Inverse Relationship of Blood Pressure to Long-Term Outcomes and Benefit of Cardiac Resynchronization Therapy in Patients With Mild Heart Failure

A Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy Long-Term Follow-Up Substudy

Yitschak Biton, MD; Arthur J. Moss, MD; Valentina Kutyifa, MD, PhD; Andrew Mathias, MD; Saadia Sherazi, MD; Wojciech Zareba, MD, PhD; Scott McNitt, MS; Bronislava Polonsky, MS; Alon Barsheshet, MD; Mary W. Brown, MS, RN; Ilan Goldenberg, MD

Background—Previous studies have shown that low blood pressure is associated with increased mortality and heart failure (HF) in patients with left ventricular dysfunction. Cardiac resynchronization therapy (CRT) was shown to increase systolic blood pressure (SBP). Therefore, we hypothesized that treatment with CRT would provide incremental benefit in patients with lower SBP values.

Methods and Results—The independent contribution of SBP to outcome was analyzed in 1267 patients with left bundle brunch block enrolled in Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT). SBP was assessed as continuous measures and further categorized into approximate quintiles. The risk of long-term HF or death and CRT with defibrillator versus implantable cardioverter defibrillator benefit was assessed in multivariate Cox proportional hazards regression models. Multivariate analysis showed that in the implantable cardioverter defibrillator arm, each 10-mm Hg decrement of SBP was independently associated with a significant 21% (P<0.001) increased risk for HF or death, and patients with lower quintile SBP (<110 mm Hg) experienced a corresponding >2-fold risk-increase. CRT with defibrillator provided the greatest HF or mortality risk reduction in patients with SBP<110 mm Hg hazard ratio of 0.34, P<0.001, when compared with hazard ratio of 0.52, P<0.001, in those with 110>SBP≥136 mm Hg and hazard ratio of 0.94, P=0.808, with SBP>136 mm Hg (P for trend=0.001).

Conclusions—In patients with mild HF, prolonged QRS, and left bundle brunch block, low SBP is related to higher risk of mortality or HF with implantable cardioverter defibrillator therapy alone. Treatment with CRT is associated with incremental clinical benefits in patients with lower baseline SBP values.

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Key Words: blood pressure ■ bundle-branch block ■ cardiac resynchronization therapy ■ cardioverter-defibrillators, implantable ■ heart failure ■ mortality

Cardiac resynchronization therapy with or without defibrillator (CRT-D/CRT) has been shown to reduce the morbidity and mortality in patients with mild and severe heart failure (HF) in several randomized clinical trials.[1–6] In patients with mild HF, this benefit was restricted to patients with left bundle brunch block (LBBB).[7]

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Low systolic blood pressure (SBP) is a well-established independent predictor of morbidity and mortality, despite medical therapy in patients with either relatively reduced or preserved systolic HF.[8] We have previously shown that in patients with ischemic left ventricular (LV) dysfunction, there is an inverse correlation between SBP and sudden cardiac mortality, which is translated to a greater risk reduction in mortality with implantable cardioverter defibrillator (ICD) when compared with optimal medical therapy in patients with low SBP.[9]

Previous studies have suggested that treatment with CRT may be associated with a significant increase in SBP.[10]

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From the Heart Research Follow-Up Program, Division of Cardiology, Department of Medicine, University of Rochester Medical Center, NY.

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Correspondence to Yitschak Biton, MD, Heart Research Follow-Up Program, Cardiology Division, University of Rochester Medical Center, 265 Crittenden Blvd, PO Box 653, Rochester, NY 14642. E-mail yitschak.biton@heart.rochester.edu

However, data on risk stratification according to SBP and the implications of SBP change on long-term outcomes are lacking. Therefore, we hypothesized that treatment with CRT-D would provide incremental clinical benefit in higher-risk HF patients with lower baseline SBP values.

Accordingly, in this Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) long-term follow-up substudy, we aimed to evaluate (1) long-term differences in clinical outcome of HF or death by baseline SBP in patients who were treated with ICD-only therapy, (2) long-term CRT-D benefit when compared with ICD-only by baseline SBP, and (3) whether changes in SBP have implications on long-term outcomes, in LBBB patients.

Methods

Study Population

In the MADIT-CRT study, 1820 patients with LVEF <30%, QRS duration of at least 130 ms, and either ischemic cardiomyopathy and New York Heart Association class I–II symptoms or non–ischemic cardiomyopathy class and New York Heart Association class II were randomly assigned to CRT-D or ICD treatment arms. The protocol and results of the study have been detailed previously.[1,11] Patients from both treatment arms received optimal medical therapy for HF consisting of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers/angiotensin II inhibitors, β-blockers, and statins. Exclusion criteria included New York Heart Association class III or IV symptoms, coronary artery bypass graft surgery, percutaneous coronary intervention, or myocardial infarction within 90 days before enrollment; second- or third-degree heart block; chronic atrial fibrillation; and comorbidities, such as uremia (blood urea nitrogen, >70 mg/dL or creatinine >3.0 mg/dL) and liver failure.

In the present study, we included MADIT-CRT patients with available baseline SBP and LBBB ECG pattern at baseline because it was previously shown that the benefit of CRT-D is restricted to patients with LBBB pattern.[6,7] Consequently, the present study population comprised 1267 LBBB patients, 69% of the total 1820 original study patients.

Follow-Up

MADIT-CRT was performed from December 22, 2004, to June 22, 2009. After publication of the primary results,[1] post-trial follow-up was conducted for all surviving study participants (n=1691) until September 10, 2010 (phase I of the extended follow-up). After September 10, 2010, ongoing patient follow-up data were obtained on 854 patients enrolled at both US and non-US enrolling centers. The Heart Research Follow-up Program at the University of Rochester Medical Center in Rochester, NY, coordinated follow-up data collection as requested by the Food and Drug Administration for 407 patients from the 48 US centers that agreed to participate. Follow-up data were collected for 447 patients from the 23 non-US centers that agreed to participate and coordinated by the Israeli Association for Cardiovascular Trials at Sheba Medical Center, Ramat Gan, Israel. Both phases of the post-trial follow-up were approved by the institutional review board of each participating center and by the Rochester University institutional review committee; all patients provided written informed consent. Post-trial clinical and adverse events were obtained at 6-month intervals during follow-up.

Definitions and End Points

Patients with an LBBB and an implanted CRT-D or an ICD device were divided into 5 subgroups based on the baseline SBP quintile (<110 mm Hg; ≥110 and ≤118 mm Hg; >118 and ≤ 125 mm Hg; >125 and ≤136 mm Hg; and >136 mm Hg). To ease the interpretation, the patients were then grouped into 3 SBP categories: low SBP (first quintile, <110 mm Hg), medium SBP (quintiles 2–4, ≥110 and ≤136 mm Hg), and high SBP (fifth quintile, >136 mm Hg).

The primary end point of the current study was HF admission or death (whichever came first), the secondary end point was death. The effect of CRT-D on SBP was predefined as the change between baseline measurement and 6-month follow-up measurement. The 6-month follow-up was chosen to avoid the influence of changes in medication on outcomes, on the one hand, and to evaluate the effect of CRT-D, on the other.

Statistical Analysis

Baseline clinical characteristics were compared between patients from the 3 SBP groups, using the χ^2 test or Fisher exact test for categorical variables. For purposes of consistency, we used the Kruskal–Wallis test for all continuous variables. Categorical data are presented as frequencies and percentages and continuous variables as medians and corresponding inner quartile ranges. The cumulative probability of long-term primary and secondary end points were displayed according to the Kaplan–Meier method by baseline SBP and by treatment arm within each SBP group, with comparisons of cumulative event rates by the log-rank test.

Multivariate Cox proportional hazards regression analysis was used to assess the effect of SBP on the risk of long-term primary and secondary end points in patients with ICD. The Cox model was adjusted for relevant clinical covariates using best subset regression modeling (age, body mass index, creatinine, LV end-systolic volume, prior congestive heart failure hospitalization, LVEF, New York Heart Association, and white race). This model was then used to assess the effect of CRT-D to reduce the risk of the long-term primary and secondary end points. Interaction *P* values and *P* value for trend were computed and reported between the SBP groups. A landmark analysis was used to assess the effect SBP change at 6 months at long-term HF or death.

All statistical tests were 2 sided; a value of $P<0.05$ was considered statistically significant. Analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC).

Results

Among 1267 study patients, 241 (19%) patients had low SBP, 776 (61%) had medium SBP, and 250 (20%) had high SBP. Baseline characteristics are shown in Table 1. Overall, patients with low SBP were younger. This group had properties of more severe HF including higher frequency of congestive heart failure hospitalizations at >3 months before enrollment, higher rates of diuretics regimen, and lower rates of calcium channel blockers. All groups were equally treated with β-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. Creatinine and blood urea nitrogen levels were slightly elevated in the low SBP group, and echocardiographic parameters were slightly better at the higher SBP group. The high SBP group was more represented in the CRT-D treatment arm. The baseline characteristics of CRT-D versus ICD arm within each SBP group are shown in Table IA to IC in the Data Supplement . Patients with low SBP from the ICD treatment arm had higher frequency of prior atrial arrhythmias, but lower rates of prior ventricular arrhythmias when compared with CRT-D arm. The characteristics of patients with medium and high SBP were similar between the CRT-D and the ICD groups.

SBP and Outcome in the ICD Treatment Arm

Kaplan–Meier analysis showed that >7 years of follow-up, the cumulative probability of the primary and secondary end point was significantly higher among ICD-only patients who had low SBP at baseline than among those who had medium or high SBP values (Figure 1). Consistently, in the multivariate

Cox proportional hazards regression analysis, low SBP was associated with the highest risk for primary end point (hazard ratio [HR], 2.70; 95% confidence interval [CI], 1.65–4.42; $P<0.001$) and the risk decreased with medium SBP (HR, 1.46; 95% CI, 0.93–2.28; $P=0.098$) when compared with high SBP. Assessment of SBP as a continuous measure showed that each 10-mm Hg decrement in SBP was associated with corresponding 21% increased risk for primary end point (HR, 1.21; 95% CI, 1.10–1.32; $P<0.001$).

Table 1. Clinical and Echocardiographic Characteristics of the Patients Stratified by Baseline SBP Groups

Clinical Characteristics	Low SBP (n=241)	Medium SBP (n=776)	High SBP (n=250)
SBP, mm Hg	100 (97–104)	120 (115–130)	145 (140–151)*
DBP, mm Hg	62 (60–67)	70 (66–78)	80 (72–86)*
Age, y	62 (53–70)	65 (57–72)	68 (62–74)*
Female	84 (35)	225 (29)	81 (32)
CRT-D assigned treatment	127 (53)	467 (60)	160 (64)*
Ischemic	102 (42)	335 (43)	120 (48)
White race	212 (88)	712 (92)	229 (92)
Prior NYHA >2	37 (16)	69 (9)	28 (12)*
Prior CHF hospitalization	107 (45)	291 (38)	88 (35)
Diabetes mellitus	66 (28)	228 (29)	86 (34)
Hypertension	124 (52)	470 (61)	200 (80)*
Smoking	30 (12)	82 (11)	21 (9)
Prior atrial arrhythmias	29 (12)	86 (11)	25 (10)
Prior ventricular arrhythmias	16 (7)	50 (7)	15 (6)
Antiarrhythmics	15 (6)	57 (7)	15 (6)
ACE inhibitor or ARB	234 (97)	745 (96)	240 (96)
β -blockers	231 (96)	729 (94)	230 (92)
Calcium channel blockers	5 (2)	55 (7)	27 (11)*
Diuretics	183 (76)	525 (68)	158 (63)*
Statins	155 (64)	479 (62)	166 (66)
QRS, ms	160 (148–174)	160 (150–176)	162 (152–176)
Heart rate, beats per minute	68 (60–76)	68 (60–74)	68 (60–76)
BMI, kg/m^2	27 (24–31)	28 (25–31)	28 (25–32)
BUN, mg/dL	21 (16–27)	20 (16–25)	18 (15–24)*
Creatinine, mg/dL	1.10 (0.98–1.39)	1.10 (0.90–1.30)	1.06 (0.90–1.30)*
LVEF, %	28 (26–31)	29 (27–31)	29 (27–31)*
LVEDV index, mL/m^2	122 (109–144)	120 (108–140)	118 (103–134)*
LVESV index, mL/m^2	89 (77–104)	86 (76–102)	83 (72–95)*
LAV index, mL/m^2	47 (40–55)	46 (40–53)	46 (40–52)

Continuous variables: median (interquartile range); categorical variables: n (% of column total). Low SBP, first quintile (<110 mm Hg); medium SBP, quintiles 2–4 (110–136 mm Hg); high SBP, fifth quintile (>136 mm Hg). ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CHF, congestive heart failure; CRT-D, cardiac resynchronization therapy with defibrillator; DBP, diastolic blood pressure; LAV index, left atrial volume indexed by body surface area; LVEDV index, left ventricle end-diastolic volume indexed by body surface area; LVEF, left ventricular ejection fraction; LVESV index, left ventricle end-systolic volume indexed by body surface area; NYHA, New York Heart Association; Prior, >3 months before enrollment; and SBP, systolic blood pressure.

*Donates P value of <0.05 for the comparison between patients from the 3 SBP groups.

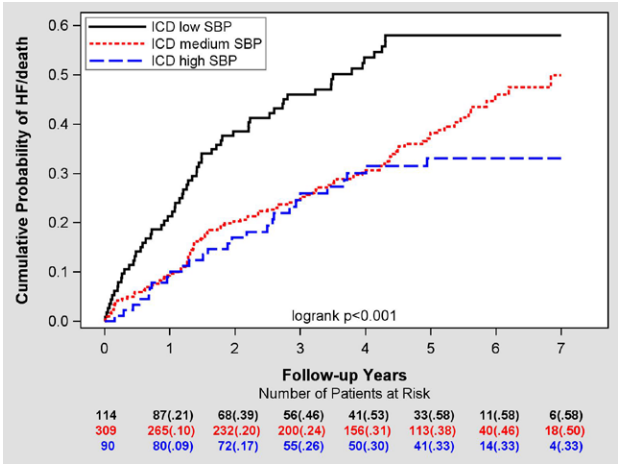

Figure 1. Cumulative probability of heart failure (HF)/death in implantable cardioverter defibrillator (ICD) patients by systolic blood pressure (SBP) subgroups.

Relation of CRT-D Benefit to SBP

The CRT-D to ICD benefit to reduce the primary end point was shown to be attenuated with the increase of SBP in a univariate Kaplan–Meier analysis (Figure 2A–2C). Accordingly, in a multivariate Cox proportional hazards regression analysis (Tables 2–3), the low SBP group (first quintile) had the highest risk reduction of the primary end point with CRT-D versus an ICD-only, whereas patients with medium SBP (quintiles 2–4) had lower reduction and patients with high SBP (fifth quintile) had no reduction at all (P for trend=0.001; P for SBP quintiles [as continuous ordinal variable] by treatment interaction=0.012).

Similar trend was shown when the secondary end point was analyzed. Low SBP was associated with the highest CRT-D versus ICD secondary end point reduction (HR, 0.48; 95% CI, 0.26–0.89; $P=0.020$), the reduction was attenuated in the medium SBP subgroup (HR, 0.71; 95% CI, 0.49–1.05; $P=0.084$) and was not evident in the high SBP subgroup (HR, 1.04; 95% CI, 0.48–2.25; $P=0.916$), P for trend=0.106.

Effect of CRT-D Versus ICD on SBP During Follow-Up

Six months after implantation of CRT-D, only patients with baseline SBP <110 (first quintile) had significant increase in SBP when compared with ICD patients (15% versus 9% accordingly; $P=0.004$; Figure 3). There was a linear inverse relationship between baseline SBP and the 6-month change with either CRT-D or ICD with patients with lower baseline SBP increasing their SBP, whereas patients with high baseline SBP had reduction in their SBP.

Relation of SBP Change to Outcome

The effect of SBP change on outcome was assessed by comparing CRT-D versus ICD benefit in patients who increased

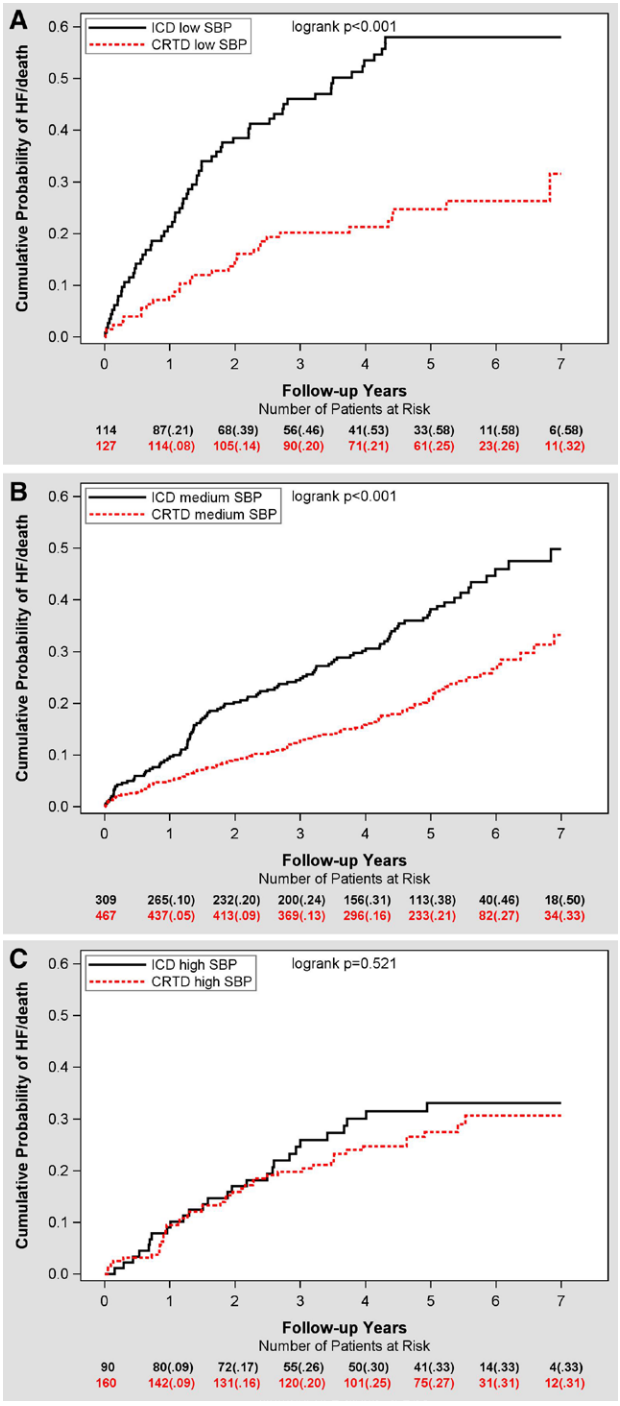

Figure 2. Cardiac resynchronization therapy with defibrillator (CRT-D) vs implantable cardioverter defibrillator (ICD) benefit in patients by blood pressure subgroups. **A**, Low systolic blood pressure (SBP) <110 mm Hg, (**B**) medium 110≤SBP≤136 mm Hg, and (**C**) high SBP>136 mm Hg. HF indicates heart failure.

their SBP to those who failed to increase their SBP at 6 months in a landmark analysis. In the multivariate analysis, patients with increased SBP at 6 months had higher risk reduction in HF or death when compared with patients without SBP increase (HR, 0.39; 95% CI, 0.28–0.54 versus HR, 0.58; 95% CI, 0.43–0.77, respectively), with a trend toward significant CRT-D treatment by SBP interaction (P=0.082).

Table 2. Hazard Ratios for Heart Failure or Death (367 Events) in Patients With CRT-D vs Implantable Cardioverter Defibrillator According to Baseline Systolic Blood Pressure by Quintile

Blood Pressure Quintile	Events	HR (95% CI)	*P* Value	*P* for Trend
Quintile 1	89/235	0.34 (0.22–0.53)	<0.001	0.008
Quintile 2	74/262	0.53 (0.34–0.85)	0.008	
Quintile 3	68/239	0.57 (0.35–0.91)	0.020	
Quintile 4	70/251	0.47 (0.29–0.75)	0.002	
Quintile 5	66/242	0.94 (0.57–1.55)	0.808	

Adjusted for age, body mass index, creatinine, left ventricle end-systolic volume indexed by body surface area, prior congestive heart failure hospitalization, white race, New York Heart Association, left ventricular ejection fraction, CRT-D treatment, and SBP quintile×CRT-D treatment interaction. When the quintiles were treated as a linear ordinal categorical variable (Q1, Q2, Q3, Q4, and Q5), *P* value for SBP by treatment interaction was 0.057. CI indicates confidence interval; CRT-D, cardiac resynchronization therapy with defibrillator; HR, hazard ratio; and SBP, systolic blood pressure.

Discussion

The main finding of this study is that patients with mild HF, LVEF under 30%, QRS longer than 130 ms, and LBBB with low SBP at baseline are at higher risk for the primary end point with ICD therapy alone and gain more benefit with CRT-D than patients with medium and high SBP. This outcome benefit is most probably attributable to SBP elevation with CRT-D. This noninvasive and simple hemodynamic measurement may be used to identify higher risk groups when considering CRT-D implantation, and it might be useful to assess response to CRT-D.

Previous studies have demonstrated an association between low blood pressure and unfavorable clinical outcomes with HF patients. Data from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry have shown that SBP<120 was an independent predictor of morbidity and mortality.[8] In the Acute Decompensated Heart Failure National Registry (ADHERE) study, SBP<115 mm Hg was the second

Table 3. Hazard Ratios for Heart Failure or Death in Patients With CRT-D vs Implantable Cardioverter Defibrillator According to Baseline SBP by SBP Subgroups

	Events	HR* (95% CI)	*P* Value	*P* for Trend
Low	89/235	0.34 (0.22–0.53)	<0.001	0.001
Medium	212/762	0.52 (0.40–0.68)	<0.001	
High	66/242	0.94 (0.57–1.55)	0.808	

Low vs medium SBP by treatment interaction *P* value=0.118, low vs high SBP by treatment interaction *P* value=0.003, medium vs high SBP by treatment interaction *P* value=0.042. When the quintiles were treated as a linear ordinal categorical variable (low, medium, and high), *P* value for SBP by treatment interaction was 0.012. CI indicates confidence interval; CRT-D, cardiac resynchronization therapy with defibrillator; HR, hazard ratio; and SBP, systolic blood pressure.

*Adjusted for age, body mass index, creatinine, left ventricle end-systolic volume indexed by body surface area, prior congestive heart failure hospitalization, white race, left ventricular ejection fraction, New York Heart Association, CRT-D treatment, and SBP group×CRT-D treatment interaction.

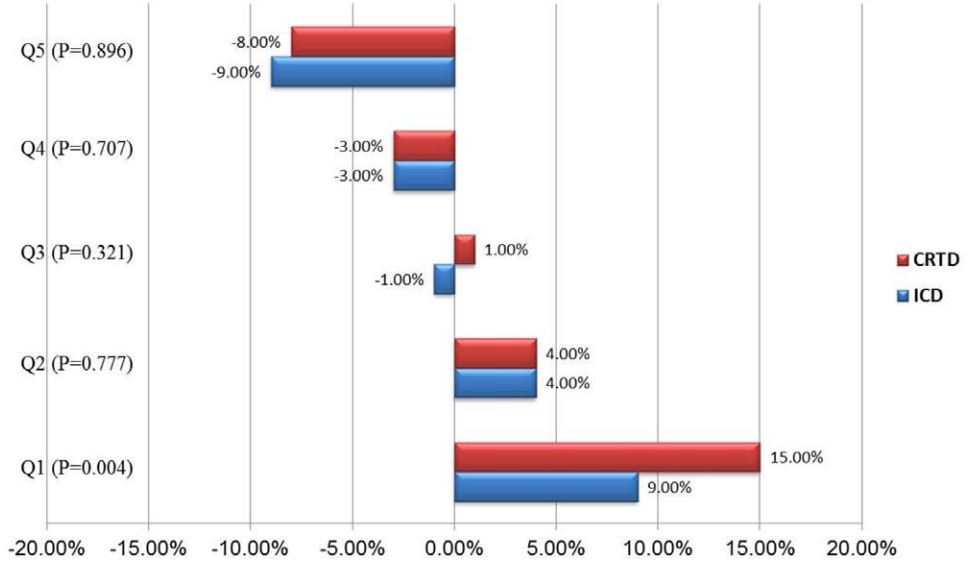

Figure 3. Blood pressure percent change at 6 months by treatment arm according to baseline systolic blood pressure quintiles. CRT-D indicates cardiac resynchronization therapy with defibrillator; and ICD, implantable cardioverter defibrillator.

best independent predictor for mortality after renal failure in patients with both preserved and reduced LVEF.[12] In another study, SBP<110 was a predictor for mortality and heart transplant among patients who were considered for heart transplant.[13] A Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II substudy demonstrated the association between low SBP and higher risk of sudden cardiac mortality in patients with ischemic cardiomyopathy and moderate to severe HF on optimal medical treatment and the reduction of risk with ICD.[9] However, in this study, we extended this observations showing that low SBP predicts HF or death and death in ICD-treated mild HF patients with both ischemic and nonischemic cause.

CRT-D is one of the fundamental treatment modalities for patients with mild HF and reduced EF, despite optimal medical therapy, currently indicated for those with prolonged QRS and LBBB morphology and seems to be less promising for non-LBBB morphology.[14,15] Previous risk stratifications were made in an era where the importance of QRS morphology was not fairly appreciated; therefore, it is important to identify higher risk patients within the LBBB group. In the current study, we have shown that CRT-D versus ICD benefit was inversely related to SBP with a significant SBP by treatment interaction, suggesting that CRT-D benefit is attenuated with high SBP.

The mechanism by which low SBP patients gain extended outcome benefit with CRT is thought to be related to SBP elevation secondary to the myocardial contractility improvement. It should be noted that there was no difference in the use of HF medications at baseline, and the relationship between CRT-D benefit and SBP persisted after adjustment to concurrent therapies with BP-lowering medications. In a systemic review of previous studies, CRT was related to mild elevation of SBP, but none of these studies had shown the relation to baseline SBP.[10] In this study, we show that the change in SBP is inversely related to the baseline measurement, and that only the low SBP group had significant elevation with CRT-D over ICD (15% versus 9%), whereas the upper SBP quintiles had SBP reduction, with a linear trend. We also conducted a landmark analysis that showed that patients who had SBP elevation had trend toward higher risk reduction of HF or death with CRT-D versus ICD than patients with unchanged or declined SBP (*P* for CRT-D treatment by SBP change interaction=0.082).

Limitations

This is a retrospective, nonrandomized post hoc study. Although multivariate analysis showed superior benefit with CRT-D in patients with lower SBP when adjusting for many confounders, it was not a prospective trial and possible unmeasured confounders may have biased the results; therefore, our results should be interpreted as hypothesis generating. Furthermore, we have only included patients with LBBB morphology because CRT-D benefit was shown to be limited to this subgroup, thus excluded about one third of the original study patients. It should be noted that LBBB was not a prespecified variable in the MADIT-CRT trial. Finally, subgroup analyses are underpowered, particularly when moving onto subgroups of subgroups and caution in the interpretation of the subgroup interactions is needed because of multiple testing.

Conclusions

In patients with mild HF, prolonged QRS, and LBBB, low SBP is related to higher risk of mortality or HF with ICD therapy alone and greater risk reduction of HF or death with CRT-D, accompanied by an increase in SBP during follow-up.

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Disclosures

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References

1. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA III, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W; MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. 2009;361:1329–1338. doi: 10.1056/NEJMoa0906431.
2. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C; REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) Study Group. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol*. 2008;52:1834–1843. doi: 10.1016/j.jacc.2008.08.027.
3. Daubert C, Gold MR, Abraham WT, Ghio S, Hassager C, Goode G, Szili-Török T, Linde C; REVERSE Study Group. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. *J Am Coll Cardiol*. 2009;54:1837–1846. doi: 10.1016/j.jacc.2009.08.011.
4. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004;350:2140–2150. doi: 10.1056/NEJMoa032423.
5. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539–1549. doi: 10.1056/NEJMoa050496.
6. Goldenberg I, Kutyifa V, Klein HU, Cannom DS, Brown MW, Dan A, Daubert JP, Estes NA III, Foster E, Greenberg H, Kautzner J, Klempfner R, Kuniss M, Merkely B, Pfeffer MA, Quesada A, Viskin S, McNitt S, Polonsky B, Ghanem A, Solomon SD, Wilber D, Zareba W, Moss AJ. Survival with cardiac-resynchronization therapy in mild heart failure. *N Engl J Med*. 2014;370:1694–1701. doi: 10.1056/NEJMoa1401426.
7. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, Cannom D, Daubert JP, Eldar M, Gold MR, Goldberger JJ, Goldenberg I, Lichstein E, Pitschner H, Rashtian M, Solomon S, Viskin S, Wang P, Moss AJ; MADIT-CRT Investigators. Effectiveness of Cardiac Resynchronization Therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation*. 2011;123:1061–1072. doi: 10.1161/CIRCULATIONAHA.110.960898.
8. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, Stough WG, Yancy CW, Young JB, Fonarow GC; OPTIMIZE-HF Investigators and Coordinators. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA*. 2006;296:2217–2226. doi: 10.1001/jama.296.18.2217.
9. Goldenberg I, Moss AJ, McNitt S, Zareba W, Hall WJ, Andrews ML; MADIT-II Investigators. Inverse relationship of blood pressure levels to sudden cardiac mortality and benefit of the implantable cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. *J Am Coll Cardiol*. 2007;49:1427–1433. doi: 10.1016/j.jacc.2006.11.042.
10. Ather S, Bangalore S, Vemuri S, Cao LB, Bozkurt B, Messerli FH. Trials on the effect of cardiac resynchronization on arterial blood pressure in patients with heart failure. *Am J Cardiol*. 2011;107:561–568. doi: 10.1016/j.amjcard.2010.10.014.
11. Moss AJ, Brown MW, Cannom DS, Daubert JP, Estes M, Foster E, Greenberg HM, Hall WJ, Higgins SL, Klein H, Pfeffer M, Wilber D, Zareba W. Multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT): design and clinical protocol. *Ann Noninvasive Electrocardiol*. 2005;10(4 suppl):34–43. doi: 10.1111/j.1542-474X.2005.00073.x.
12. Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boscardin WJ; ADHERE Scientific Advisory Committee, Study Group, and Investigators. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA*. 2005;293:572–580. doi: 10.1001/jama.293.5.572.
13. Aranda JM Jr, McIntyre SE, Klodell CT Jr, York KM, Dragstedt CA, Chaille PJ, Conti JB, Pauly DF, Hill JA, Schofield RS. Initial heart rate and systolic blood pressure predict outcomes in chronic heart failure patients who are evaluated for cardiac transplant. *Clin Cardiol*. 2007;30:282–287. doi: 10.1002/clc.20080.
14. Dickstein K, Vardas PE, Auricchio A, Daubert JC, Linde C, McMurray J, Ponikowski P, Priori SG, Sutton R, van Veldhuisen DJ; ESC Committee for Practice Guidelines (CPG). 2010 Focused Update of ESC Guidelines on device therapy in heart failure: an update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy. Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. *Eur Heart J*. 2010;31:2677–2687. doi: 10.1093/eurheartj/ehq337.
15. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Tracy CM, Epstein AE, Darbar D, DiMarco JP, Dunbar SB, Estes NA III, Ferguson TB Jr, Hammill SC, Karasik PE, Link MS, Marine JE, Schoenfeld MH, Shanker AJ, Silka MJ, Stevenson LW, Stevenson WG, Varosy PD; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Heart Rhythm Society. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2013;61:e6–75. doi: 10.1016/j.jacc.2012.11.007.

CLINICAL PERSPECTIVE

Patients with heart failure have poor long-term prognosis if they have low systolic blood pressure (SBP). Implantable cardioverter defibrillator has been shown to reduce mortality in this cohort to some extent; however, both morbidity and mortality remain a concern. In recent years, cardiac resynchronization therapy (CRT) was shown to improve the outcomes and increase SBP in heart failure patients with prolonged QRS, mainly in left bundle branch block configuration. Patients with heart failure who had increase in their SBP with CRT exhibited a more pronounced benefit. In the present study, we show that in the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) population, patients with low baseline SBP (<110 mm Hg) derived greater long-term benefit with CRT with defibrillator when compared with implantable cardioverter defibrillator than patients with high SBP (≥110 mm Hg). Furthermore, we showed that blood pressure was predominantly increased after treatment with CRT among those with a low baseline SBP. These findings suggest that this noninvasive and simple hemodynamic measurement may be used for improved risk stratification and assessment of the response to CRT.

Circulation
Heart Failure

Inverse Relationship of Blood Pressure to Long-Term Outcomes and Benefit of Cardiac Resynchronization Therapy in Patients With Mild Heart Failure: A Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy Long-Term Follow-Up Substudy

Yitschak Biton, Arthur J. Moss, Valentina Kutyifa, Andrew Mathias, Saadia Sherazi, Wojciech Zareba, Scott McNitt, Bronislava Polonsky, Alon Barsheshet, Mary W. Brown and Ilan Goldenberg

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Supplemental Material

Supplemental Table 1. Clinical and echocardiographic characteristics stratified by treatment arm for each baseline systolic blood pressure: A. Low SBP = first quintile (<110 mmHg), B. Medium SBP=Quintiles 2-4 (110-136 mmHg) and C. High SBP= fifth quintile (>136 mmHg).

A.

Clinical Characteristics	ICD n=114	CRT-D n=127
SBP mmHg	100.0(96.0-102.0)	100.0(98.0-105.0)
DBP mmHg	62.0(58.0-66.0)	62.0(60.0-68.0)
Age at enrollment years	62.0(55.0-70.0)	63.0(53.0-69.0)
Female	36(32)	48(38)
Ischemic	48(42)	54(43)
White Race	103(90)	109(87)
Prior NYHA > 2	15(14)	22(18)
Prior CHF Hospitalization	52(47)	55(43)
Diabetes	28(25)	38(30)
Hypertension	62(54)	62(50)
Smoking	18(16)	12(9)

Prior Atrial Arrhythmias	19(17)	10(8)*
Prior Ventricular Arrhythmias	3(3)	13(10)*
Antiarrhythmics	111(97)	123(97)
ACE Inhibitor or ARB	7(6)	8(6)
Beta-blockers	110(96)	121(95)
Diuretic	87(76)	96(76)
Statins	67(59)	88(69)
QRS msec	160.5(148.0-179.0)	160.0(146.0-170.0)
Heart Rate bpm	70.0(60.0-78.0)	67.0(60.0-76.0)
BMI kg/m^2	27.2(24.6-30.5)	27.7(24.5-31.0)
BUN mg/dl	21.0(16.8-26.0)	20.0(16.0-28.0)
Creatinine mg/dl	1.10(1.00-1.30)	1.10(0.97-1.40)
LVEF %	28.2(25.7-30.5)	28.4(25.9-30.7)
LVEDV Indexed by BSA ml/m^2	127.1(110.3-153.0)	121.1(108.7-136.8)
LVESV Indexed by BSA ml/m^2	90.1(77.4-112.4)	87.8(76.5-99.6)
LAV Indexed by BSA ml/m^2	47.2(42.0-59.5)	46.5(39.3-53.2)

B.

Clinical Characteristics	ICD n=309	CRT-D n=467
SBP mmHg	66.0(58.0-73.0)	64.0(57.0-72.0)
DBP mmHg	120.0(115.0-130.0)	120.0(116.0-130.0)
Age at enrollment years	70.0(64.0-76.0)	70.0(68.0-80.0)*
Female	85(28)	140(30)
Ischemic	140(45)	195(42)
White Race	284(93)	428(92)
Prior NYHA > 2	29(10)	40(9)
Prior CHF Hospitalization	104(34)	187(40)
Diabetes	98(32)	130(28)
Hypertension	196(64)	274(59)
Smoking	34(11)	48(10)
Prior Atrial Arrhythmias	39(13)	47(10)
Prior Ventricular Arrhythmias	26(9)	24(5)
Antiarrhythmics	29(9)	28(6)

ACE Inhibitor or ARB	298(96)	447(96)
Beta-blockers	287(93)	442(95)
Diuretic	214(69)	311(67)
Statins	198(64)	281(60)
QRS msec	160.0(150.0-177.0)	160.0(148.0-176.0)
Heart Rate bpm	68.0(60.0-74.0)	66.0(60.0-73.0)
BMI kg/m^2	28.3(25.7-31.0)	28.1(25.2-31.4)
BUN mg/dl	20.0(16.0-25.0)	19.0(15.0-24.8)*
Creatinine mg/dl	1.10(0.90-1.30)	1.10(0.90-1.30)
LVEF %	28.9(27.0-31.0)	28.9(26.8-30.8)
LVEDV Indexed by BSA ml/m^2	120.9(107.7-142.0)	119.9(107.6-136.3)
LVESV Indexed by BSA ml/m^2	86.4(74.9-103.2)	85.8(75.8-100.1)
LAV Indexed by BSA ml/m^2	46.3(40.5-53.2)	45.4(40.0-52.4)

C.

Clinical Characteristics	ICD n=90	CRT-D n=160
SBP mmHg	145.0(140.0-150.0)	144.0(140.0-152.0)
DBP mmHg	80.0(73.0-85.0)	80.0(72.0-88.0)
Age at enrollment years	68.5(61.0-76.0)	68.0(62.0-74.0)
Female	31(34)	50(31)
Ischemic	39(43)	81(51)
White Race	80(90)	149(93)
Prior NYHA > 2	8(9)	20(13)
Prior CHF Hospitalization	32(36)	56(35)
Diabetes	31(34)	55(34)
Hypertension	72(80)	128(81)
Smoking	7(8)	14(9)
Prior Atrial Arrhythmias	11(13)	14(9)
Prior Ventricular Arrhythmias	5(6)	10(6)

Antiarrhythmics	3(3)	12(8)
ACE Inhibitor or ARB	85(94)	155(97)
Beta-blockers	84(93)	146(91)
Diuretic	57(63)	101(63)
Statins	55(61)	111(69)
QRS msec	165.0(154.0-178.0)	160.0(151.5-173.5)
Heart Rate bpm	67.5(60.0-76.0)	68.0(60.0-76.0)
BMI kg/m^2	28.4(24.7-31.7)	28.0(25.4-31.8)
BUN mg/dl	20.0(15.0-24.0)	18.0(15.0-24.0)
Creatinine mg/dl	1.10(0.90-1.30)	1.03(0.90-1.26)
LVEF %	29.7(27.4-30.8)	29.1(27.4-31.4)
LVEDV Indexed by BSA ml/m^2	113.6(102.9-132.4)	119.2(103.2-134.4)
LVESV Indexed by BSA ml/m^2	80.6(71.4-93.8)	83.7(72.0-96.0)
LAV Indexed by BSA ml/m^2	44.0(38.8-49.3)	46.9(40.9-52.4)*

* - Donates P value <0.05 for the comparison between patients from the three SBP groups.

Continuous variables: Median (Interquartile Range)

Categorical variables: N (% of column total)

Abbreviations: ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; BUN = blood urea nitrogen; CABG = coronary artery bypass graft; IQR = inter quartile range; LAV index = left atrial volume indexed by body surface area; LVEDV index = left ventricle end diastolic volume indexed by body surface area; LVESV index = left ventricle end systolic volume indexed by body surface area ; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association, Prior = more than 3 months prior to enrollment.