Discussion

Our study included 170 consecutive patients with chronic systolic heart failure scheduled for CRT device implantation in Zentralklinik, Bad Berka, Germany from March 2011 to September 2011. Clinical, electrocardiographic, echocardiographic and flouroscopic evaluation was done before, during and after CRT implantation in order to identify the predictors of response to CRT implantation.

Baseline characteristics:

The baseline characteristics of our study population was similar to other study populations in major CRt trial. Table 4.1 summarizes the baseline characteristics of our population study compared to major trials.[13-16,217,236,269-271] The mean values of some parameters and the prevalence of other parameters among the populations in different trials are not different from our study population. The prevalence of hypertension as well as diabetes mellitus was noticeably high in our study.

Response to CRT:

Among the study population, 114 patients (67.1%) responded to CRT implantation (defined as improvement of NYHA functional class by $\geq$ 1 NYHA class, increased 6.MWD $\geq$ 10% and reduction of LVESV $\geq$ 15% at 6 months after CRT implantation), 56 patients didn't respond. Improvement of NYHA class was maintained 1 year after CRT implantation. Mortalities and hospitalization related to unprovoked worsening of heart failure during the 1st 6 months postimplantation was considered CRT-nonresponse. CRT implantation was associated with significant improvement in LV dimensions, functions and markers of LV dys-synchrony. CRT implantation was associated with improvement in NYHA class and 6 min walk distance. CRT was also associated with significant improvement in LV diastolic dysfunction and the grade of mitral regurgitation. There were no significant effects on renal function and RV diastolic dimension and function (tables3.5, 36).

Trial	Our study	MUSTIC[13]	MIRACLE[14]	RAFT[298]	REVERSE[270]	COMPANION[15]	MADIT-CRT[271]	CARE-HF[16]	RETHINQ[217]	PROSPECT[236]
Age Ys; mean	69	64	64	66.1	62.9	67	65	67	60	67.8
Male %	77.7	78	68	84.8	78	67	74.7	74	71	71
ICM %	46	33	50	68.7	56	55	55	40	54	54
NYHA II %	14	0	0	79.2	82	0	86	0	0	0
NYHA III %	80	100	90	20.8	0	87	0	94	100	96
NYHA IV %	6	0	10	0	0	13	0	6	0	4
6 min walk dis.	275	328	305	351.3	399	266	359	NA	301	274
EF %; mean	28.3	24	21.8	22.6	26.8	21	24	25	25	23.6
LVIDd (mm)	67.5	70	70	NA	69	68	NA	NA	66	NA
LVEDV (ml)	205.7	NA	NA	NA	268	NA	245	NA	216	230
TAPSE (mm)	18	NA	NA	NA	NA	NA	NA	NA	NA	NA
LVPEI (msec)	128.5	NA	NA	NA	NA	NA	NA	NA	112	NA
Ts- sep-lat msec	63	NA	NA	NA	NA	NA	NA	NA	81	NA
SPWD msec	120.7	NA	NA	NA	NA	NA	NA	NA	109	NA
IVD (msec)	39.3	NA	NA	NA	33.9	NA	NA	49	9	NA
QRS mean D	145	190	167	157	153	160	>130	160	107	163
LBBB %	55.3	58	NA	72.9	NA	73	69.9	NA	NA	NA
AF %	30	48	NA	12.8	0	0	11.1	NA	0	NA
S Cr. Mg/dl	1.2	NA	NA	NA	NA	NA	1.2	NA	NA	NA
eGFR ml/min/1.73m^2	53.7	NA	NA	59.5	84.2	NA	NA	60	NA	NA
BMI > 30 %	32	NA	NA	NA	NA	NA	35.9	NA	NA	NA
HTN %	81	NA	NA	45	NA	NA	63.7	NA	NA	NA
DM %	50	NA	NA	32.8	22	41	30.2	NA	NA	NA
B Blocker use %	94	24	62	90.4	96	68	93.3	70	97	85
ACEi/ARB use%	96	98	93	96.1	96	90	97.8	95	89	92
MRA use %	46	18	NA	41.6	NA	55	32.3	54	NA	40
Diuretics use %	92	96	94	84.7	81	97	75.7	43	84	83

There were 27 HF related hospitalizations and 15 HF related mortalities during the 1st postimplantation year.

Numerous criteria believed to define a positive response to cardiac resynchronization therapy have been used in the literature. The 26 most-cited publications on predicting response to cardiac resynchronization therapy used 17 criteria to define response, which severely limits the ability to generalize results over multiple studies.(272)

Several trials have documented both increased functional capacity, as evaluated by means of the 6-minute walking test and the MVO2 peak, and improvements in quality of life and New York Heart Association (NYHA) class. (13-16,206-209,273,274) Moreover, CRT has been seen to reduce HF hospitalizations and mortality by 36% (15), and the total number of days of hospitalization by 77%.(14) The COMPANION study evaluated the efficacy of CRT, with or without an Implantable Cardioverter Defibrillator (ICD), versus medical therapy alone, in reducing the risk of death and hospitalizations in HF patients. In 1520 patients with advanced HF (LVEF ≤ 35%, LVIDd ≥ 60 mm, NYHA class III-IV) and intraventricular conduction delay (QRS ≥120 ms), both CRT with and without ICD reduced the primary end-point of mortality/hospitalization for HF by 20% in one year compared with optimal medical therapy. It was clearly demonstrated that CRT in addition to optimal medical therapy with beta-blockers, ACE-inhibitors and mineralocorticoid receptor antagonists (MRA), further reduced mortality in HF patients, and that this reduction reached a value of 36% in the long term.(15)

The CARE-HF study(16) evaluated the effect of CRT on morbidity and mortality in 813 patients with advanced HF and a clinical and instrumental profile similar to that of the COMPANION study population. The primary end-point was the combination of all-cause death and hospitalization for major cardiovascular events over a mean follow-up of 29.4 months. In this study, CRT reduced the primary end-point by 37% compared with medical therapy (HR 0.63, 95% CI 0.51-0.77, P <0.0001).

In the REVERSE study[275] the long-term benefits of CRT were evaluated in 610 European patients in NYHA class II (83%) or I (previously symptomatic), with QRS ≥120 ms, LVEF ≤40%, LVIDd ≥55 mm, with or without indication for an ICD, and undergoing optimized medical therapy. Patients were randomized 2:1 to CRT-ON or CRT-OFF and followed up prospectively for 24 months. The end-points of the study were the combined clinical score of all-cause mortality, hospitalizations for HF, cross-over due to worsening HF and NYHA class, and LVESV reduction. Echocardiography revealed a significant improvement in LVESV, left ventricular end-diastolic volume (LVEDV) and LVEF (69.7 vs. 94.5 ml/m2, 103 vs. 132 ml/m2, 34.8% vs. 29.9%, CRT-ON vs. CRT-OFF, respectively). Clinically, a significant 62% reduction was reported in mortality and hospitalizations for HF at 24 months (11.7% vs. 24%, HR 0.38, 95% CI 0.20-0.73, *P* =0.003, CRT-ON vs. CRT-OFF).

Similarly, the MADIT-CRT study[9] enrolled 1820 patients in NYHA class I or II (85%) and with QRS ≥130 ms and LVEF ≤30%. Patients were randomized 3:2 to CRT with ICD or ICD alone and followed up for a mean of 2.4 years. The end-point of the study was the reduction in all-cause mortality and/or hospitalizations for HF. CRT with ICD showed a significant advantage over ICD alone with regard to the primary end-point (17.2% vs. 25.3%, HR 0.66, 95% CI 0.52-0.84, *P* =0.001), the reduction in left ventricular volume (LVESV -57 ml vs. -18 ml, LVEDV -52 ml vs. -15 ml, *P* <0.01, CRT with ICD vs. ICD alone, respectively) and the increase in LVEF (+11% vs. + 3%, *P* <0.001, CRT with ICD vs. ICD alone). The MADIT-CRT results were largely confirmed by the RAFT study[269] , which enrolled 1798 HF patients in NYHA class II (80%) and III, with QRS ≥130 ms, LVEF ≤ 30%, randomized to CRT with ICD or ICD alone and followed up for 40 months. The reduction in the primary end-point of all-cause mortality/hospitalizations for HF was 25% greater in the CRT with ICD group than in the ICD alone group (HR 0.75, 95% CI 0.64-0.87, *P* <0.001), with 29% reduction of the risk of mortality in the sub-group of patients in NYHA class II.[269]

Alan D. Waggoner et al performed chocardiographic and Doppler measurements of left ventricular (LV) systolic and diastolic function in 50 patients prior to and after 4 ± 1 months of CRT implantation. The LV diastolic function improved only in the patients who increased LV ejection fraction >5% after CRT..[276] LV diastolic function was found to improve with CRT in another recent study. Clinical responders without echocardiographic response show improvement in parameters of diastolic function. That suggests that clinical-only response to CRT is secondary to a real effect of the therapy, rather than a placebo effect.[277] Howevere CRT didnot improve the diastolic function as evaluated by radionuclide angiography in another study.[278] CRT also improves the grade of mitral regurgitation.[279-281]

Despite compelling evidence supporting CRT in severe heart failure,[15,16,208,282,283] variable proportions of patients with implants show no or little benefit. Several studies have focused on clinical/instrumental predictors of outcome. Although some studies have demonstrated relations between specific parameters and clinical outcome,[217,236,284] others have failed to confirm these results.[285] Such discrepancy may be related to different factors including variable definitions of response to CRT, different statistical methods, different pre or postimplantation parameters, and variable durations of follow-up. In addition, use of NYHA class improvement may be misleading as suggested by significant CRT-related improvement in patients with no echocardiographic benefit and by device-related placebo effect, demonstrated in up to 1/3 of patients reporting benefit when CRT is turned inactive.[283] These observations likely support the wide range (25% to 92%) of responders reported in different studies. [15,16,208,282,283]

Responders vs. non-responders

In our study, responders had significantly wider baseline QRS duration than non-responders (152±24.9 msec vs. 130.7±24 msec respectively, P=0.0001). Compared to non-responders, responders had significantly lower BMI and baseline serum Creatinine level, smaller baseline RV diastolic dimension and significantly greater TAPSE value. Responders were more frequently females, more likely to have non-ischemic etiology and less

likely to have PAP>50mmhg at baseline than non-responders. There were no significant differences between responders and non-responders in echocardiographic measures of LV, echocardiographic markers of dyssynchrony or baseline NYHA class. There were no significant differences in BiV pacing percent between responders and nor-responders (tables 3.7, 3.8).

In a recent study, responders to CRT showed a significantly lower LV ejection fraction, wider QRS, radial dyssynchrony, and a more frequent presence of septal flash and of larger septal flash excursion at baseline, when compared with nonresponders in patients with AF. CRT response occurred in 71.3% of patients with a septal to lateral velocity delay of ≥65 ms, compared with 51.1% of patients with a velocity delay of <65 ms (P < 0.05). The response to CRT occurred in 68.0% of patients with radial strain dyssynchrony ≥130 ms but only 42.5% of those with <130 ms dyssynchrony (P < 0.03).[286] In observational studies, responders to CRT have wider baseline QRS duration and more QRS narrowing with CRT pacing, than non-responders.[287] In another study, the nonresponders were more frequently male (81.9% vs. 74.3%, P = .030) and had ischemic cardiomyopathy (69.7% vs. 53.2%, P=0 .001), shorter QRS duration (150.6 ± 29.9 milliseconds vs. 156.0 ± 32.5 milliseconds, P = 0.041), worse New York Heart Association functional class (2.8 ± 0.6 vs. 2.7 ± 0.6, P = 0.008) and shorter 6-minute walk distance (297.9 ± 110.7 m vs. 331.8 ± 112.6 m, P = 0.001), larger left atrial volumes (44.9 ± 16.9 mL/m2 vs. 40.9 ± 17.6 mL/m2, P = 0.006), less baseline LV dyssynchrony (56.2 ± 41.3 milliseconds vs. 69.1 ± 39.9 milliseconds, P = 0.001), and, more frequently, anterior LV lead position (12.4% vs. 4.0%, P = 0.007).[288]

Predictors of CRT response:

Gender differences:

In our study, females have been more likely to respond to CRT than males (86% vs. 61% respectively, P=0.003). This difference was not significant in multinominal regression analysis (OR 3.3; 95% CI 0.8-13.2, P= 0.09).

Data from multicenter studies evaluating the effects of sex on CRT benefit have been contradictory. COMPANION and CARE-HF found similar benefit in women and men,[16,289] and REVERSE, RAFT, and MADIT-CRT suggested greater benefit in women than in men.[9,10,270] These beneficial CRT-D effects among women were associated with consistently greater echocardiographic evidence of reverse cardiac remodeling in women than in men. In most studies female patients were more likely to have nonischemic cardiomyopathy, LBBB and less likely to have renal dysfunction than male patients, which might explain these differences. However, additional explanations have been proposed, including that QRS duration is normally, on average, 10 ms shorter in women vs. men. Thus, for a given QRS duration, women might have more conduction disturbance and greater cardiac dyssynchrony vs. men.[271]

Baseline NYHA class and response:

In our study, patients with NYHA class II and III at baseline did well after CRT implantation (response rate 69.6 and 68.4 respectively). The response rate in patients with baseline ambulatory NYHA IV was worse than other patients (45.5% response rate) but was not statistically significant due to small number of patients in NYHA IV included.

CRT proved to be effective in patients with NYHA II and III in multiple randomized trials.[9,10,16,270,288] The highly symptomatic NYHA IV patients generally have limited myocardial reserve and poor survival, and thus it has been suggested that they may not realize the time dependent benefits of CRT on cardiac function, or they may be destabilized by the implant procedure resulting in worse short-term outcomes.[290] The COMPANION trial included 217 NYHA class IV patients (14% of the total population, mean LVEF 21%), all of whom were considered “ambulatory” in that they had no hospital admissions or vasoactive therapy in excess of 4 hours in the month before enrollment.[15] A post hoc analysis of this subset of patients revealed a significant improvement compared with that from

optimal medical therapy (OMT) in time to all-cause mortality or hospitalization for both CRT-P (hazard ratio [HR], 0.64; P = 0.02) and CRT-D (HR, 0.62; P = 0.01), an improvement in QoL (P < 0.01), as well as a significant functional improvement (NYHA class improved in 78% in the CRT group compared with 52% in OMT; P < 0.01). However, only a nonsignificant trend toward benefit in all-cause mortality alone was demonstrated (HR, 0.67; P = 0.11 for CRT-P; HR, 0.63; P = 0.06 for CRT-D).[291]

The 2012 ACCF/AHA/HRS guidelines include ambulatory class IV patients in the class I recommendation for CRT but note that data are few in these patients and comment that the sickest patients, who are dependent on inotropic therapy, have refractory fluid retention, or have progressive renal dysfunction, are at highest risk for complications from implantation and early mortality, and also are unlikely to benefit significantly from concomitant defibrillator therapy.[292]

The 2010 and 2012 ESC guidelines also support CRT in ambulatory class IV patients, but recognize that the use of CRT in these patients is supported to improve morbidity, but not mortality.[23,293]

Comorbidities and CRT response:

In our study, the presence of lung disease in the form of significant COPD was an independent predictor of non-response to CRT (OR 0.26; 95%CI 0.08-0.8, P=0.022). The CRT response rate in patients with COPD was 47.7% vs. 73.8% response rate in patient without COPD, P= 0.002. There was a non-significant trend that non-hypertensive respond to CRT better than hypertensive and non-diabetic patients respond to CRT better than diabetic patients.

In a retrospective study, 164 patients underwent CRT implantation. Twenty two patients had coexisting COPD, of which only six patients (28%) responded to CRT vs. 58.9 in the overall study population (p = 0.008).[294]

In the majority of CRT patients, multiple comorbid conditions may affect clinical status and prognosis.[295] Remarkably, these comorbid

conditions have generally been ignored by landmark CRT trials, and their impact on ventricular remodeling, functional status, and clinical outcome after CRT remains insufficiently elucidated.[296] in a recent study, the presence of comorbid conditions including arterial hypertension (HTN), diabetes (DM), history of renal disease and COPD was associated with hospital admission for heart failure after CRT implantation.[296] On univariate Cox analysis and multivariate analysis, diabetes mellitus and chronic kidney disease were associated with all-cause mortality. History of hypertension and chronic kidney disease were significantly associated with hospital admission for heart failure on univariate analysis but no longer after multivariate analysis. A trend toward more heart failure admissions with COPD on univariate analysis became significant in multivariate analysis (HR 1.89, 95% CI 1.02-3.53). Reverse ventricular remodeling, measured by left ventricular diameter reduction after 6 months of follow-up, was independent from comorbidity burden.[296]

In a study of the effect of diabetes mellitus on CRT response, significant LV reverse remodeling was observed both in diabetic and non-diabetic patients. However, the response to CRT occurred more frequently in non-diabetic patients than in diabetic patients (57 vs. 45%, $P < 0.05$). Furthermore, a significant improvement in LV diastolic function was observed both in diabetic and non-diabetic patients, but was more pronounced in non-diabetic patients. The determinants of the response to CRT among diabetic patients were LV dyssynchrony, ischemic cardiomyopathy, and insulin use. Particularly, diabetes was independently associated with all-cause mortality together with ischemic cardiomyopathy, renal function, LVESV, LV dyssynchrony, and LV diastolic dysfunction.[293]

Impact of renal dysfunction

In our study, history of renal disease was also an independent predictor of non-response in our study (OR 0.14; 95% CI 0.04-0.44, P= 0.001). The responders had significantly lower baseline serum creatinine level. However, there were no significant differences in CRT response between patients with eGFR above or below 60 ml/min/1.73m^2.

Renal dysfunction is a common disorder in the general population and one of the most serious comorbidities in HF patients.[298–300] A baseline creatinine $\geq$ 1.4 mg/dl was associated with an increased risk of subsequent HF or all-cause death in MADIT-CRT trial.[271] Data from a retrospective analysis from MADIT-II population [301] confirmed that renal function was the most powerful predictor of mortality risk and showed that there was no benefit in survival among patients with eGFR < 35 ml/min/1.73m^2. In the specific subset of patients who are candidates to CRT, renal function, as assessed by eGFR, has been proven to be a powerful predictor of survival: An improvement of 21% for each 10 ml/min/1.73 m2 increase in baseline eGFR (P<0.0001) was observed in a population of 787 patients implanted with a CRT-D device.[302] In these patients, the degree of basal renal impairment had important effects on the advantage in survival expected after the implantation of a CRT-D device. When compared with 88 controls in whom the implant of a LV lead was unsuccessful, a better survival for CRT-D patients was demonstrated only for those with moderate renal impairment, whereas in patients with severe or end-stage renal disease, as well as the ones with eGFR < 60 ml/min/1.73 m^2, no differences arose. Other authors have found that preventing further decrease in eGFR after CRT, rather than the absolute baseline values, is an effect of CRT-induced LV reverse remodeling and predicts better overall survival in patients with moderately reduced eGFR.[303] In the CARE-HF trial, the benefit of CRT was present independently of eGFR being above or below 60 ml/min/1.73m^2, although it was slightly greater for the former.[16] Discrepancies among studies might reflect the fact that the investigated populations were not perfectly comparable, for example in the use of CRT in association with an ICD [302] or not [16], and in the percentage of patients with more severe chronic renal disease (CKD). Moreover, in patients with severe/end-stage CKD, the use of B blockers and ACE-I/ARBs is significantly reduced [304], and this fact might partially explain why these patients show such a poor outcome. Besides, in end-stage CKD, also the efficacy of ICD therapy is reduced, while the risk of ventricular arrhythmias is greatly increased, so that sudden cardiac death becomes one of the first causes of death.[289,301,305,306]

Obesity:

In our study, the CRT response rate didn't differ significantly between obese and non-obese patients. The CRT response rate in patients with BMI < 30 kg/m^2 was 69.3% vs. 65.6% in patients with BMI≥30 kg/m^2, P=0.378.

In a substudy of the MADIT-CRT trial, it was found that BMI < 30 kg/m2 predicted LVEF super-response.(307) This was the first study to associate a lower BMI with cardiac reverse remodeling attributed to CRT-D therapy. Because BMI is a complex variable composed of both height and weight, assessing its association with LVEF response may prove difficult. For example, human weight composition varies person to person and can be influenced by lean body mass, adiposity, and volume overload, particularly in an HF population. Additionally, these findings contrast with previous studies reporting an "obesity paradox" of BMI and HF outcomes, such that higher BMI was associated with improved HF outcomes(308). Authors found that lower BMI was associated with LVEF super-response, which itself was associated with improved clinical outcomes. Future studies of response to CRT-D therapy should focus on the determinants of BMI and associations with cardiac remodeling. In addition, whether a lower BMI predicts LVEF response to CRT-D is specific to a mildly symptomatic HF population, such as the one studied in the MADIT-CRT trial, is unknown and deserves further investigation.

ECG

QRS duration

In our study, QRS duration ≥ 150 msec was the strongest independent preimplantation predictor of response (OR 9; 95% CI 3.1-27.8, P< 0.001). CRT response was documented in 84.5% of patients with baseline QRS duration ≥ 150 msec vs. only 50% of those with QRS < 150 msec, P<0.001. There was no significant difference between patients with 150> QRS ≥ 120 msec and those with QRS < 120 msec as regards CRT response (52.5% vs. 44% respectively, P= 0.4).

Data from most CRT trials have consistently demonstrated increased benefit from CRT in patients with very prolonged QRS duration. The Pacing Therapies in Congestive Heart Failure (PATH-CHF) II study prospectively compared the benefit of CRT in patients with QRS duration between 120 and 150 ms and those with QRS duration ≥150 ms; it identified an improvement in MVO2, 6MWD, and QoL only in patients with QRS duration ≥150 ms. Only 38% of patients with QRS duration <150 ms had increased peak MVO2 by more than 1 ml/min/kg.[209] In the COMPANION trial, among patients with progressively increasing QRS intervals, there was an incrementally greater benefit among patients receiving CRT for the combined endpoint of death or hospitalization for any cause.[15] In a large registry of Medicare patients who received CRT-D with an average follow-up of 40 months, baseline QRS duration ≥150 ms was associated with improved short- and long-term survival compared with patients with QRS duration between 120 and 149 ms (HR, 0.77 at 1 year; HR, 0.86 at 3 years; P < 0.001).[309] Similarly, very prolonged QRS duration also has proved to be an important factor in the less symptomatic HF population in RAFT[269] and REVERSE.[275] The updated US guidelines therefore stratify patients by the extent of QRS prolongation, extending the strongest recommendation in support of CRT only for otherwise qualifying patients with LBBB and QRS duration ≥150 ms; patients with LBBB and QRS duration between 120 and 149 ms or highly symptomatic patients with non- LBBB pattern and QRS duration ≥150 ms are given a class IIa recommendation.[292]

Research is ongoing to evaluate a potential role for CRT in patients with normal QRS duration who have evidence of dyssynchrony on echocardiography (20%- 50% of patients with HF and narrow QRS complexes).[310] The effect of CRT among patients without dramatic QRS prolongation (<130 ms) was assessed in 172 patients in the prospective RethinQ Study, which found an improvement in MVO2 after 6 months of CRT only in patients with QRS duration >120 ms, but not in patients with QRS duration <120 ms, despite evidence of dyssynchrony on echocardiography in all individuals. Among all patients with QRS duration <130 ms, there was a significant reduction in NYHA functional class with CRT, but no change in QoL, 6MWD, or LV size and function.[217] Similarly,

in the LESSER-EARTH trial [311], which randomized patients with an LVEF ≤35%, symptoms of HF, and a QRS duration <120 milliseconds to active versus inactive CRT therapy, CRT did not result in an improvement in exercise capacity, symptoms, quality of life, or reverse LV remodeling. Alarmingly, biventricular pacing significantly reduced the 6-min walk distance, increased QRS duration, and was associated with a nonsignificant trend toward an increase in HF–related hospitalizations. More recently, the EchoCRT study [312] showed that in patients with systolic heart failure and QRS duration of less than 130 msec, CRT does not reduce the rate of death or hospitalization for heart failure and may increase mortality. At this point, there are no convincing data to suggest a benefit of CRT in patients with narrow native QRS complexes (<120 ms), regardless of echocardiographic dyssynchrony. QRS prolongation remains the sole indicator of dyssynchrony used in the guidelines to select patients for CRT.

QRS Morphology:

In our study, patients with LBBB were more likely to respond to CRT than patients without LBBB (83% vs. 47.4%, P=0.0001). However, LBBB morphology was not an independent predictor of response in multinominal regression (OR 2; 95% CI 0.75-5.4, P = 0.16).

In patients with LBBB morphology, LV activation between the septum and LV free wall is significantly delayed; it may be corrected with CRT, in which pacing of the septum and the LV free wall may resynchronize mechanical contraction. However, in RBBB or LV hypertrophy with associated QRS prolongation, the LV endocardium is activated normally via the purkinje system and thus may not benefit from LV pacing.[313] several large trials have been consistent in demonstrating a greater benefit from CRT in patients with LBBB, and a lack of benefit (and even potential for harm) in other patients with non-LBBB QRS prolongation. In the COMPANION trial, patients without LBBB did not have a statistically significant benefit from CRT in terms of reduction of hospitalizations or mortality.[15] In a subanalysis of the Cardiac Resynchronization in Heart Failure (CARE-HF) study, although only 5% of

patients had RBBB, by multivariable analysis RBBB was a predictor of increased all-cause mortality and unplanned hospitalization for HF (HR, 2.74; P < 0.0001).[314] Similarly, in the 14,946 patient Medicare registry, evaluating real-world long-term outcomes after CRT-D implantation, RBBB was associated with higher short- and long-term mortality, even after adjusting for covariates, compared with patients with baseline LBBB (HR 1.44, at 1 year; HR, 1.37 at 3 years; P < 0.001). In this registry, patients with nonspecific intraventricular conduction delay had intermediate outcomes, and QRS duration did not have any significant effect on outcomes in the setting of RBBB.[309] Similarly, in less symptomatic patients in the RAFT trial, a reduction in the primary endpoint of death or HF hospitalization was demonstrated for patients with LBBB, but not patients with RBBB, nonspecific intraventricular conduction delay, or paced rhythm (P = 0.046 for interaction).[10,269] In a recent study, echocardiographic response (change in ejection fraction) was better in patients with LBBB and QRSd $\geq$150 ms (12 $\pm$ 12%) than in those with LBBB and QRSd <150 ms (8 $\pm$ 10%), non-LBBB and QRSd $\geq$150 ms (5 $\pm$ 9%), and non-LBBB and QRSd <150 ms (3 $\pm$ 11%) (P < 0.0001). Long-term survival was better in LBBB patients with QRSd $\geq$150 ms (P = 0.02), but this difference was not significant after adjustment for other baseline characteristics (P = 0.15).[315] In a post-hoc analysis of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial.[316] Patients with LBBB (n = 369) experienced a significant reduction in LVESVI, whereas non- LBBB patients did not. Baseline QRS duration was also a strong predictor of change in LVESVI, with monotonic increases as QRS duration prolonged. Similarly, the clinical composite score improved with CRT for LBBB but not for non-LBBB patients. The association between clinical composite score and QRS duration was highly significant, with improved responses associated with longer QRS durations. Importantly, such benefit was due primarily to the LBBB patients.

Accordingly, LBBB morphology should be considered, along with QRS duration, as the most important criterion in predicting CRT benefit. As noted, updated consensus guidelines now indicate a class I indication only for patients with very wide LBBB and lesser recommendations for patients

with non-LBBB morphology (class IIa if QRS duration is ≥150 ms and NYHA III/ ambulatory IV symptoms, and class IIb for QRS 120-149 ms and NYHA III/ambulatory IV symptoms or QRS ≥150 ms and NYHA II symptoms).[292]

Sub-group analyses based on QRS morphology [9,12,19] and a meta-analysis [317] suggested that patients with complete LBBB showed a greater benefit on the composite of morbidity/mortality from CRT, compared with patients with non-specific intraventricular conduction delay or right bundle branch block. However, recent studies showed that fragmented QRS complexes in the electrocardiograms of patients with nonischemic dilated cardiomyopathy and narrow QRS complexes are associated with significant intraventricular dyssynchrony [318,319], and other studies suggested that fragmented QRS complexes might be useful in predicting response to CRT[320,321]. A recent electrical mapping study showed that "true LBBB" was only seen in patients with a QRS duration >140 ms.[322] Indeed, patients with QRS duration ≥150 ms and LBBB morphology showed the highest response rates in large multicenter trials.

Atrial fibrillation and CRT response:

In our study, AF at time of implantation was an independent predictor of non-response (OR 0.17; 95% CI 0.04-0.66, P=0.01). The CRT response rate was much better in patients with SR during CRT implantation than patients with AF (72.1% vs. 34.8% respectively, P <0.0001). There was a significant difference in BiV pacing % between Patients with AF and patients with sinus rhythm at 1day postimplantation (91.2 ± 15 % vs. 96.9 + 5.7% respectively, P= 0.001) and at 3 months postimplantation (92.4 + 10 % vs. 96.4 + 6.8 respectively, P = 0.01).

As atrial fibrillation is common in patients with HF and is associated with increased morbidity and mortality.[323] However, the vast majority of patients included in the large trials of CRT were in sinus rhythm, and in most, patients in AF were excluded.[9,13-16,208,209,275] The efficacy of CRT in patients with permanent AF is less certain. It is unclear if patients without

regular, organized atrial activity derive the same benefit from CRT, as atrioventricular (AV) timing appears important for the response to CRT.[324,325] Moreover, even moderately rapid ventricular rates during AF might lead to a significant reduction in biventricular pacing, further reducing the potential benefit of CRT.[326] Further complicating the matter, outcomes are difficult to measure in patients with AF, as the effects of CRT may be confounded by changes in heart rate control.[290] Observational studies suggest that the benefits of CRT are reduced among patients with a history of AF vs. those without such a history.[327] Moreover, the benefits of CRT appear greatest in patients with ≥95% biventricular pacing.[328] Importantly, though device counters are often used to estimate the percent of biventricular pacing, these data might be unreliable in patients with permanent AF.[329]

The benefit of CRT in patients with AF may be dependent on the frequency of BiV pacing achieved. In 1 large, prospective, observational registry, the effect of CRT was compared between 162 patients with permanent AF and 511 patients in sinus rhythm (LVEF ≤35%, QRS duration ≥120 msec, NYHA class ≥II). After 2 months of CRT, devices were interrogated and revealed that BiV pacing was achieved 98.5% of the time in patients in sinus rhythm, and only 74.6% of the time in patients in AF. Subsequently, patients with AF who had BiV pacing ≤85% of the time underwent prospective atrioventricular nodal ablation; this study found overall sustained improvements in functional capacity and indices of reverse remodeling for patients in sinus rhythm as well as those in AF at a mean follow-up of 25.2 months; however, the benefit from CRT in the setting of AF was seen entirely among the subgroup that underwent atrioventricular nodal ablation. In these patients with AF and atrioventricular nodal ablation, BiV pacing was achieved 98.4% of the time, and the LVEF, LVESV, and functional capacity scores increased to a similar degree as the patients in sinus rhythm. No benefit was seen from CRT in the patients with AF who were treated medically with negative chronotropic therapy and programmed device features, although BiV pacing was eventually achieved 88.2% of the time. The authors concluded that the magnitude of benefit with CRT, in terms of symptoms and LV function, was similar between patients in sinus rhythm and in permanent AF only in those patients undergoing

atrioventricular nodal ablation, likely related to the near 100% BiV pacing time achievable only by ablating the atrioventricular node.[230] RAFT, the largest randomized evaluation of CRT in patients with permanent AF, failed to show a significant improvement in clinical outcomes, quality of life, or hall walk distance with CRT-D vs. an ICD alone in these patients.[269] However, only one-third of patients with AF assigned to CRT-D in RAFT received $\geq$ 95% ventricular pacing and only 1 patient underwent an AV junctional ablation. A pooled analysis of 3 observational studies found a 60% reduction in the rate of nonresponse to CRT in CRT-treated patients who did vs. did not undergo of AV junctional ablation.[327] Moreover, an observational study of CRT-treated patients with permanent AF reported lower annual mortality rate among CRT-treated patients with permanent AF who did (4.3%) vs. did not (15.2%) undergo AV junctional ablation ($P <$ 0.001).[328]

These findings are reflected in both updated US and ESC guidelines: The 2012 ACC/AHA/HRS guidelines support CRT with a class IIa indication for patients with AF and LVEF $\leq$35% who otherwise meet CRT criteria and have concomitant atrioventricular nodal ablation or pharmacologic rate control that will allow near 100% ventricular pacing with CRT.[23,292]

Etiology and CRT response:

In our study, dilated cardiomyopathy was an independent predictor of response (OR 3.1; 95% CI 1.1-8.4,P= 0.028). The CRT response rate among patients with DCM was 80.2% vs. 51.9% in patients with ischemic cardiomyopathy, P<0.0001. Patients with ICM without previous infarction were not significantly different from those who experienced previous myocardial infarction. Previous revascularization did not induce significant difference in response rate among ischemic patients.

Data suggest that the benefit of CRT is more pronounced in HF patients with nonischemic cardiomyopathy. A post hoc analysis of the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial demonstrated greater improvements in LVEDV (P < 0.001) and LVEF

(6.7% increase vs. 3.2%; P < 0.001) among nonischemic patients compared with patients who had ischemic cardiomyopathy.[330] In the PROSPECT study among more than 400 patients with conventional indications for CRT, there was a greater rate of improvement in composite clinical response (75% vs. 64%; P = 0.01) and in LVESV (63% vs. 50%; P = 0.03) among nonischemic patients.[236] In REVERSE, the reduction in LVESV index was 3 times greater among nonischemic patients relative to those with an ischemic etiology.[275] In the European substudy of REVERSE with a 24 month follow-up, the magnitude of CRT-related reduction in the LVESV index was also more than double among patients with nonischemic cardiomyopathy, although the improvements in clinical status and LV function were similar.[17] In the Medicare population, ischemic cardiomyopathy was a predictor of early and late mortality after CRT-D, and the highest mortality was seen in patients with a combination of RBBB and ischemic cardiomyopathy.[309] In one recent study, Non-ischemic HF etiology was an independent predictor of a positive clinical response (OR 4.89, 95% CI 1.39 - 17.15; p = 0.01).[331] Lack of prior myocardial infarction predicted LVEF super-response in a sub-study of the MADIT-CRT.[307] Regardless of the mechanism, in this study showed that in multivariate analysis, absence of prior myocardial infarction predicts LVEF super-response to CRT. Previous studies [332,333] demonstrated that patients with ischemic heart disease had a lower likelihood of response to CRT. Sylvain Reuter et al.[334] reported that patients in the non-coronary artery disease (CAD) group had a significantly greater increase in LVEF (p = 0.007) and decrease in NYHA class (p < 0.05) compared to patients with CAD. He also explained differences of response according to etiology of HF, suggesting that left ventricular pacing lead was not placed at the optimal site with regard to ischemic areas.[335] One possible mechanism is that there is insufficient viable tissue to allow an increase in contractility by CRT. Another possible mechanism lies in modification of the electrical substrate. According to this idea, the extent of resynchronization would be limited as a result of slow-conducting or non-conducting regions.[335]

In contrast, the effect of CRT did not differ with regard to etiology of disease in Cardiac Resynchronization Therapy for the Treatment of Heart

Failure in Patients with Intraventricular Conduction Delay and Malignant Ventricular Tachyarrhythmias (CONTAK CD)[207] or MIRACLE ICD,[208] and there was no difference in the mortality benefit from CRT between patients with ischemic or nonischemic cardiomyopathies seen in the COMPANION,[15] CARE-HF,[16] MADIT-CRT,[9] or RAFT trials.[10] Molhoek et al.[336] reported no differences in CRT response in ischemic HF vs. idiopathic dilated cardiomyopathy groups. However, in this study response to CRT was defined only by improvement in NYHA functional class. Previous studies on the effect of scar on response to CRT have been contradictory.[337,338]

Both the 2012 ACC/AHA/HRS guidelines and the 2010 ESC guidelines make no differentiation between ischemic and nonischemic patients with regard to recommendations for CRT, although the US guidelines do qualify the recommendation for patients with NYHA class I symptoms to those with LVEF <30% and an ischemic etiology of HF, reflecting the population studied in MADIT-CRT.[23,292]

Echocardiography:

In our study, patients with grade III diastolic dysfunction were less likely to respond to CRT compared to patients with less than grade III diastolic dysfunction (51.5% vs. 70.8% respectively, P=0.034). The probability of CRT response was not related to the severity of baseline mitral regurgitation or the left ventricular dimensions, volumes nor function. In univariate analysis, SPWMD≥130 msec, IVD≥40 msec and Ts-septal-lateral≥60 msec were significant predictors of CRT response. However, in multinominal logistic regression analysis, none of them proved to be an independent predictor of CRT response.

Multiple single center studies demonstrated the potential role of echocardiographic markers of LV dyssynchrony on the prediction of CRT response.[191,233,234,285,339,340] In 2008, the PROSPECT study tested the performance of echocardiographic parameters to predict CRT response.[236] The PROSPECT trial was a multicenter, prospective, non-randomized study designed to evaluate selected echocardiographic indices of mechanical

dyssynchrony for their capability in predicting responses to CRT. There were 12 parameters tested for a clinical composite score and LV end-systolic volume (LVESV) at 6 months as the primary outcomes, which being useful in previous single-center studies. The study reported a large variability in the analysis of mechanical dyssynchrony by echocardiography (up to 70% when using M-mode method) and a low area under the curve (AUC) in the prediction of the endpoints by mechanical dyssynchrony (≤ 0.62 for all parameters). The results suggested that measures of mechanical dyssynchrony had limited incremental value in patient selection, including those indices derived from TVI that had demonstrated a large body of evidence before PROSPECT. Out of such results, the investigators stated that echocardiographic parameters assessing dyssynchrony do not have enough predictive value to be recommended as selection criteria for CRT beyond current indications.

Of note, the PROSPECT study had a number of major limitations in the design and execution which raised further controversies and biased the conclusion.[341-344] The trial commenced in 2005 when the implantation technique of CRT devices became quite mature due to systematic proctoring, hands-on training, and high-volume implantation in centers selected and supported by device companies. On the contrary, there were only a few laboratories in the world that regularly performed dyssynchrony analysis by echocardiography at that time where knowledge sharing and hands-on training had yet to develop. Inevitably, some technical problems were introduced in this study, including methodology in dyssynchrony assessment by offline analysis was not standardized, training was inadequate, and echocardiographic equipment was not uniform and in some centers too obsolete for adequate TVI images. Dyssynchrony measurements adopted in the PROSPECT trial were criticized by their unexpected high interobserver variabilities, which ranged from 32% to 72% and intraobserver variabilities from 16% to 24%, presented by the reproducibility test within the core laboratories. This may reflect the general difficulty in dyssynchrony analysis by echocardiography. However, it is worth mentioning that the variability test was conducted retrospectively after all the offline analysis had been completed, but not before the study. It is arguable that these 3 core laboratories should have been trained and adopted a common algorithm for

dyssynchrony analysis before offline analysis was commenced. Of note, the interobserver variability for the measurement of LVESV by Simpson's method was as high as 14.5%.[236] Consequently, concerns are raised that ''failure'' of mechanical dyssynchrony by echocardiography could be attributed to the lack of standards in online acquisition and offline analysis due to insufficient training and feedback between the core laboratories and the study sites, in particular during the initial phase of the trial.[341-344]

Furthermore, the use of modern echocardiographic equipment capable of decent TVI image quality cannot be overemphasized.[345] Recently, van Bommel et al.[346] found in a sub-analysis of the PROSPECT study that 'super-responders' were significantly more dyssynchronous than the 'negative' responders with both a larger interventricular and septal-to-lateral delay by TVI assessment.

A number of studies were conducted in the post-PROSPECT era to examine the ability of mechanical dyssynchrony in predicting favorable responses after CRT.[191,230,331,332,347-367] When compared with early studies in this field, recent studies have a few advancements which are worth mentioning. Although most of these studies were single-centered, a couple of them were conducted in 2 centers with common protocol and standardized technique of dyssynchrony analysis ensured.[349,358] While we are waiting for more confirmative data derived from future multicenter trials that are well designed and executed, it is encouraging to look at a few 2- and 3-center studies where the feasibility of dyssynchrony assessment among different sites is verified as well as its predictive value in CRT. Secondly, the selection of primary endpoints in these trials was more appropriate with longer duration of follow up, by using mid-term reverse remodeling (i.e.LVESV reduction at 6 months) or long-term clinical outcome such as all-cause mortality and cardiovascular events. Although LV reverse remodeling could be regarded as a surrogate marker but not a hard endpoint, its occurrence after CRT has been proved to correlate with improvement in clinical status and favorable long-term prognosis.[191,362] Thirdly, the predictive value of mechanical dyssynchrony by echocardiography was tested in a multivariate model with the inclusion of other possible predictors at baseline such as age, gender, etiology of heart failure, severity of mitral

regurgitation, presence of atrial fibrillation, and LV lead position.[363-366] In a systematic review, mechanical dyssynchrony was able to independently predict LV reverse remodeling or better clinical outcome after CRT.[345]

Previous analyses suggesting the larger cardiac diameters are associated with poorer response to CRT.[332,367] Smaller left ventricular end-diastolic and end-systolic diameters were associated with better response to CRT in one study.[331] In another nonrandomized, open-label clinical study, extensive LV dilatation at baseline negatively impacted CRT results in terms of LV function improvement and incidence of cardiac events at follow-up.[368] It was also found in another study that patients with an increased left ventricular end-systolic diameter and concomitant diastolic dysfunction had a significantly worse outcome after CRT implantation.[366] In a recent study, the baseline LVEF was no significantly related to the response rate to CRT, showing that the CRT has beneficial effects even in patients with very low LVEF.[369] Cheuk-Man Yu et al. demonstrated that LV Reverse remodeling response to CRT is predicted by the severity of pre-pacing systolic asynchrony, but not diastolic dysfunction.[370]

Right ventricular dysfunction and CRT response:

Among our study population, the presence of RV dysfunction defined as TAPSE <15 mm was an independent predictor of non-response in multinominal logistic regression (OR 0.32; 95% CI 0.11-0.9, P=0.036). Patients with baseline TAPSE≥15 mm had better response rate than those with baseline TAPSE < 15 mm (76.1% vs. 50.8% respectively, P=0.001). Baseline RV dilatation was associated with CRT nonresponse; 57.1% of patients with dilated RV (RVd>35mm) were responders vs. 75.3% of those with RVd≤35mm, P=0.012. Presence of more than mild pulmonary hypertension was associated with reduced response rate to CRT. The response rate was 78%, 71% and 51% for no PHT, mild PHT, more than mild PHT respectively, P= 0.027. Both RV dilatation and PHT were not significant predictors of CRT response in multinominal logistic regression analysis.

In patients affected by moderate and severe systolic HF, the right ventricle (RV) plays a major role in determining functional status and survival, and its dysfunction is a well established prognostic predictor, independently of the degree of concomitant LV systolic impairment, HF etiology, NYHA class, and maximal oxygen consumption.[371-375] In systole, the tricuspid annulus will normally descend toward the apex 1.5–2.0cm.[376] Tricuspid annular excursion of less than 1.5cm has been associated with poor prognosis in a variety of cardiovascular diseases.[377] There is evidence that preserved RV function is a necessary condition for a positive response to biventricular pacing.[378-380] Although the echocardiographic assessment of the right ventricular ejection fraction is unreliable [381], due to RV complex morphology, there are simple and fast indexes which have been tested in the perspective of the response to CRT. Authors have demonstrated that patients who remodeled had better values of pre-implant RV systolic pulmonary artery pressure, end-diastolic and end-systolic areas, fractional area change and tricuspid annular plane systolic excursion (TAPSE).[379] The assessment of TAPSE is of special interest, as it has been proven to be a reliable marker of RV function, with values < 14 mm being a sure index of severe RV dysfunction and poor prognosis [382], and a predictor of the absence of LV reverse remodeling at midterm follow-up, regardless of the nature of the cardiomyopathy.[379] In CARE-HF patients, the cutoff of 14 mm in pre-implant TAPSE could predict the grade of LV reverse remodeling at 18 months.[333] The investigators found a strong interaction between CRT and basal TAPSE for the increase in LVEF and for the reduction in LVESV. This was ascribed to the consequent reduction in the interventricular mechanical delay (IVMD), a parameter which showed a positive, albeit moderate, correlation with LV reverse remodeling.[333] Scuteri et al used an extensive echo-Doppler examination and found that preimplantation M-mode (TAPSE), RV systolic pressure measured by Doppler, RV dimensions and RV area change to be related with post-implant LVESV remodeling.[379] They also found these relations to be consistent independent of etiology and degree of dyssynchrony indicating the important role of the pre-implant RV function. They suggest TAPSE < 14 mm, a simple and highly reproducible method, as cut-off value to define advanced RV dysfunction and found this

cut-off to be associated with a two-fold risk of the combined end point of death and emergency heart transplantation.

These findings are supported by other researches using other indicators of RV function and longer follow-up to study the importance of preimplantation RV systolic function.[383,384] The role of RV myocardial performance index (MPI) in identifying CRT patients who are likely to have a poor outcome (all-cause mortality, heart transplantation, LV assist device (LVAD) implant) has been studied in 77 consecutively implanted patients.[378] MPI is a standard Doppler-derived index, calculated as the ratio of the isovolumic contraction and relaxation times to the ejection time, which assesses the global ventricular function, with higher ratios expressing worse ventricular performance (normal values 0.28 ± 0.04).[381,385] After a median follow-up of 21 months, patients who experienced an adverse event had significantly worse median RV MPI (0.83 vs. 0.69, P 0.004), while there were no differences in terms of LV indexes. Analyzed as a continuous variable, each increase of 0.1 in RV MPI was associated with an increase of 16% of the risk of death, heart transplantation, or LVAD implant (P=0.001); it is noteworthy that this was the only significant parameter in multivariable analysis. Patients with the highest values of MPI had a relative risk of events of 3.3-fold when compared with patients with the lowest (P= 0.01).[378]

Other authors reported that Pre-implant decreased RV systolic function as assessed by tissue Doppler derived right ventricular systolic maximum velocity (RV-SMV) might be an important way to predict a poor response to CRT.[383] In another study by Tabereaux et al a visual grading by 2D echocardiography of the RV function was used. RV EF < 40% was the definition of RV systolic dysfunction and found to be associated to less response to CRT during 6 month's follow-up.[384]

In a study on ninety-three patients with heart failure undergoing CRT implantation, PHT had no prognostic effects on heart function improvement in patients undergone CRT. However, it was associated with worse LV remodeling and increased death due to aggravation of heart failure.[386] Recently, Chatterjee et al. Conducted a study on 101 patients to examined

the prognostic significance of pre- and post-capillary components of PHT in patients receiving cardiac resynchronization therapy. Clinical endpoints were assessed at 2 years and included all-cause mortality and a composite of death, left ventricular assist device, or cardiac transplantation. Patients with transpulmonary gradient (TPG) ≥12 mm Hg were more likely to experience all-cause mortality (hazard ratio [HR]: 3.2; 95% confidence interval [CI]: 1.3 to 7.4; p = 0.009) and the composite outcome (HR: 3.0; 95% CI: 1.4 to 6.3; p = 0.004) compared with patients with TPG <12 mm Hg. After multivariate adjustment for hemodynamic, clinical, and echocardiographic variables, only TPG ≥12 mm Hg and baseline right ventricular (RV) dilation (RV end-diastolic dimension >42 mm) were associated with the composite clinical outcome (p = 0.05 and p = 0.04, respectively).[387]

Ventricular interdependence is one of the factors that contribute to the low cardiac output of patients with RV dysfunction. Right ventricular dilatation and pressure overload determine a change of LV geometry with a leftward shift and dyskinesia of the inter-ventricular septum. In addition, RV volume overload leads to increased pericardial constraint. Consequently, LV compliance and preload are reduced contributing to the 'low cardiac output state'.[388] The global evaluation of RV function at pre-implant echocardiogram adds important information on the conditions of the heart as a whole; as it can reliably forecast the patient's clinical evolution and the chance of LV reverse remodeling. Simple indexes, such as MPI, SMV and TAPSE, can be measured in a very short course of time and should be part of the standard echocardiographic evaluation. Although there are so far no data coming from studies comparing CRT-implanted patients and controls enrolled according to such parameters, question arise about the usefulness of implanting a CRT device in patients with severely impaired RV function.

Device optimization and CRT response:

Device optimization using device based automated algorithms was performed at the same implantation day in 57.6% of our patients. The AV delay was set empirically at 120 msec and VV delay at 0 msec in

patients with no device optimization. Device optimization was done in the non-responders at 6 months with no improvement in NYHA class at 12 months post-implantation. There was no significant difference in CRT response rate between patients underwent device optimization and others who didn't undergo device optimization (69.4% vs. 63.9% respectively, P= 0.09).

Sawhney in 2004 in an single centre randomized controlled single blinded study showed that AV optimization with VTIao improved LVEF, NYHA class and quality of life after 3 months of follow- up when compared with empiric AV delay at 120 ms.[239] Optimization did not improve any of the endpoints in the optimized arm above the results of the empiric AV delay arm in several studies.[234,389-392] In 2010, Ellenbogen published the results of SMART-AV trial – a multicenter double-blind study in 980 patients randomized to either empirical AV delay of 120 ms, to AV delay optimized according to the mitral inflow pattern (iterative method) or to the Smart Delay algorithm. Primary end-point was the change in left ventricular end systolic volume (LVESV), secondary end points were the change in NYHA class, quality of life, 6-min walking test and left ventricular end diastolic volume. Optimization did not improve any of the end points in the optimized arm above the results of the empiric AV delay arm.[389,390] FREEDOM trial was a multicenter randomized prospective double blind study with the hypothesis that frequent AV and VV optimization using Quick Opt is better or is not worse than empiric AV delay or AV delay optimized by some other method not based on intracardiac electrogram (IEGM). The trial randomized 1525 patients either to Quick Opt algorithm or to the control group where either empiric AV delay was programmed (470 persons) or optimization was performed only at the beginning of the study (274 persons). After12 months of follow-up, no significant difference between groups could be found.[391] A multicenter, randomized, double-blind non inferiority Adaptive CRT Study evaluated the aCRT algorithm. It included 522 patients who were randomized in 2:1ratio to the aCRT algorithm or to the optimization using echocardiographic parameters the (iterative method for AV delay and VTIao for VV interval. There were three end points: clinical composite score (CCS) used in multiple CRT trials

reflecting overall course of the disease (death, hospitalization for heart failure or worsening of heart failure); concordance correlation coefficient between the velocity time integral at aotic valve (VTIao) and aCRT algorithm; safety of a CRT algorithm. During 6 months of follow-up, all three primary objectives were met.[393] The aforementioned data show that methodically strict studies do not unequivocally prove the benefit from CRT optimization. However, the number of studies is limited and majority of them used the IEGM based algorithms incorporated in CRT devices.

LV lead position and CRT response:

In our study, optimal short axis and long axis position of the LV lead was associated with improved response to CRT. Patients with LV leads in a lateral, posterior or posterolateral position compared to anterior and anterolateral sites were more likely to be responders (74.9% vs. 53.3%, P=0.005), also they had better LVEF after 6 months (37.4+10.5 vs. 28.9 +11.9, P=0.002). Patients with LV leads in the apical position compared to basal and mid cavity sites had significantly higher heart failure related mortality rates at 1 year (44.4% vs. 6.8%, P<0.001, P=0.0001) and lower LVEF after 6 months (27.1+7.8 vs. 36.8+11, P=0.007). Optimal LV lead position (combined optimal long axis and short axis position) was an independent predictor of CRT response (OR 11.3; 95% CI 2-63.8). The CRT response rate with optimal LV lead site was 71.2% vs. 29.4% with non-optimal LV lead site, P<0.0001.

Short-term studies have suggested that the lateral wall is a preferred site of LV stimulation to achieve effective CRT.[102,176] Gasparini et al[394] conducted a study to evaluate the effects of different pacing sites in patients treated with CRT. The data from this study revealed that, during long term follow-up, the most important clinical and echocardiographic parameters improved significantly in the patients, independently of the stimulation site. A recent publication about the MADIT-CRT study showed that LV apical pacing provided an inferior effect.[268] The location of the LV lead was assessed by means of coronary venograms and chest x-rays recorded at the time of device implantation. The LV lead location was classified along the short axis into an anterior, lateral, or posterior position and along the long

axis into a basal, midventricular, or apical region. The primary end point of MADIT-CRT was heart failure (HF) hospitalization or death, whichever came first. The LV lead position was assessed in 799 patients, (55% patients ≥65 years of age, 26% female, 10% LV ejection fraction ≤25%, 55% ischemic cardiomyopathy, and 71% left bundle-branch block) with a follow-up of 29±11 months. The extent of cardiac resynchronization therapy benefit was similar for leads in the anterior, lateral, or posterior position (P=0.652). The apical lead location compared with leads located in the nonapical position (basal or midventricular region) was associated with a significantly increased risk for heart failure/death (hazard ratio=1.72; 95% confidence interval, 1.09 to 2.71; P=0.019) after adjustment for the clinical covariates. The apical lead position was also associated with an increased risk for death (hazard ratio=2.91; 95% confidence interval, 1.42 to 5.97; P=0.004).[268] A potential explanation for these findings may be that LV apex pacing requires a shorter AV delay to be optimal in canine hearts.[395] In CRT patients the increase in LV dP/dt max during LV apex pacing is low when using an average AV delay, but almost maximal when using the optimal AV delay.[245] A retrospective analysis from the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) study suggesting a similar benefit among anterior, lateral, and posterior LV lead locations.[396]

Prior work has recommended that targeting the lateral or posterolateral wall by way of either an appropriate coronary sinus branch or surgical (epicardial) placement is a determinant of improved clinical outcomes.[201,397] This strategy is based on the contention that most patients eligible for CRT usually have a LBBB; typically, the latest activated site of the ventricle is along the lateral or posterolateral wall.[70] Earlier work has also suggested that appropriately positioning the LV lead in the region of greatest electric or mechanical delay[107,398] may achieve optimal resynchronization, thereby influencing patient response. However several reports have indicated that there is considerable variability in the ventricular activation pattern and distribution of mechanical dyssynchrony even in the LBBB patient and consequently interindividual variability in the most optimal pacing site.[93,397,399] Importantly, a significant percentage of patients

do not have the typical LBBB morphology indicating a more heterogeneous activation sequence; consequently, the most effective LV pacing site to restore LV synchrony becomes even more unpredictable. Other published reports have indicated that LV pacing along the lateral or posterolateral wall in patients with ischemic cardiomyopathy and transmural scars in this area may actually limit benefit from CRT.[400] Furthermore, the presence of scar may add to the heterogeneity of the ventricular activation pattern.[96]

CRT involves synchronizing the ventricles via electric stimulation from RV and LV pacing sites that should ideally be positioned as far away from each other as possible.[401] An anteriorly positioned or apically positioned LV lead is in close proximity to an RV lead, which is usually positioned in the RV apex, and would be associated with reduced inter-electrode distance and inter-lead electric separation.

CRTscore

We developed a new simple CRTscore based on preimplantation date to predict CRT response. The CRTscore consists of maximum 9 point. Initially all significant independent preimplantation predictors of CRT response in multinominal logistic regression analysis were included in the CRTscore according to their relative effect in the regression model to generate an initial CRTscore. It has been shown that the magnitude of benifit from CRT is highest in patients with wider QRS complex, LBBB, female gender and nonischemic cardiomyopathy (figure 3.10).[46]

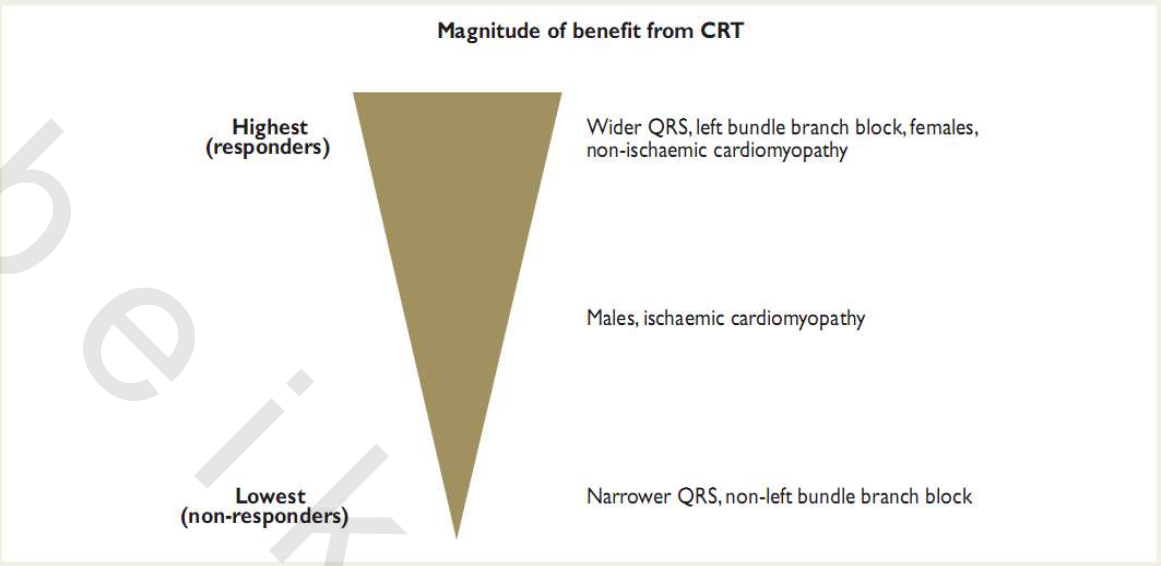

Figure 3.10: Magnitude of benefit from CRT[46]

When LBBB and female gender were added to other variables, the statistical power of the score increased, so they were included in the final CRTscore. The CRTscore includes QRS duration $\geq$ 150 msec, LBBB morphology of the QRS complex, non-ischemic etiology of cardiomyopathy, sinus rhythm at time of CRT implantation, preserved RV function with TAPSE $\geq$ 15 mm, female gender, absence of history of renal disease and finally absence of significant COPD (based on specialized respiratory assessment and use of specific medications). Each parameter was assigned to a single point except QRS duration $\geq$ 150 msec was assigned to 2 points. The CRTscore is the sum of all points (table 3.15).

The CRT response rate has been markedly different according to the CRTscore. Patients with CRTscore $\geq$ 6 had CRT response rate of 97.5% vs. only 40.7% if CRTscore <6, P<0.001.

In a previous scoring model, factors that are associated with favorable reserve remodeling were used to predict CRT responders in the MADIT-CRT trial.[402] Using regression analysis in the CRT with ICD (CRT-D) arm of the trial, 7 factors associated with a favorable chocardiographic response (defined as a 10% reduction in left ventricular end-diastolic volume at 1 year) to CRT-D therapy were first identified;

female sex, nonischemic cardiomyopathy, QRS duration ≥150 ms, the presence of left bundle branch block on baseline ECG, hospitalization for HF at any time before enrollment, baseline left ventricular end-diastolic volume ≥125 ml/m2, and baseline left atrial volume ≥40 ml/m2. Each of the 7 factors was assigned a numerical score on the basis of its relative effect in the regression model. The factor with the lowest effect, prior HF hospitalization, was assigned the lowest score of 1; the intermediate factors, which included female sex, nonischemic cardiomyopathy, left bundle branch block, QRS interval ≥150 ms, and LVEDV, were assigned a score of 2; the highest factor, left atrial volume, was assigned a score of 3. A response score was constructed by adding the number values of the factors identified in each patient. Four patient groups were created on the basis of the response scores. Group 1, the lowest score quartile, had a score of 0 to 4, Group 2 had a score of 5 to 6, Group 3 had a score of 7 to 8, and Group 4, the highest quartile, had a score of 9 to 14. Cox proportional hazards regression modeling showed that when compared to the ICD-only arm, CRT-D patients in Group 2 and higher showed a significant reduction in the risk of HF or death, whereas Group 1 patients derived no benefit. The degree of reduction was incremental between groups with a 33% ($p = 0.04$), 36% ($p = 0.03$), and 69% ($p = 0.001$) risk reduction for Groups 2, 3, and 4, respectively.[402]

Xuedong Shen et al. hypothesized a patient selection score (PSS) to improve patient selection for cardiacresynchronization therapy. They generated the PSS score based on analysis of 100 patients retrospectively and validated the score on another 36 patients. ther CRT response was only 37% in the study population. The PSS composed of 7-point based on six variables. The cutoff point for PSS to predict a positive response to CRT was >4. They initially evaluated 25 variables and they used P walue < 0.1 as the level of significance in univariate analysis. Significant predictors were used in multivariate analysis to generate the PSS. They assigned 1 point each for RV pacing-induced LBBB, use of beta-blockers, wall motion score index (WMSI) ≤ 1.59, left atrial volume index ≤ 59.4 mL/m2, and CrCl ≥ 42 mL/min per 1.73 m2 and 2 points for T_{TDI-PW} >50. CRT responders in patients with a PSS > 4 and ≤ 4 were 33/40 (83%), and 4/60 (7%, P < 0.001), respectively.[403]

In anither study, ninety-three patients receiving CRT were enrolled. A patient selection score system was generated by the clinical, echocardiographic and electrocardiographic parameters achieving a significance level by univariate and multivariate Cox regression model. Fifty-four patients were responders (58.06%). A 4-point score system was generated based on tricuspid annular plane systolic
excursion (TAPSE), longitudinal strain (LS), CLBBB combined with a wide QRS duration (QRSd). They assigned 1 point each for CLBBB combined with a wide QRSd, and LS ≤ -7.22%, and 2 points for TAPSE≥14.8mm. The sensitivity and specificity for prediction a positive response to CRT at a score >2 were 0.823 and 0.850 respectively.

The CRTscore in the scope of guidelines

According to the 2013 European Society of Cardiology guidelines on cardiac pacing and CRT, 87 of our patients met class I indication for CRT implantation, 33 met class IIa indication , 25 patients met class IIb and 25 met class III indication for CRT implantation.[46]

Patients with class I indication for CRT implantation had a response rate of 85%. The CRTscore was ≥ 6 in 68 patients (66 (97%) responders and 2 (3%) nonresponders), while the CRTscore was less than 6 in 19 patients (8 (42.1%) responders and 11 (57.9%) nonresponders, P <0.0001).

Patients with class IIa indication for CRT implantation had a response rate of 48.5%. The CRTscore was ≥ 6 in 9 patients (9 (100%) responders), while the CRTscore was less than 6 in 24 patients (7 (29.2%) responders and 17 (70.8%) nonresponders, P <0.0001).

Patients who met class IIb or III indication for CRT implantation had a response rate of 48%. The CRTscore was ≥ 6 in 2 patients (both are responders), while the CRTscore was less than 6 in 48 patients (22 responders and 26 nonresponders). Most of the nonresponders had a CRTscore < 4. The CRT response was better in patients with CRTscore ≥ 4 compared to those with lower CRTscore (77.3% vs 25%, P<0.001).