Effectiveness of Cardiac Resynchronization Therapy in Diabetic Patients with Ischemic and Nonischemic Cardiomyopathy

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Background: Diabetes mellitus (DM) increases the risk for the development of both ischemic and nonischemic cardiomyopathy. We aimed to identify differences in response to cardiac resynchronization therapy with a defibrillator (CRT-D) among DM patients with ischemic or nonischemic cardiomyopathy.

Methods: Cox proportional hazards regression modeling was used to assess clinical response to CRT-D (defined as CRT-D vs. defibrillator-only reduction in the risk of heart failure [HF] or death) and echocardiographic response (defined as percent reduction in left ventricular end diastolic and systolic volume [LVEDV and LVESV, respectively] at 12 month of follow-up compared with baseline values) among 552 diabetic patients with ischemic (n = 367) or nonischemic (n = 185) cardiomyopathy enrolled in MADIT-CRT.

Results: The clinical benefit of CRT-D was more pronounced among nonischemic patients (HR = 0.30 [P < 0.001] than among ischemic patients (HR = 0.59 [P = 0.004]; P for interaction = 0.10). Nonischemic patients also experienced significantly greater reductions in LVESV and LVEDV at 12 months with CRT-D compared with ischemic patients (P < 0.001 for both). Subgroup analysis showed that the most pronounced reduction in HF or death with CRT-D therapy occurred in nonischemic patients who were women (83% risk-reduction [P < 0.001]), had a lower BMI (<30/kg/m²: 79% risk-reduction [P < 0.001]), or had left bundle branch block at enrollment (82% risk-reduction [P < 0.001]).

Conclusions: The present study shows that treatment with CRT-D in at-risk cardiac patients with DM is associated with substantial reductions in the risk of HF or death and improvement in cardiac remodeling in those with ischemic and nonischemic cardiomyopathy, with a more pronounced benefit in patients with nonischemic disease.

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Diabetes mellitus (DM) is responsible for diverse cardiovascular complications such as increased atherosclerosis in large arteries and increased coronary atherosclerosis, which increases the risk for myocardial infarction and heart failure (HF) but may also affect cardiac structure and function in the absence of overt coronary artery disease, a condition called diabetic cardiomyopathy.^{1–3} Thus, DM may be associated with cardiac dysfunction

through both ischemic and nonischemic pathways. Despite currently available therapeutic modalities for the treatment of HF, morbidity and mortality in DM patients with ischemic and nonischemic cardiomyopathy remain high.⁴ We have recently shown that cardiac resynchronization therapy (CRT) is associated with a significant reduction in the risk of HF or death among DM patients with mildly symptomatic left ventricular dysfunction.⁵

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However, currently there is limited information regarding differences in the characteristics and outcomes of ischemic and nonischemic patients with DM who receive device therapy for the treatment of HF. Accordingly, the present study was carried out among 552 DM patients enrolled in MADIT-CRT, and was designed to: (1) compare the clinical and echocardiographic characteristics of ischemic and nonischemic patients with DM who were enrolled in the trial; (2) evaluate differences in the clinical and echocardiographic response to CRT-D in the two DM groups; and (3) identify risk subsets among ischemic and nonischemic patients with DM who derive enhanced benefit from CRT.

METHODS

Study Population

The design and primary results of MADIT-CRT have been recently published.⁶ Briefly, MADIT-CRT was designed to determine whether CRT with a defibrillator (CRT-D) would reduce the risk of death or HF events in patients with mild cardiac symptoms, a reduced ejection fraction and wide QRS complex when compared to implantable cardioverter defibrillator (ICD) therapy. The patients were randomly assigned in a 3:2 ratio to receive either CRT-D or ICD. From December 22, 2004, through April 23, 2008, a total of 1820 patients were enrolled at 110 hospital centers. Patients of either sex who were at least 21 years of age were enrolled in the study if they had ischemic cardiomyopathy (New York Heart Association [NYHA] class I or II) or nonischemic cardiomyopathy (NYHA class II only), sinus rhythm, an ejection fraction of <0.30 , and prolonged intraventricular conduction with a QRS duration of >130 ms. All eligible subjects met the guideline indication for ICD therapy.⁷ Patients were excluded from enrollment if they had reversible nonischemic cardiomyopathy such as acute viral myocarditis or discontinuation of alcohol in alcohol-induced heart disease. The protocol was approved by the institutional review board at each of the participating centers.

The present study population comprises 552 patients with DM who were enrolled in MADIT-CRT.

Echocardiographic Studies

Echocardiograms were obtained according to a study-specific protocol at baseline for 549 (99%)

study patients, which was prior to device implantation, and follow-up echocardiograms were obtained at 1 year. Paired echocardiograms from baseline and at 12 months with device turned on were available in 412 (75%) of 552 DM patients included in the present study.

Echocardiograms were sent on video tape or digital storage to the echocardiographic core laboratory at Brigham and Women's Hospital where they were screened for quality, and left ventricular, right ventricular, and left atrial measurements were made. Echocardiographic parameters were measured according to established American Society of Echocardiography protocols.⁸ Left ventricular volumes were measured by Simpson's method of discs in the apical four-chamber and two-chamber views and averaged. Left ventricular ejection fractions were calculated according to standard methods. Left atrial volumes were measured using Simpson's method of discs in the apical four-chamber view. Reproducibility of the primary volumetric measures was assessed by having the primary observer re-analyze 101 random studies. The coefficient of variation for end-diastolic volume, end-systolic volume, and ejection fraction were 5.2%, 6.2%, and 5.5%, respectively.

Definitions and End Points

Etiology of Cardiomyopathy

Patients with DM were classified as having ischemic cardiomyopathy if they experienced a previous myocardial infarction, coronary artery bypass graft surgery, and/or percutaneous coronary intervention more than 90 days before enrollment in the trial. Patients without coronary artery disease and/or without a prior ischemic event were classified as having nonischemic cardiomyopathy.

Remodeling Effects

An echocardiographic response was defined as percent reduction in left ventricular end diastolic and systolic volumes (LVEDV, LVESV) and left atrial volume (LAV) between enrollment and 1-year (calculated as the difference between 1-year cardiac volumes and baseline cardiac volumes, divided by baseline cardiac volumes).

Clinical Response

The primary end point for clinical response was defined as a first HF event or death, whichever came first, during follow-up. Secondary end points included the separate occurrences of all-cause mortality or HF.

Statistical Analysis

The clinical characteristics of study patients were compared by the etiology of cardiomyopathy using the chi-square test for categorical variables, and the *t*-test for continuous variables. Kaplan–Meier estimates for HF or all-cause mortality in each treatment group, stratified according to the etiology of cardiomyopathy, were determined and statistically evaluated with the log-rank test. The Cox proportional-hazards regression model was used to evaluate the independent contribution of baseline clinical factors to the development of the end point. All models included the following prespecified covariates: age >65 years, gender, QRS ≥ 150 msec, EF <25%, left bundle branch block (LBBB), body mass index (BMI) ≥ 30 kg/m². The consistency of the results was also assessed in a secondary analysis that included systolic blood pressure ≥ 130 mmHg, heart rate ≥ 80 bpm, and medical therapies with beta-blockers, angiotensin-converting enzyme

inhibitors, and diuretics as additional covariates. The benefit of CRT-D compared with ICD-only therapy in reducing the primary and secondary end points in ischemic and nonischemic patients was assessed by including a cardiomyopathy etiology-by-treatment interaction-term in the multivariate models. Interaction-term analysis was also used to assess the benefit of CRT-D in prespecified risk subsets of ischemic and nonischemic patients (categorized by BMI, gender, QRS duration, and the presence of LBBB). Percent changes in cardiac volumes and ejection fraction with CRT-D therapy were compared between the ischemic and nonischemic groups with the *t*-test. All P values were two-sided, and a P value < 0.05 was considered significant. Analyses were performed with the use of SAS software (version 9.20).

RESULTS

Among the 552 study patients with DM, 367 had ischemic (66%) and 185 had a nonischemic (34%) heart disease. The baseline clinical and echocardiographic characteristics of study patients by the etiology of cardiomyopathy are shown in Table 1. Diabetic patients with an ischemic etiology were older, had a higher frequency of hypertension, increased serum creatinine, and a higher BMI, whereas the

Table 1. Baseline Characteristics of Study Patients with DM by the Etiology of Cardiomyopathy. Data are presented as percentage or mean $\pm$ SD

Characteristic	Ischemic (n = 367)	Nonischemic (n = 185)	P-Value
CRT-D	60%	59%	0.83
Age (yr)	67 $\pm$ 9	63 $\pm$ 10	<0.001
Female sex	14%	44%	<0.001
QRS ≥ 150 (msec)	54%	76%	<0.001
Body mass index (kg/m ²)	25 $\pm$ 5	23 $\pm$ 5	<0.001
Hypertension	82%	73%	<0.001
Blood urea nitrogen (mg/dL)	24 $\pm$ 10	23 $\pm$ 10	0.54
Creatinine (mg/dL)	1.3 $\pm$ 0.5	1.2 $\pm$ 0.3	0.01
Left bundle branch block	60%	87%	<0.001
Baseline Echocardiography			
Ejection fraction $\geq 25\%$,	11%	12%	0.85
Left ventricular end diastolic volume/ body surface area (ml/m ²)	105 $\pm$ 24	104 $\pm$ 25	0.69
Left ventricular end systolic volume/ body surface area (ml/m ²)	68 $\pm$ 19.9	66 $\pm$ 21	0.48
Left atrial volume/body surface area (ml/m ²)	37 $\pm$ 10	36 $\pm$ 9	0.58
Baseline Medications			
Angiotensin-converting enzyme inhibitors	75%	78%	0.53
Beta-blockers	91%	96%	0.04
Digitalis	20%	35%	<0.001
Aldosterone	26%	41%	<0.001
Diuretic	76%	82%	0.09

Figure 1. Cumulative probability of HF or death by treatment arm in diabetic patients with (A) nonischemic cardiomyopathy; and (B) ischemic cardiomyopathy. CRT-D = cardiac resynchronization therapy-defibrillator; HF = heart failure; ICD = implantable cardioverter defibrillator.

nonischemic group comprised a higher proportion of women, patients with prolonged QRS, and patients with LBBB. Medical therapy with beta-blockers, diuretics, and aldosterone antagonists was administered at a higher frequency in nonischemic patients. There were no statistically significant differences in baseline echocardiographic parameters between the two groups at enrollment (Table 1).

Clinical Response to CRT-D therapy

Diabetic patients with ischemic or nonischemic cardiomyopathy who were treated with CRT-D therapy experienced significantly lower events

rates as compared with the corresponding patients who were allocated to ICD-only therapy (Figs 1 and 2). However, the relative reduction in event rates with CRT-D therapy was more pronounced in the nonischemic group as compared with the ischemic group. Thus, in the nonischemic group, 3-year relative reductions in the rates of HF or death (Fig. 1A) and of HF alone (Fig. 2A) with CRT-D therapy were 65% and 72%, respectively, whereas in the ischemic group the respective relative reductions were 27% and 34% (Figs 1B and 2B, respectively). Consistent with these findings, multivariate analysis showed that CRT-D therapy was associated with a significant reduction in the risk of HF or death and of HF alone in diabetic patients with

Figure 2. Cumulative probability of a first HF event in diabetic patients with (A) nonischemic cardiomyopathy; and (B) ischemic cardiomyopathy. CRT-D = cardiac resynchronization therapy-defibrillator; HF = heart failure; ICD = implantable cardioverter defibrillator.

either ischemic or nonischemic cardiomyopathy (Table 2). However, the adjusted risk-reductions with CRT-D therapy were higher among nonischemic patients (70% reduction in the risk of HF or death [$P < 0.001$] and 74% reduction in the risk of HF alone [$P < 0.001$]) than among nonischemic patients (42% reduction in the risk of HF or death [$P = 0.005$] and 50% reduction in the risk of HF alone [$P < 0.001$]; P -values for interactions of treatment-by-ischemic/nonischemic etiology = 0.10 and 0.14, respectively).

Subgroup analysis (Table 3) showed that the most pronounced reductions in the risk of HF or death occurred in diabetic patients with a nonischemic etiology of cardiomyopathy who were women (83% risk-reduction [$P < 0.001$]), had a

lower BMI ($<30/\text{kg}/\text{m}^2$: 79% risk-reduction [$P < 0.001$]), or had LBBB at enrollment (82% risk-reduction [$P < 0.001$]).

Echocardiographic Response to CRT-D

Diabetic patients with either ischemic or nonischemic cardiomyopathy who were treated with CRT-D therapy experienced pronounced reductions in cardiac volumes and improvements in ejection fraction (Fig. 3). However, despite the fact that baseline echocardiographic measurements were similar in the two groups (Table 1), echocardiographic response to CRT-D therapy was significantly greater in the nonischemic group as compared with the ischemic group. There were

Table 2. Multivariate Analysis: CRT-D Versus ICD Risk of End Points by the Etiology of Cardiomyopathy in Patients with DM^a

End Point ^b	Ischemic			Nonischemic		
	Hazard Ratio	95% CI	P-Value	Hazard Ratio	95% CI	P-Value
HF or death	0.58	0.40–0.85	0.005	0.30	0.15–0.61	<0.001
HF	0.50	0.33–0.75	<0.001	0.26	0.12–0.56	<0.001
Death	0.74	0.38–1.42	0.36	0.43	0.12–1.46	0.18

^aAll models were further adjusted for age >65 years, gender, QRS >150 msec, EF <25%, left bundle branch block, body mass index ≥ 30 kg/m²; results were consistent when systolic blood pressure ≥ 130 mmHg, heart rate ≥ 80 bpm, and medical therapies with beta-blockers, angiotensin-converting enzyme inhibitors, and diuretics were included as additional covariates.

^bP-value for etiology-by-treatment interaction by end point:
HF or death = 0.10. HF = 0.14. Death = 0.44.

Table 3. Multivariate Analysis: CRT-D Versus ICD Risk of HF or Death in Risk Subsets of Diabetic Patients with Ischemic and Nonischemic Heart Disease^a

Risk Subset ^b	Ischemic			Nonischemic		
	Hazard Ratio	95% CI	P-Value	Hazard Ratio	95% CI	P-Value
BMI (kg/m²)						
<30	0.46	0.27–0.78	0.004	0.21	0.09–0.53	<0.001
≥ 30	0.72	0.42–1.23	0.23	0.47	0.16–1.43	0.18
Gender						
Female	0.38	0.12–1.18	0.09	0.17	0.06–0.48	<0.001
Male	0.61	0.41–0.91	0.01	0.51	0.19–1.39	0.19
QRS duration						
≥ 150	0.42	0.25–0.71	0.001	0.23	0.10–0.54	<0.001
<150	0.84	0.47–1.49	0.54	0.51	0.14–1.92	0.32
QRS morphology						
LBBB	0.45	0.27–0.74	0.002	0.18	0.08–0.40	<0.001
Non-LBBB	0.81	0.45–1.47	0.49		NA ^c	

^aModels were carried out separately in the ischemic and nonischemic subgroups; the CRT-D versus ICD risk in each risk subset was assessed using interaction-term analysis; models were further adjusted for age >65 years, gender, QRS >150 msec, EF <25%, left bundle branch block, body mass index ≥ 30 kg/m²; results were consistent when systolic blood pressure ≥ 130 mmHg, heart rate ≥ 80 bpm, and medical therapies with beta-blockers, angiotensin-converting enzyme inhibitors, and diuretics were included as additional covariates.

^bAll P-values for risk subset-by-treatment interactions in both ischemic and nonischemic patients >0.05.

^cSample size and number of events among non-LBBB patients with nonischemic cardiomyopathy were not adequate for assessment using multivariate modeling.

significantly greater percent reductions in LVEDV (mean reductions: 24% vs. 18%, respectively; $P < 0.001$), in LVESV (mean reductions: 36% vs. 29%, respectively; $P < 0.001$), and in LAV (mean reductions: 31% vs. 26%, respectively; $P = 0.005$).

DISCUSSION

Our findings have several important implications regarding the clinical and echocardiographic effects of CRT in diabetic patients with ischemic and nonischemic etiology of cardiomyopathy. We have shown that: (1) diabetic patients with cardiomy-

opathy display distinctive, etiology-specific, clinical characteristics at baseline assessment that may affect the response to treatment with the device following implantation; (2) DM patients with either ischemic or nonischemic cardiomyopathy exhibit a significant reduction in the risk of HF or death and significant reverse remodeling effects with CRT-D therapy. However, nonischemic patients derive a more pronounced clinical benefit and significantly greater reverse remodeling effects with CRT-D therapy than ischemic patients; and (3) important patient subsets within the nonischemic DM population derive even a further enhanced clinical

Figure 3: Changes in cardiac volumes and ejection fraction among ischemic and nonischemic patients treated with CRT-D. Changes were calculated as the difference between 1-year value and baseline value divided by the value LAV = left atrial volume; LVEDV = left ventricular end diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume.

response to CRT-D therapy, including women, patients with a prolonged QRS or LBBB, and those who have a lower BMI values (in the nonobese range). These findings suggest that CRT is a particularly effective therapy for the prevention of HF or death in diabetic patients with nonischemic cardiomyopathy.

Patients with diabetes are characterized by an increased likelihood of HF, largely reflecting the contribution of diabetes to coronary artery disease and its association with hypertension. Over the past three decades, a number of epidemiological, autopsy, animal, and clinical studies have proposed the presence of diabetic heart disease as a distinct clinical entity.^{9,10} The term diabetic cardiomyopathy was introduced 30 years ago by Rubler et al.,¹¹ who described four diabetic patients with congestive HF and normal coronary arteries. The pathophysiology of this condition remains to be fully elucidated, but includes interstitial fibrosis, cardiomyocyte loss, impaired energy utilization, small vessel disease, and neuropathy.¹² These processes result in increased risk for HF among diabetic patients. The Framingham Heart Study showed that the frequency of HF is twice in diabetic men and five times in diabetic women compared with age-matched control subjects.¹³ This increased incidence of HF in diabetic patients persisted despite correction for age, hypertension, obesity, hypercholesterolemia, and coronary artery disease.¹³

Echocardiographic changes consistent with systolic dysfunction and left ventricular hypertrophy have been described in a number of studies of diabetic populations and may portend an increased risk for the subsequent development of HF, particularly in the presence of coexisting hypertension.^{14,15}

The present study consistently shows that diabetic patients without overt coronary heart disease (who comprised approximately one-third of DM patients enrolled in MADIT-CRT) display distinct clinical characteristics. Thus, compared with DM patients with an ischemic etiology, diabetic patients with nonischemic cardiomyopathy were younger, had a lower frequency of hypertension, more preserved renal function, and a lower BMI. In addition, this subset of the DM population comprised a higher proportion of women, patients with a more prolonged QRS, and an increased frequency of LBBB. These factors were previously shown to be associated with a more favorable response to CRT,^{16–21} and may have contributed to the pronounced clinical and echocardiographic effects of CRT-D in nonischemic DM patients during the study. Notably, the present study shows that diabetic patients with nonischemic cardiomyopathy experienced a 70% reduction in this risk of HF or death with CRT-D therapy. Furthermore, important subsets within the nonischemic DM group experienced approximately an 80% reduction in the risk of HF or death following implantation

of a CRT-D device (including those with a lower BMI, women, patients with a prolonged QRS, and those with LBBB), whereas risk reduction in the total MADIT-CRT population was 34%.⁶ These findings suggest incremental benefits of CRT-D therapy among DM patients with nonischemic cardiomyopathy.

Several limitations of this study should be noted. The present findings regarding enhanced benefit of CRT-D therapy in DM with nonischemic cardiomyopathy pertain only to patients with mildly symptomatic HF enrolled in MADIT-CRT. Diabetic patients were not randomized by the presence of the etiology of cardiomyopathy. Thus, differences in enrollment characteristics may have affected the differential response to CRT-D in the two groups despite adjustment for multiple factors in the multivariate models. Furthermore, enrollment of ischemic and nonischemic patients was imbalanced with respect to baseline NYHA class. However, secondary analysis among NYHA class II-only DM patients with ischemic cardiomyopathy yielded virtually identical results.

Over the next two decades the incidence of both type II diabetes and congestive HF is anticipated to increase to epidemic levels in both the industrialized and developing worlds. Furthermore, morbidity and mortality in this population remain high despite currently available therapeutic modalities.⁴ The results of the present study suggest that CRT is associated with important reverse remodeling effects and clinical benefits in diabetic patients in general, and with enhanced benefits in DM patients with nonischemic cardiomyopathy, specifically. These findings stress the importance of including CRT-D therapy as a major component of the therapeutic regimen in this population.

REFERENCES

- Singh S, Dhinra S, Ramdath DD, et al. Risk factors preceding Type 2 diabetes and cardiomyopathy. *J Cardiovasc Transl Res* 2010;3:580–596.
- Boudina S, Abel ED. Diabetic cardiomyopathy revisited. *Circulation* 2007;115:3213–3223.
- Boudina S, Abel ED. Diabetic cardiomyopathy, causes and effects. *Rev Endocr Metab Disord* 2010;11(1):31–39.
- Das SR, Drazner MH, Yancy CW, et al. Effects of diabetes mellitus and ischemic heart disease on the progression from asymptomatic left ventricular dysfunction to symptomatic heart failure: A retrospective analysis from the Studies of Left Ventricular Dysfunction (SOLVD) Prevention trial. *Am Heart J* 2004;148(5):883–888.
- Martin DT, McNitt S, Nesto RW, et al. Cardiac resynchronization therapy reduces the risk of cardiac events in patients with diabetes enrolled in the multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy (MADIT-CRT). *Circ Heart Fail* 2011;4:332–338.
- Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;361(14):1329–1338.
- ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). *Circulation* 2008;117:e350–e408.
- Lang RM, Bierig M, Devereux RB et al. Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. 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 Am Soc Echocardiography* 2005;18:1440–1463.
- Iltis I, Kober F, Dalmaso C, et al. Noninvasive characterization of myocardial blood flow in diabetic, hypertensive, and diabetic-hypertensive rats using spin-labeling MRI. *Microcirculation* 2005;12:607–614.
- Fein FS. Diabetic cardiomyopathy. *Diabetes Care* 1990;13:1169–1179.
- Rubler S, Dlugash J, Yuceoglu YZ, et al. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol* 1972;30:595–602.
- Zhi YF, Johannes BP, Thomas HM. Diabetic cardiomyopathy: Evidence, mechanisms, and therapeutic implications. *Endocr Rev* 2004 25: 543–567.
- Kannel WB, McGee DL. Diabetes and cardiovascular disease: The Framingham study. *JAMA* 1979;241:2035–2038.
- Bella JN, Devereux RB, Roman MJ, et al. Separate and joint effects of systemic hypertension and diabetes mellitus on left ventricular structure and function in American Indians (the Strong Heart Study). *Am J Cardiol* 2001;87:1260–1265.
- Galderisi M, Anderson KM, Wilson PW, et al. Echocardiographic evidence for the existence of a distinct diabetic cardiomyopathy (the Framingham Heart Study). *Am J Cardiol* 1991;68:85–89.
- Verhaert D, Grimm RA, Puntawangkoon C, et al. Long-term reverse remodeling with cardiac resynchronization therapy: Results of extended echocardiographic follow-up. *J Am Coll Cardiol* 2010;55:1788–1795.
- Lilli A, Ricciardi G, Porciani MC, et al. Cardiac resynchronization therapy: Gender related differences in left ventricular reverse remodeling. *Pacing Clin Electrophysiol* 2007;30:1349–1355.
- Cleland JG, Daubert JC, Erdmann E, et al. 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.
- St John Sutton MG, Plappert T, Abraham WT, et al. Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study Group. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation* 2003;107:1985–1990.
- Adelstein EC, Saba S. Usefulness of baseline electrocardiographic QRS complex pattern to predict response to cardiac resynchronization. *Am J Cardiol* 2009;103:238–242.
- Wokhlu A, Rea RF, Asirvatham SJ, et al. Upgrade and de novo cardiac resynchronization therapy: Impact of paced or intrinsic QRS morphology on outcomes and survival. *Heart Rhythm* 2009;6:1439–1447.