaluated as a predictor of mortality/morbidity. Of 691 randomized subjects, 624 had paired DE data for one or more analyses at 6, 12, 18 or 24 months. Biventricular pacing significantly reduced LV volume indices and intraventricular mechanical delay (IVMD), and improved LVEF, consistent with LV reverse remodeling. These parameters showed little change with RV pacing alone, indicating no systematic reverse remodeling with RV pacing. LVESVI was predictive of mortality/morbidity; the estimated risk increased up to 1% for every 1 mL/m² increase in LVESVI.

Conclusions—LVESVI is a significant predictor of mortality/morbidity in this population. Cardiac structure and function are improved with BIV pacing for patients with AVB and LV systolic dysfunction.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00267098.

Key Words: BLOCK HF, LVESVI, BIV pacing, RV pacing
The BLOCK HF (Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block) trial met its primary endpoint and showed that biventricular (BIV) pacing reduces the risk of all-cause mortality, heart failure (HF)-related urgent care visits, or an increase ≥15% left ventricular (LV) end systolic volume index (LVESVI) for patients with atrioventricular block (AVB) and systolic dysfunction. Several randomized clinical trials including MIRACLE², COMPANION³, CARE-HF⁴, REVERSE⁵, MADIT-CRT,⁶ and RAFT⁷ have demonstrated the efficacy of BIV pacing in HF patients by inducing structural and functional LV reverse remodeling.⁸ Traditionally, patients with New York Heart Association (NYHA) class II-IV HF and a class I indication for permanent pacing have been treated with right ventricular (RV) pacing and optimization of medical therapy. However, chronic RV pacing has been shown to be associated with new-onset HF, a condition that has been called “RV pacing-induced cardiomyopathy.”⁹ ¹¹ This condition occurs in ~20% of patients after prolonged periods of RV pacing.¹¹ In this analysis, we assessed the impact of BIV versus RV pacing in HF patients with AVB with two specific aims: 1) to determine whether BIV pacing has a consistently greater and more favorable impact than RV pacing on LV reverse remodeling and attenuation of progressive LV dysfunction; and 2) to detect differences in LV architecture, function and intraventricular mechanical delay (IVMD) associated with BIV versus RV pacing using transthoracic echocardiography.

Methods

Enrollment criteria for the BLOCK HF trial have been published previously.¹ The institutional review board of each participating institution approved the study protocol and all patients provided written informed consent. All patients had a standard class I or IIa indication for
permanent pacing due to AVB, NYHA class I-III systolic HF, and LV ejection fraction (LVEF) \( \leq 50\% \). Patients with permanent atrial arrhythmias who had intrinsic AVB or AVB due to AV node ablation, as well as patients meeting class I indications for implantable cardiac defibrillators (ICDs) were enrolled. All subjects received a cardiac resynchronization therapy (CRT) pacemaker (CRT-P), or CRT defibrillator (CRT-D) if there was an indication for defibrillation therapy, and were RV paced for 30-60 days while HF medical therapy was optimized. Subjects were subsequently randomly assigned 1:1 to BIV or RV pacing, and underwent an echocardiographic examination at randomization and 6-, 12-, 18-, and 24-months post-randomization.

Echocardiograms and Doppler velocity signals were digitized to calculate changes in LVEF, LVESVI, LV end diastolic volume index (LVEDVI), LV dimension at end diastole (LVEDD), LV dimension at end systole (LVESD), LV mass, mitral regurgitation (MR), cardiac index (CI), intraventricular mechanical delay (IVMD), defined as the time difference between peak septal and peak posterior wall excursion, and trans-mitral peak E-wave and A-wave velocity ratio. LV volumes were estimated according to Simpson’s method and indexed to body surface area, and LVEF was calculated using a standardized protocol.\(^{12}\) The severity of MR was assessed as the regurgitant jet area/left atrial area. All 2D echocardiographic measurements were made by a senior sonographer (T.P.) with more than 30-years’ experience in quantitative analysis of echocardiograms at the Echo Core laboratory.

**Statistics**

At the time the trial was designed, the lack of data for patients in this population receiving BIV therapy added uncertainty to the sample size and follow-up requirements for the primary
objective. Thus, an adaptive Bayesian study design allowing up to 1,200 patients to undergo randomization was used, featuring sample size re-estimation and two interim analyses with pre-specified trial-stopping rules. All objectives were evaluated with intention-to-treat analyses. SAS 9.2, R, and WinBUGS1.4 statistical software were utilized to implement the statistical models. The primary tool for analysis of change in echo parameters was the posterior distribution, which defines the likely set of values a parameter (e.g. BIV–RV difference in mean LVEF improvement) can take using study data and pre-specified prior distributions. For each echo parameter, the overall (combining CRT-P and CRT-D subjects) posterior distributions for the BIV–RV difference in average changes were generated for 6-, 12-, 18-, and 24-month visits (follow-up – randomization), and a 95% two-sided credible set was obtained, which consists of 2.5% to 97.5% of the posterior distribution, and can be thought of as the range of values within which the parameter falls with 95% probability. Statistical significance was defined by the 95% credible set falling to the left or right of zero.

Additionally, for each parameter, a device poolability assessment was performed by generating the posterior distribution for the CRT-P–CRT-D difference in BIV–RV average changes from randomization. A significant difference between device groups was defined by the corresponding 95% two-sided credible set not containing zero.

Modeling analyses were performed utilizing data from all time-points at once. For each echo parameter, a mixed effects model was fit with randomized arm serving as a fixed effect, time (6, 12, 18, and 24 months) serving as both linear and quadratic fixed effects, and subject serving as a
random effect. The 95% credible sets were generated from these models to assess the effect of BIV pacing on each parameter.

Ancillary analyses were performed using frequentist methods, with p-values serving as the metric of evaluation. We assessed the individual and combined modifying effects of age, gender, NYHA class and LVESVI at randomization on changes in the 10 Echo parameters using mixed effects models, with interaction terms for the treatment effect with each covariate, and subject treated as a random effect.

Cox proportional hazards model were fit to assess the predictive value of LVESVI on mortality, first HF hospitalization, mortality or first HF hospitalization, and mortality or first HF urgent-care visit, a primary endpoint of the trial. LVESVI was treated as a time-dependent covariate, using values at randomization and later time-points to account for worsening or improvement over time.

Additional sub-group analyses were conducted to determine whether relationships existed that were not apparent when the whole data-set was explored. These compared changes in the 10 pre-defined echo parameters: history of atrial fibrillation (AF) versus no AF, left bundle branch block (LBBB) versus no LBBB, and RV lead apical versus non-apical placement.

Reproducibility

We assessed intra-observer reproducibility of the echo parameters in 100 non-BLOCK HF patients. Concordance Correlation Coefficients were 0.88 for LVEDVI, 0.90 for LVESVI, 0.71 for LVEF, 0.91 for trans-mitral peak A-wave and 0.78 for trans-mitral peak E-wave.
Results

A total of 918 patients were enrolled from December 2003 through November 2011 at 58 sites in the United States and 2 sites in Canada. Of enrolled subjects, 691 were randomized, with 624 (442 CRT-P and 182 CRT-D) having paired data for one or more analyses of echo parameters (Figure 1). Reasons for missing echo data included: no body surface area recorded, echocardiogram not performed or not analyzable, or follow-up visit missed. Within device groups, average demographics and cardiac function values were comparable between arms at randomization (Table 1). For most echo parameters, results were consistent across time-points regarding statistical significance (Table 2), and poolability analyses did not show significant differences between CRT-D (average enrollment LVEF 33%) and CRT-P (average enrollment LVEF 43%) subjects.

Linear LV Dimensions and Volumes

The randomization arms differed significantly with regard to change in LVEDD (Table 2), but the small differences were unlikely clinically or biologically meaningful. BIV subjects had an average 0.1 cm reduction in LVEDD at all time-points (Figure 2). In contrast, RV subjects showed no change.

BIV subjects showed a significantly greater reduction in LVESVI and LVEDVI than RV subjects at each time-point (Figure 2, Table 2). The average reduction in LVESVI among BIV subjects varied from 6 to 8.8 mL/m$^2$, while RV subjects, on average, had little change. The average reduction in LVEDVI among BIV subjects ranged from 6.2 mL/m$^2$ to 9.8 mL/m$^2$, while the average reduction among RV subjects varied from 0.1 mL/m$^2$ to 1.1 mL/m$^2$ (Figure 2).
A reduction in LVESVI $\geq 15\%$ was more often encountered in BIV compared to RV subjects (Figure 3). At 6 months 44% of BIV subjects experienced $\geq 15\%$ reduction in LVESVI, compared to 25% of RV subjects. A total of 68% of BIV subjects had any reduction in LVESVI at 6 months, compared to only 50% of RV subjects. This was a consistent finding at each time-point and typifies the magnitude of response to BIV pacing in HF patients.$^{2-7}$

**LVEF**

BIV subjects experienced significant improvements in LVEF compared to RV subjects. (Table 2, Figure 2). On average, BIV subjects experienced a 3% increase in LVEF at 6 months, while RV subjects experienced a 0.3% decrease. Similar changes were seen in BIV subjects at 12, 18, and 24 months; RV subjects’ LVEF did not improve at any time-point.

**LV Mass**

There was a consistent trend for greater reduction in LV mass in BIV compared to RV subjects (Figure 2). The average reduction in LV mass in BIV subjects ranged from 8.4 g to 19.4 g, while in RV subjects the average reduction ranged from 4.2 g to 7.2 g. A significant difference between arms was observed at 12 and 24 months.

**IVMD**

Average IVMD was similar at randomization but shortened significantly in BIV subjects at 6 months (49.9 ms; Figure 2) compared to virtually no change in RV subjects (−4.2 ms; Figure 2). These significant differences persisted throughout 24 months.
Mitral E/A Wave Velocity Ratio, CI and MR

The mean values for trans-mitral peak E- and A-waves, E/A velocity ratio, CI and MR for BIV versus RV and CRT-P versus CRT-D subjects were similar over 24 months of follow-up.

Modeling Analyses

The results of modeling accounting for all time-points were similar to those of the individual time-point analyses, as there was a significant difference between arms with regard to LVEF, LVESVI, LVEDVI, LVEDD, IVMD, and LV mass. The quadratic effect for time was not significant for any of the 10 parameters, while the linear time effects were significant for LVESVI, LVEDVI, and LV mass, suggesting greater reductions over time.

Effect Modification

We assessed the potential effect modification of baseline covariates such as age, gender, LVESVI, LVEF and NYHA on LV reverse remodeling. Interaction terms for BIV therapy with these covariates were not significant with the exception of randomization LVESVI in predicting LVESVI and LVEDVI over time. This showed a treatment effect that was consistent across baseline LVEF and NYHA class. However, the treatment effect was greater for subjects with higher baseline LVESVI (p = 0.03), although the incremental effect was small. With regards to age and gender, we could not confirm the disproportionate beneficial reverse remodeling in women compared to men reported previously.\(^6\)\(^{14}\) There was no detectable independent confounding effect of age during follow-up.
Predictive Value of LVESVI

All 653 subjects with measureable LVESVI at randomization were included in the analyses assessing how LVESVI affects the risk of clinical outcomes. For all four study endpoints (mortality, mortality or HF urgent care, mortality or HF hospitalization, and HF hospitalization), elevated LVESVI measures at either randomization or follow-up were found to significantly increase relative risk (Table 3). The estimated hazard ratios ranged from 1.007 for mortality to 1.01 for first HF hospitalization, meaning that a 10 mL/m² increase in LVESVI would be associated with a 7% increase in the risk of death, and 10% increase in the risk of HF hospitalization.

Subgroup Analyses

We performed additional subgroup analyses to determine whether any discoverable relationships existed using the following: history versus no history of AF, LBBB versus no LBBB, and RV lead apical versus non-apical location. The only analysis that showed a consistently significant difference between randomized arms was history of AF. Among subjects with a history of AF, MR reductions between 2.21% and 4.53% over time were observed in BIV subjects, compared to changes between 0.14% and 1.33% in RV subjects. Conversely, among subjects with no history of AF, the BIV arm saw less average change (ranging from a 0.35% reduction to a 1.14% increase), while the RV arm saw both average reductions and average improvements of over 1-2% over time.
Discussion

In this echo analysis of the BLOCK HF trial, cardiac structure and function were improved with BIV pacing for patients with AVB and LV systolic dysfunction. Relative to randomization, which followed 30-60 days of RV pacing, BIV pacing significantly reduced LV volume indices and IVMD, and improved LVEF, consistent with LV reverse remodeling. These parameters showed little change with RV pacing alone, indicating no systematic reverse remodeling with RV pacing. In addition, LVESVI was found to be a significant predictor of mortality and HF hospitalization in this population.

As heart disease progresses into HF, heart size increases, cardiac function deteriorates and symptoms of HF ensue. This dynamic process is known as LV remodeling. Understanding the extent of LV remodeling can help to assess the prognosis of HF – the greater the extent of remodeling, the poorer the prognosis. Relatively small increases in ventricular volume have been associated with an increased risk of death in patients with coronary artery disease, recent MI or HF. Therefore, treatments that prevent or reverse LV remodeling are clinically beneficial. Almost all successful contemporary therapies for HF including drug therapy and CRT attempt to reduce LV size and thereby reverse remodel the LV. Early HF trials demonstrated that drug therapy that limited or reversed LV remodeling resulted in improved long-term survival. However, most large multicenter HF trials have shown that pharmaceutical agents attenuate rather than reverse remodel the LV, with a few notable exceptions. In addition to improvements in exercise capacity, NYHA class, and quality of life, evidence of the arrest or reversal of ventricular remodeling has been demonstrated with CRT.

While most previous CRT trials have excluded patients with AVB, these new data from BLOCK HF provide evidence that BIV pacing in patients with high-grade AVB and LV dysfunction
(LVEF ≤50%) is associated with progressive reverse remodeling, improvement in LVEF and attenuation of disease progression. These changes were sustained through 24 months of follow-up. In contrast, traditional RV pacing was not associated with progressive LV reverse remodeling or change in LVEF at follow-up. Importantly, in the BLOCK HF trial, randomization occurred after implant and 30-60 days of RV pacing while HF medical therapy was optimized, so changes or lack of changes observed are relative to this time-point. The difference in LV remodeling between BIV and RV pacing could not be explained by any skewed distribution at randomization of CRT-D patients who had larger LV volumes, lower EF and greater prevalence of NYHA class III than CRT-P patients, because CRT-D patients were equally distributed across the two randomized arms.

The importance of LV size, particularly LVESVI and its relationship to clinical outcomes, has been previously documented.27-31 The REVERSE trial reported that significant reverse LV remodeling at a threshold of >15% reduction in LVESVI at 12 months was associated with a clinical response to CRT.30 In a quantitative echocardiographic sub-study of the SAVE (Survival and Ventricular Enlargement) trial, LVESVI was shown to be the most powerful predictor of outcome that included death, development of HF, or recurrent myocardial infarction.29 Similarly, in the BLOCK HF trial, more than two-thirds of the BIV subjects had an improvement in LVESVI that was durable over time. BIV pacing resulted in greater LVESVI reductions than RV pacing and for every 10 mL/m² increase in LVESVI, there was a 7% increased risk of death, 7% increased risk of death or HF urgent care, 8% increased risk of death or HF hospitalization, and 10% increased risk of HF hospitalization (Table 3). In BLOCK HF, LVESVI was smaller than in NYHA class II subjects in REVERSE and NYHA class III/IV subjects in MIRACLE and MIRACLE ICD,2,32 indicating less advanced HF and a better prognosis.
In the BLOCK HF trial, subjects in both pacing arms had similarly prolonged IVMD at randomization because of a comparable degree of intraventricular dyssynchrony. However, coincident with BIV pacing, there was a reduction in IVMD consistent with decreased dyssynchrony and restoration of more normal coordinated LV and RV contraction patterns that was sustained through 24 months. By contrast, there was no change in IVMD in RV paced subjects. The trigger for reverse remodeling in HF patients with AVB may have been the onset of BIV pacing. A robust direct relationship previously has been demonstrated between improvement in LV volume indices and IVMD with CRT in the REVERSE trial.\textsuperscript{28, 33}

We found no evidence for RV pacing-induced cardiomyopathy, which has been reported to involve up to 20\% of patients.\textsuperscript{10} Our failure to detect either LV dilation or progressive decrease in LVEF may reflect that the randomization visit served as the baseline measure, which came after 30-60 days of RV pacing per the study design. An alternative explanation for our findings is that RV pacing-induced cardiomyopathy must be mild, rare or occur only after considerably longer RV stimulation.\textsuperscript{11}

We examined the potential modifying effects of a number of possible confounders that included age, gender, NYHA class and LVESVI. Prior studies have reported a greater response to BIV pacing in women than men,\textsuperscript{6, 14} which we were unable to confirm. We also assessed the modifying effects of baseline LVESVI. Treatment effect on LV remodeling (LVESVI and LVEDVI) was greater for patients with higher baseline LVESVI (p = 0.03) although the incremental effect was small.

When the patient population was divided into those with or without LBBB, there were no differences in LV reverse remodeling or in the 10 echocardiographic parameters between BIV and RV pacing. In similar fashion, there were no consistent differences in reverse remodeling
between CRT-P patients (~LVEF ≥35%) or CRT-D patients (~LVEF <35%), or with RV lead apical placement compared to non-apical placement, with BIV or RV pacing. However, among subjects with a history of AF, reductions in MR over time were observed in BIV subjects as compared to RV subjects.

**Limitations**

A potential short-coming of this study was the degree of missing echo data, due in part to subjects failing to return for follow-up echocardiograms and clinic visits, technically-limited echo data that precluded quantification, and the absence of body surface area. Additionally, the trial was designed to allow follow-up of all subjects through 12 months, and was stopped once a pre-specified endpoint was met. This prevented some subjects from completing an 18- or 24-month visit. However, all available comparative data were used in the statistical analyses of each echo parameter at each time-point, and the modeling analysis, which used all available data at all scheduled visits, produced similar results to those of the individual time-point analyses.

Finally, a further limitation to be noted is the relative paucity of data on mitral and tricuspid valve ideal, although both appeared mild. We also report the interaction of AF and MR.

**Conclusions**

In patients with AVB and NYHA class I-III systolic HF, BIV pacing results in reverse structural and functional LV remodeling, while traditional RV pacing does not. Worsening LVESVI was associated with increased risk of adverse clinical outcomes. BIV pacing resulted in superior improvement in LVESVI compared to RV pacing through 24 months. This detailed
echocardiographic analysis has important clinical implications in supporting the use of BIV pacing de novo rather than RV pacing for this patient population.

**Sources of Funding**

Medtronic Inc., Minneapolis, MN, USA funded this study.

**Disclosures**

Dr. Curtis reports receiving fees for serving on the advisory boards of Biosense Webster, St. Jude Medical, Sanofi-Aventis, Pfizer, and Bristol-Myers Squibb; receiving consulting fees from Medtronic; receiving lectures fees from Sanofi-Aventis, St. Jude Medical, and Medtronic; and receiving payment for the development of educational presentation from Horizon CME, WebMD Health Services, and the North American Center for Continuing Medical Education. Dr. Chung reports receiving consulting fees from Boston Scientific, Medtronic, and CardioMEMS; payment for the development of educational presentations from Boston Scientific; and grant support through his institution from Gambro, Medtronic, and Boston Scientific. Dr. Adamson reports receiving consulting fees from Medtronic, St. Jude Medical, and CardioMEMS; and lecture fees from St. Jude Medical. Dr. Pei and Dr. Christman report being employees of and holding stock and stock options in Medtronic. Dr. St. John Sutton reports receiving consulting fees from Medtronic and BioContro Medical. No other potential conflicts of interest relevant to this article were reported.
References


12. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: A report from the american society of
echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European association of echocardiography, a branch of the European society of cardiology. *J Amer Soc Echocardiogr*. 2005;18:1440-1463.


Table 1. Demographics and Cardiac Function Measurements at Randomization

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<thead>
<tr>
<th>Demographics</th>
<th>CRT-P (N=484)</th>
<th>CRT-D (N=207)</th>
<th>All Randomized Subjects (N=691)</th>
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<tr>
<td></td>
<td>BIV Arm (N=243)</td>
<td>RV Arm (N=241)</td>
<td>BIV Arm (N=106)</td>
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<tr>
<td>Male</td>
<td>181 (74.5%)</td>
<td>168 (69.7%)</td>
<td>87 (82.1%)</td>
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<tr>
<td>Age, years</td>
<td>74.4 ± 10.2</td>
<td>73.8 ± 10.8</td>
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<td>Heart rate, beats per minute</td>
<td>68.7 ± 23.4</td>
<td>68.7 ± 23.9</td>
<td>68.2 ± 16.9</td>
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<td>QRS duration, ms</td>
<td>125.4 ± 32.8</td>
<td>124.5 ± 31.1</td>
<td>122.5 ± 30.1</td>
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<tr>
<td>NYHA class</td>
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<tr>
<td>NYHA I</td>
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<td>47 (19.5%)</td>
<td>11 (10.4%)</td>
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<tr>
<td>NYHA II</td>
<td>141 (58.0%)</td>
<td>126 (52.3%)</td>
<td>67 (63.2%)</td>
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<tr>
<td>NYHA III</td>
<td>66 (27.2%)</td>
<td>68 (28.2%)</td>
<td>28 (26.4%)</td>
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<tr>
<td>Cardiomyopathy</td>
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<tr>
<td><strong>Ischemic</strong></td>
<td>94 (38.7%)</td>
<td>91 (37.8%)</td>
<td>67 (63.2%)</td>
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<td>47 (19.3%)</td>
<td>65 (27.0%)</td>
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<td>6 (3.1%)</td>
<td>2 (1.9%)</td>
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<td><strong>Other</strong></td>
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<td>6 (2.5%)</td>
<td>2 (1.9%)</td>
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<tr>
<td><strong>AF</strong></td>
<td>136 (56.0%)</td>
<td>133 (55.2%)</td>
<td>44 (41.5%)</td>
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</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Degree</td>
<td>39 (16.0%)</td>
<td>35 (14.5%)</td>
<td>29 (27.4%)</td>
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<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Degree</td>
<td>84 (34.6%)</td>
<td>70 (29.0%)</td>
<td>35 (33.0%)</td>
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<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Degree</td>
<td>120 (49.4%)</td>
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<td>42 (39.6%)</td>
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<td><strong>LBBB</strong></td>
<td>86 (35.4%)</td>
<td>75 (31.1%)</td>
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<td><strong>Measurements</strong></td>
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<tr>
<td>(Mean±SD)</td>
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<tr>
<td>LVEF, %</td>
<td>35.5 ± 9.1</td>
<td>35.0 ± 8.9</td>
<td>29.6 ± 8.0</td>
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<tr>
<td>LVESVI, mL/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>59.1 ± 23.2</td>
<td>59.7 ± 22.0</td>
<td>76.3 ± 27.7</td>
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<tr>
<td><strong>LVEDVI, mL/m²</strong></td>
<td>89.7 ± 27.4</td>
<td>90.2 ± 26.0</td>
<td>106.1 ± 31.1</td>
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<tr>
<td><strong>LVEDD, cm</strong></td>
<td>5.4 ± 0.8</td>
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<td>5.8 ± 0.8</td>
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<td><strong>LVESD, cm</strong></td>
<td>4.2 ± 0.9</td>
<td>4.2 ± 0.8</td>
<td>4.7 ± 0.8</td>
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<td><strong>LV Mass, g</strong></td>
<td>238.4 ± 65.4</td>
<td>240.5 ± 63.2</td>
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<td><strong>IVMD, ms</strong></td>
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<td>-79.4 ± 99.8</td>
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<td><strong>MR, %</strong></td>
<td>13.3 ± 12.3</td>
<td>13.3 ± 11.9</td>
<td>15.8 ± 12.8</td>
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<td><strong>CI, L/min/m²</strong></td>
<td>2.1 ± 0.6</td>
<td>2.1 ± 0.6</td>
<td>2.0 ± 0.6</td>
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<td><strong>E-wave/A-wave</strong></td>
<td>1.4 ± 0.9</td>
<td>1.4 ± 1.0</td>
<td>1.5 ± 1.0</td>
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</tbody>
</table>

Values are number (percent), except where otherwise indicated.

SD=Standard Deviation; AVB=Atrioventricular block; AF=Atrial Fibrillation; AV=Atrioventricular; LBBB=Left Bundle Branch Block; LVEF=Left Ventricular Ejection Fraction; LVESVI=Left Ventricular End Systolic Volume Index; LVEDVI=Left Ventricular End Diastolic Volume Index; LVEDD=Left Ventricular Dimension at End Diastole; LVESD=Left Ventricular Dimension at End Systole; IVMD=Intraventricular Mechanical Delay; MR=Mitral Regurgitation; CI=Cardiac Index.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>(1.89, 4.82)</td>
<td>(1.62, 4.84)</td>
<td>(0.42, 4.07)</td>
<td>(1.62, 5.60)</td>
</tr>
<tr>
<td>LVESVI</td>
<td>(-10.12, -4.21)</td>
<td>(-10.59, -3.83)</td>
<td>(-11.86, -4.57)</td>
<td>(-11.69, -2.85)</td>
</tr>
<tr>
<td>LVEDVI</td>
<td>(-9.09, -2.56)</td>
<td>(-9.47, -2.04)</td>
<td>(-12.91, -4.68)</td>
<td>(-11.37, -1.74)</td>
</tr>
<tr>
<td>LVEDD</td>
<td>(-0.24, -0.01)</td>
<td>(-0.29, -0.04)</td>
<td>(-0.29, -0.03)</td>
<td>(-0.39, -0.10)</td>
</tr>
<tr>
<td>LVESD</td>
<td>(-0.19, 0.06)</td>
<td>(-0.24, 0.03)</td>
<td>(-0.20, 0.09)</td>
<td>(-0.34, -0.02)</td>
</tr>
<tr>
<td>LV Mass</td>
<td>(-12.13, 3.95)</td>
<td>(-19.33, -0.86)</td>
<td>(-18.19, 1.62)</td>
<td>(-21.11, -0.96)</td>
</tr>
<tr>
<td>MR</td>
<td>(-2.83, 1.51)</td>
<td>(-2.84, 1.78)</td>
<td>(-2.38, 2.43)</td>
<td>(-3.34, 2.05)</td>
</tr>
<tr>
<td>CI</td>
<td>(-0.03, 0.20)</td>
<td>(-0.02, 0.20)</td>
<td>(-0.22, 0.06)</td>
<td>(-0.10, 0.19)</td>
</tr>
<tr>
<td>IVMD</td>
<td>(10.04, 48.64)</td>
<td>(2.84, 40.87)</td>
<td>(6.25, 47.19)</td>
<td>(2.00, 44.53)</td>
</tr>
<tr>
<td>E-wave/A-wave Ratio</td>
<td>(-0.18, 0.09)</td>
<td>(-0.29, 0.06)</td>
<td>(-0.14, 0.22)</td>
<td>(-0.09, 0.31)</td>
</tr>
</tbody>
</table>

LVEF=Left Ventricular Ejection Fraction; LVESVI=Left Ventricular End Systolic Volume Index; LVEDVI=Left Ventricular End Diastolic Volume Index; LVEDD=Left Ventricular Dimension at End Diastole; LVESD=Left Ventricular Dimension at End Systole; MR=Mitral Regurgitation; CI=Cardiac Index; IVMD=Intraventricular Mechanical Delay.
Table 3. LVESVI as a Predictor of Clinical Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>p-value</th>
<th>Hazard Ratio (95% CI) for 1 mL/m² increase in LVESVI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0.0119</td>
<td>1.007 (1.001, 1.012)</td>
</tr>
<tr>
<td>Mortality/HF Urgent Care</td>
<td>0.0042</td>
<td>1.007 (1.002, 1.011)</td>
</tr>
<tr>
<td>Mortality/HF Hospitalization</td>
<td>0.0002</td>
<td>1.008 (1.004, 1.012)</td>
</tr>
<tr>
<td>HF Hospitalization</td>
<td>0.0001</td>
<td>1.010 (1.005, 1.015)</td>
</tr>
</tbody>
</table>

LVESVI=Left Ventricular End Systolic Volume Index; HF=Heart Failure; CI=Confidence Interval
Figure Legends

Figure 1. Consort Diagram.

Figure 2. Average Absolute Improvement in Echo Parameters over Time. The number of subjects providing data at each time-point is presented on the x-axis.
LVEF=Left Ventricular Ejection Fraction; LVESVI=Left Ventricular End Systolic Volume Index; LVEDVI=Left Ventricular End Diastolic Volume Index; LVEDD=Left Ventricular End Diastolic Dimension; IVMD=Intraventricular Mechanical Delay.

Figure 3. Distribution of Subjects by Degree of Change in LVESVI from Randomization
Enrollment

918 Assessed for eligibility

691 Randomized 1:1

Allocation

227 Subjects not randomized:
- 95 Inclusion criteria not met prior to implant
- 14 Subject withdrawals prior to implant
- 51 Unsuccessful implants
- 67 Implanted subjects not randomized

349 Allocated to Biventricular Pacing
- 346 Received allocated intervention
- 3 Did not receive allocated intervention

331 Completed 6 Month Visit in Window
306 Completed 12 Month Visit in Window
269 Completed 18 Month Visit in Window
237 Completed 24 Month Visit in Window

Follow-up

342 Allocated to Right Ventricular Pacing
- 342 Received allocated intervention

319 Completed 6 Month Visit in Window
298 Completed 12 Month Visit in Window
270 Completed 18 Month Visit in Window
243 Completed 24 Month Visit in Window

Analysis

318 Analyzed
- 303 Analyzed at 6 Months
- 279 Analyzed at 12 Months
- 237 Analyzed at 18 Months
- 211 Analyzed at 24 Months

306 Analyzed
- 285 Analyzed at 6 Months
- 269 Analyzed at 12 Months
- 240 Analyzed at 18 Months
- 215 Analyzed at 24 Months
The graphs illustrate the changes in various cardiac metrics over different time periods:

- **LVESVI (Left Ventricular End-Systolic Volume Index)**
  - Reduction in Mean LVESVI (ml/m²): BIV N=279, RV N=272 (6 months), BIV N=260, RV N=256 (12 months), BIV N=256, RV N=225 (18 months), BIV N=187, RV N=204 (24 months).

- **LVEDVI (Left Ventricular End-Diastolic Volume Index)**
  - Reduction in Mean LVEDVI (ml/m²): BIV N=281, RV N=273 (6 months), BIV N=261, RV N=256 (12 months), BIV N=220, RV N=225 (18 months), BIV N=189, RV N=206 (24 months).

- **LVEF (Left Ventricular Ejection Fraction)**
  - Improvement in Mean LVEF (%): BIV N=282, RV N=273 (6 months), BIV N=263, RV N=260 (12 months), BIV N=223, RV N=226 (18 months), BIV N=192, RV N=205 (24 months).

- **LVEDD (Left Ventricular End-Diastolic Diameter)**
  - Reduction in Mean LVEDD (cm): BIV N=254, RV N=242 (6 months), BIV N=241, RV N=232 (12 months), BIV N=201, RV N=204 (18 months), BIV N=175, RV N=186 (24 months).

- **LV Mass**
  - Reduction in Mean LV Mass (g): BIV N=220, RV N=208 (6 months), BIV N=211, RV N=199 (12 months), BIV N=188, RV N=176 (18 months), BIV N=150, RV N=163 (24 months).

- **IVMD (Interventricular Septal Mass Index)**
  - Reduction in Mean IVMD (g/m²): BIV N=220, RV N=208 (6 months), BIV N=202, RV N=198 (12 months), BIV N=173, RV N=172 (18 months), BIV N=150, RV N=160 (24 months).
Left Ventricular Reverse Remodeling With Biventricular Versus Right Ventricular Pacing in Patients With Atrioventricular Block and Heart Failure in the BLOCK HF Trial
Martin St. John Sutton, Ted Plappert, Philip B. Adamson, Pei Li, Shelly A. Christman, Eugene S. Chung and Anne B. Curtis

_Circ Heart Fail_. published online February 19, 2015;
_Circulation: Heart Failure_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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