Co-Morbidities and Cardiac Resynchronization Therapy: When Should They Modify Patient Selection?

Martin H. Ruwald, MD, PhD

[1]Department of Cardiology, Gentofte Hospital, Denmark. [2]Department of Cardiology, Bispebjerg Hospital, Copenhagen, Denmark.

Abstract

Cardiac resynchronization therapy (CRT) improves symptoms, reduces heart failure related hospitalizations and death in selected patients with heart failure. Based on thousands of patients enrolled in major clinical landmark trials, current guidelines describe in relatively precise terms which cardiac patients should receive a device. However, clinical trials often excluded sicker patients leaving clinicians with the dilemma of how to treat real-life patients with major co-morbidities, frailty, and increasing age, who are otherwise candidates for CRT implantation. This review investigates results from clinical trials and available observational data on the influence of co-morbidities on CRT benefit in order to provide better insight of when and why co-morbidities should modify patient selection for CRT.

Introduction

Cardiac resynchronization therapy (CRT) has evolved vastly since its early stages as a treatment for patients with advanced heart failure (HF) and reduced systolic function. Mainly the improvement could transpire because of technical development and improved physician-related device skills. Furthermore, multiple randomized clinical trials have now shown a significant benefit in both morbidity and mortality associated with implantation of the device, and additionally identified patients who benefit most from this therapy.

International guidelines[1-7] for CRT supports the use of CRT in patients with characteristics similar to those enrolled in the trials[8-13] but with minor differences of opinion regarding left ventricular ejection fraction (LVEF) and QRS duration and morphology in current Canadian,[7] US[4] and European guidelines.[2] A current, simple and practical synthesis is that CRT is a highly recommended and beneficial treatment in patients with sinus rhythm, left ventricular ejection fraction (LVEF) ≤35%, NYHA class II - IV and left bundle branch block (LBBB) QRS morphology with width ≥150 ms. However, the recent European CRT Survey[14] found that CRT indications used in daily practice include patients with QRS less than 120 ms, patients with non-LBBB, asymptomatic patients in NYHA class I, and subjects with atrial fibrillation (AF) thus going far beyond guideline recommended indications, despite a well-known significant non-responder rate around 30%.[15,16] Apart from these

typical CRT indication criteria individual patient co-morbidities and co-morbidity burden may play an influential role in determining patients' clinical response to CRT. Co-morbidities can be perceived as related to cardiac conditions such as AF and disease of the conduction system, and non-cardiac co-morbidities such as chronic obstructive pulmonary disease, chronic kidney disease, diabetes, cancers, and others. This review covers the importance of patient selection and the influence of cardiac and non-cardiac co-morbidities in relation to CRT efficacy and outcomes.

Typical Non-Responders

Analyses have consistently shown that patients with non-LBBB QRS morphology, patients with ischemic cardiomyopathy, those with higher scar burden, males and those with increased disease burden (larger atrial and ventricular volumes and lower baseline LVEF) derive a relatively reduced benefit of CRT implantation.[15,17,18] A simple and better selection of patients may reduce this number of non-responders substantially. A suboptimal response to CRT is believed to be multifactorial and depends on patient selection and CRT delivery techniques (lead positions, AV-delay etc.). Mullens et al.[19,20] further showed that a protocol-driven assessment of CRT non-responders improves reverse remodeling by 50%. Additionally, a retrospective analysis comparing a multidisciplinary care setting to "conventional" care found a significant improvement in patient care and reduction in clinical outcomes.[21] In addition to the factors above, several cardiac and non-cardiac co-morbidities may influence the efficacy of the CRT device and the overall outcome as discussed below. Evaluation and management of non-responders is beyond the scope of this review but recent reviews cover this matter.[22,23]

Scar burden in Ischemic HF

Among patients with ischemic HF a large scar burden as well

as a lead position on top of localized scar is associated with lack of response.[24-26]

The myocardial scar burden determined by magnetic resonance, speckle track echocardiography or single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI)may add prognostic value,[27-30] but so far no definitive comparative studies have been able to select any one of these to be included in pre-selection of CRT candidates. Adelstein et al.[24] compared 190 CRT patients with ischemic cardiomyopathy to 380 CRT patients with non-ischemic cardiomyopathy and 50 patients referred for CRT but with unsuccessful LV implant. They showed that a large scar burden score ≥23 (defined as a score based on 17 segments each allocated 0-4 points, 0=normal, 4=absence of uptake) of the ischemic patients was associated with significantly worse survival and less improvement in LVEF. Further ischemic patients with a low score <23 exhibited similar survival and LVEF improvement as the comparison group of non-ischemic. Overall this study indicated that patients with large scar burden may not benefit from CRT and this group of patients is very likely to be CRT non-responders.

In addition to the total scar burden, localized scar tissue near the LV lead site may directly prevent resynchronization with the septum and further reduce the electrical propagation from the stimulation site to the viable myocardium. Many LBBB patients experience super response to CRT which is most likely due to the presence of a large anatomic sweet spot of potential response, particularly for non-ischemic patients. If lead placement was guided by imaging it seems that particularly non-LBBB and non-responder subgroup populations such as ischemic patients with large areas of scar burden could have improved outcomes, but this remains to be shown in prospective trials. Although quantification of scar by magnetic resonance imaging seems particularly promising a SPECT/MPI is mostly used in clinical practice and is safe in patients with implanted devices. The quadripolar LV leads increases the number of pacing vectors compared to bipolar leads allowing a more optimal posterolateral lead placement and potentially avoiding areas of scar. The clinical value of quadripolar lead has been evaluated in non-randomized observational studies showing a decreased risk of hospitalization, reduced cost[31] and better survival.[32]

Atrial Fibrillation in HF

AF is the most common arrhythmia in patients with HF. The EuroHeart Failure survey reported that up to 45% of patients with HF also had intermittent or permanent AF.[14] AF is a typical cause of decompensated HF and complicates management significantly. Despite the huge number of patients with both permanent AF and HF, accounting for more than 20% of CRT recipients in Europe,[14] these patients were included in very small numbers in the large randomized clinical trials. The studies published, in which the efficacy of CRT in patients in sinus rhythm was compared to those with AF, showed a lower clinical efficacy and a higher rate of non-responders in the AF group, which can partly be explained by the difficulty in achieving an acceptable biventricular pacing percentage.[33,34] However for paroxysmal or intermittent AF the case is less clear; in a MADIT-CRT sub-analysis, the clinical benefit of cardiac resynchronization therapy with implantable cardioverter defibrillator (CRT-D) was not attenuated neither by a prior history of intermittent atrial tachyarrhythmias nor by the development of in-trial atrial tachyarrhythmias.[35] In the RAFT trial patients were

stratified by presence of permanent AF and then randomized to CRT-D (N=114) or implantable cardioverter defibrillator (ICD)-alone (N=115). The results showed no difference in the primary outcome of death or HF hospitalization between those assigned to CRT-D versus ICD (HR= 0.96; P=0.82).[36] This indicated that patients with permanent AF who are otherwise CRT candidates appear to gain minimal benefit from CRT-D compared with a standard ICD. AV node ablation for the management of AF in CRT HF patients is a treatment that permits complete rhythm and heart rate control resulting in constant biventricular pacing. In a systematic review and meta-analysis Wilton et al.[37] compared the outcomes of patients (n=7,495) with and without AF receiving CRT and evaluated the influence of AV node ablation in those with AF. AF was prevalent in 26% and was associated with significantly increased risk of non-response to CRT (35 % vs 27%) and all-cause mortality (11% vs 7% per year). AV node ablation appeared favorable with a lower risk of clinical non-response (RR= 0.40) and a reduced risk of death. One year later, in 2012, Ganesan et al. published a similar meta-analysis with fewer studies but focusing on the role of AV node ablation in the patients with AF. Results were similar showing AV node ablation was associated with a substantial reduction in all-cause mortality (RR = 0.42) and cardiovascular mortality (RR= 0.44) and with improvements in NYHA class compared with medical therapy in CRT plus AF patients.[38] Therefore overall the benefits of CRT appear to be attenuated in patients with permanent AF, in particular in those with low biventricular pacing rates, but AV node ablation can improve CRT outcomes in patients with AF.

The APAF[39] study from 2011 and the PAVE[40] study from 2005 were both conducted on patients with AF and AV node ablation was performed. CRT, compared to RV pacing alone, decreased both mortality and the number of hospitalizations due to HF. The observational CERTIFY study[41] (N=7,384) compared mortality between CRT patients in sinus rhythm with AF patients who had undergone either AV node ablation or medical treatment. The results showed that cardiac as well as total mortality were higher in patients with AF and medically treated; while there were no significant differences between patients in sinus rhythm and those with AF who underwent AV node ablation. The rationale and evidence for optimal outcomes among CRT patients based on biventricular pacing percentage refer to the hypotheses that effective delivery of CRT may be hindered by the presence of native ventricular conduction, by inappropriate long AV delay programming, by atrial or ventricular tachycardia, AF or frequent premature atrial and ventricular complexes.[1,23,33] AF is considered a major determinant of loss of biventricular pacing.[42]

The optimal biventricular pacing percentage has been evaluated in four studies. Initially, in 2006 Gasparini et al. set an arbitrary cut-off of 85% biventricular pacing to define CRT in AF patients as successful. Koplan et al[43] followed in 2009 and reported 92% while Hayes et al. in 2011[44] found 98.5% to be the cut-off with the greatest magnitude of separation for total mortality. In the MADIT-CRT trial (sinus rhythm patients) a biventricular pacing percentage ≥90% was needed to show CRT-D efficacy when compared to ICD-only[45] and biventricular pacing ≥97% was associated with an even further decrease in the risk of HF events, as well as a significantly reduced risk of death. Of importance Hayes et al. found that patients with AF had similar survival as sinus rhythm patients as long as they achieved biventricular pacing percent of 98.5% or more. Biventricular pacing

percentage is a practical evaluation and measurement of biventricular pacing success, however Kamath et al.[46] demonstrated in 2009 that that the absolute percentage of biventricular pacing alone, as obtained from the CRT device interrogation, was an unreliable marker of effective pacing. Although the interrogation documented more than 90% pacing, a concomitant Holter monitor revealed that fusion and pseudo-fusion beats constituted as much as 40% of the overall paced beats. Therefore using data from CRT interrogation counters alone to estimate percentage of biventricular pacing can be misleading and results in overestimation.

Current European guidelines give a IIa recommendation with level of evidence B for patients in permanent AF with LVEF≤35%, NYHA class III, QRS≥120 ms provided that close to 100% biventricular pacing can be achieved. Otherwise an AV node ablation is recommended with same level of evidence.[2]

Atrio-Ventricular Block in HF

Smaller proof-of-concept studies proposed that patients with traditional pacemaker indications and moderate to severely reduced LV function could benefit from CRT instead of RV apical pacing alone. The HOBIPACE[47] (n=30) and COMBAT[48] (N=60) showed effect on both echocardiographic and patient symptom parameters. The rationale was that early intervention with CRT could prevent deterioration and progression of HF due to chronic RV pacing. For patients with preserved LV function and pacemaker indication however the PREVENT-HF trial[49] (n=108) showed no benefit of CRT in terms of LV remodeling as compared to RV pacing, while the PACE study (n=177) found the reduction in LVEF and the increase in LV end-systolic volume observed at 1 year with RV apical pacing was prevented by CRT but without any significant difference in clinical endpoints. The BLOCK-HF[50] included 691 patients with AV conduction disorders of different severity with a traditional pacemaker indication and LVEF ≤50%. Patients were randomized to CRT or RV pacing (LV pacing off) (either with or without ICD based on standard indications). Patients assigned to RV pacing showed a significantly higher incidence of the combined endpoint of HF hospitalization or death or 15% increase in LV end-systolic volume). The study suggests that CRT can be beneficial in patients with a lower degree of systolic dysfunction and an indication for pacemaker avoiding the deleterious effect of stimulation from the right ventricle. Another large trial, the BioPace trial enrolled 1,810 patients and has not yet published the final results. Preliminary results presented at the ESC 2014 were negative with only a trend towards benefit for patients randomized to CRT versus RV (HR =0.87, p=0.08) but final results are pending.[51,52] The above evidence suggests that patients with HF and reduced LVEF who require frequent ventricular pacing should be considered for CRT despite native QRS width. Further studies should evaluate the long-term benefits of CRT for patients with normal LV function and frequent ventricular pacing.

Non Cardiovascular Co-Morbidities

Among HF patients undergoing CRT implantation the burden of non-cardiovascular co-morbidities is generally high. In general, patients with significant co-morbidities were excluded in the major trials[8-13,53-55] and efficacy of CRT in these patients has not been tested in randomized trials.

Patients enrolled in the major randomized controlled trials were most often male (75%), had a mean age of 65 years, a prevalence of diabetes of 30-40% but the prevalence of COPD, active or prior cancer and chronic kidney disease was rarely reported if the patient was not excluded by enrollment criteria, see Table 1. The MADIT-CRT and MIRACLE both excluded patients with creatinine >3 mg/dL and in the MADIT-CRT a total of 89 (5%) of the patients had severe renal dysfunction defined as eGFR <30 mL/min/1.73m2.[56] As an example from the MADIT-CRT protocol exclusion criteria involved patients that had "presence of any disease, other than the subject's cardiac disease, associated with a reduced likelihood of survival for the duration of the trial (average follow-up 40 months), e.g., cancer, uremia, liver failure, etc.[57]" From HF registry data of real-life CRT patients we know that the patients are approximately 5 years older, obesity in general affects 30%, diabetes 30%, COPD 30%,

Table 1:	Triggers and risk factors for developing LAF									
Trial (year)	Patients	NYHA	LVEF Critera Mean	QRS Critera Mean	Primary end point	Secondary End points	Non-ischemic	Diabetes	Renal dysfunction	COPD
PATH-CHF (2002)	41	III, IV	NA 22%	≥150 175	6-MWT, peak VO2	NYHA, QoL, HF hosp.	71%	NR	NR	NR
MIRACLE (2002)	228/225	III, IV	≤35% 22%	≥130 166	NYHA 6-MWT QoL	Peak VO2, LVEDD, LVEF, MR, CCR	76%	NR	NR	NR
MIRACLE –ICD (2003)	187/182	III, IV	≤35% 25%	≥130 164	NYHA 6-MWT QoL	Peak VO2, LVV, LVEF, MR, CCR	31%	NR	NR	NR
CONTAK-CD (2003)	245/245	II,III,IV	≤35% 22%	≥120 158	NYHA 6-MWT QoL	LVV, LVEF, CCR	31%	NR	NR	NR
COMPANION (2004)	617/595/308	III, IV	≤35% 21%	≥120 159	All-cause mortality or hosp.	Cardiac mortality	44%	41%	NR	NR
MIRACLE –ICD II (2004)	85/101	II	≤35% 25%	≥130 166	Peak VO2	NYHA QoL, 6-MWT, LVV, LVEF, CCR	43%	NR	NR	NR
CARE-HF (2005)	409/404	III,IV	≤35% 25%	≥120 160	All-cause mortality or cardiovascular hosp.	NYHA, QoL, LVEF, LVESV, HF hosp.	46%	21%	18%	19%
REVERSE (2008)	419/191	I,II	≤40% 28%	≥130 153	CCR	LVESVi	45%	22%	Mean eGFR 83 mL/min	NR
MADIT-CRT (2009)	1089/731	I,II	≤30% 25%	≥130 162	All-cause mortality or HF hosp.	LVESV, LVEDV, LVEF	45%	30%	32%	NR
RAFT (2010)	894/904	II,III	≤30% 24%	≥120 158	All-cause mortality or HF hosp.	Cardiac death Non-fatal HF Hosp.	33%	34%	43%	NR

CCR: Clinical composite response, 6-MWT: 6 minute walking test, Qol: quality of life, LVEDD: left ventricular end-diastolic diameter, LVESV: left ventricular end-systolic volume, LVESVi: : left ventricular end-systolic volume index; LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction, eGFR: estimated glomerular filtration rate, COPD: chronic obstructive pulmonary disease, NR: not reported, NYHA : New York Heart Association, MR: mitral regurgitation

chronic kidney disease 30% and anemia 10%.[58,59] Co-morbidities additionally affect optimal medical treatment, i.e. insufficient use of antithrombotic medications in anemic patients, reduced use of beta-blockers for COPD and reduced use of angiotensin blockers and spironolactone among patients with chronic kidney disease.

Everyday physicians encounter patients who have per guideline indication for CRT but also often present with one or more of these co-morbidities possible affecting expected cardiac prognosis and CRT efficacy.

Theuns et al.[60] prospectively followed 463 patients who received a CRT-D. They found that non-cardiac co-morbidities were common in their population of HF patients with 81% of the patients having at least three comorbid conditions. They reported that patients with a high co-morbidity burden had an increased risk with a hazard ratio of 3.7 for mortality as compared to those with a lower burden. However, since there was no control group, the study could not assess whether there were any relative benefit of CRT among the patients with high co-morbidity burden. Bai et al.[61] also demonstrated that renal failure and diabetes were strong independent predictors of mortality in patients treated with CRT. In this study patients with one of three co-morbidities, chronic renal failure (OR = 4.9), diabetes mellitus (OR = 4.1), and history of AF (OR = 1.5) had a higher risk of death but again without a control group leaving the question of CRT efficacy based on co-morbidity burden unanswered. Dominguez-Rodrigues et al.[62] recently reported that frailty defined as a syndrome of wasting and malnutrition, weakness, slowness, and inactivity, was a strong predictor of HF decompensation (HR = 4.6) in patients with non-ischemic cardiomyopathy undergoing CRT-D. Frailty and high co-morbidity burden, illustrated by Charlson Index >4, has previously been associated with high risk of non-sudden death in HF but non-CRT patients6. These observational data and other reports[58,59,63] suggest that patients with high burden of non-cardiac co-morbidity are at higher risk of death on both short and long-term, but so far no reports have been able to set a cut-off of where patients with high co-morbidity burden no longer benefit from a CRT device. In particular frailty and cachexia might reduce the overall benefit of CRT, but many of contributing factors in frailty may be reversible through CRT effect. Consultation with geriatrician could be helpful in these borderline cases. Recent detailed statistical analysis[64] of five landmark CRT trials (COMPANION, CARE-HF, MADIT-CRT, RAFT and REVERSE) found that the lifespan gain from biventricular pacing rises nonlinearly with time. They showed that lower-risk patients seemed to gain less over the first 1 or 2 years, but ultimately they could be the ones who gained the most from implantation of the device.

Chronic Kidney Disease

Renal dysfunction is one of the most important co-morbidities in HF and is associated with increased mortality and affects cardiac function and renal function bidirectionally so that worsening HF or acute decompensated HF can accelerate worsening of renal function--the so-called cardiorenal syndrome.[65] Beneficial effects of CRT can be related to improvement in renal function leading to the hypothesis that CRT is a renal-protective strategy in HF. From the MIRACLE study the patients were categorized according to their baseline eGFR≥90, 60-89 and 30-59 mL/min per 1.73 m². CRT improved LV function in all three categories and when compared with controls, CRT increased eGFR and reduced blood urea nitrogen in those with worst renal function, whereas no differences were observed in the

group of eGFR 60-89 and eGFR≥90.[66] Goldenberg et al. showed in the MADIT-CRT that pre-implantation patients with an elevated ratio of blood urea nitrogen to creatinine experienced a significantly greater reduction in the risk of HF or death with CRT-D therapy as compared with patients with a low ratio56. The cumulative 3-year incidence of HF or death was 35% among ICD patients with high BUN:crea level compared to 18% for those with low BUN:crea level. This is in contrast to 18% versus 22% for the patients treated with CRT-D in the same categories, leaving a relative risk reduction markedly higher for CRT-D patients with high BUN:crea levels of 0.46 compared to 0.85 for those with low BUN:crea levels. These findings suggested important interaction between prerenal function and response to CRT, but importantly these data were from less symptomatic NYHA II and I patients. This was supported by smaller studies where elderly patients who had a higher prevalence of renal dysfunction still had positive response to CRT,[67,68] while others report that the effect of CRT was attenuated in patients with more advanced chronic kidney disease (<30 mL/min/1.73m²). Adelstein et al.[69] reported no echocardiographic or survival improvement in 64 of 787 CRT patients with eGFR <30 mL/min/1.73m² compared to a control group of unsuccessful LV implant. Considering increased procedural risk among patients with advanced chronic kidney disease or on dialysis benefit/risk assessment needs to be cautiously evaluated.[70]

Based on the available data, the possible attenuated benefits and the increased risk should be taken into consideration when considering the implantation of a CRT device in a dialysis patient. The role of CRT in end-stage renal failure patients or on dialysis therapy has therefore not been fully established.[56, 63, 71-73] Recent appropriate use criteria for ICD and CRT-D gives an M for "may be appropriate" for the implantation of ICD/CRT-D in patients with advanced renal dysfunction or in patients on dialysis.[74]

Diabetes and HF are associated and each condition is a risk factor for the development of the other. Several analyses both from HF populations and HF with CRT populations have found diabetes as an independent predictor of morbidity and mortality,[75-79] while some studies disagree and find similar mortality with or without diabetes.[80] The pathophysiology underlying HF in diabetic patients differs from that of non-diabetic patients[81] and therefore CRT might have reduced efficacy however there is overwhelming evidence that CRT performs equally well in both diabetic and non-diabetic patients.[80,82-84]

Clinical risk scores have been encouraged as a means of identifying patients who are less likely to benefit from ICD therapy, notably the very elderly, patients with very advanced symptoms of HF, and those with chronic kidney disease but similar clinical risk scores have not been developed in CRT patients.[85-88] Furthermore, none of these risk scores have been independently validated and there are no randomized data to guide clinical decision-making.

Currently patient selection for CRT considering co-morbidities relies on individual physician judgement.

Age as a Factor?

Elderly patients differ substantially from younger patients and age-related changes in cardiac structure include increased left ventricular mass, decreased myocyte function and increased apoptosis.[89] As mentioned above there is a natural age-dependent increase in coexisting co-morbidities such as cerebral vascular disease, renal dysfunction, anemia, hyponatremia, etc. in elderly patients leading to higher rates of mortality and hospitalizations when compared

with younger patients.[90] It was hypothesized that the elderly would not benefit as much from CRT as the young maybe because of high incidence of non-cardiac death, on the other hand even a small relative risk reduction with CRT can become evident when the absolute risk for mortality is high.

In a MADIT-CRT sub-analysis[91] a multivariate analysis demonstrated that CRT-D therapy was associated with a significant reduction in the risks of HF or death in patients aged 60-74, and ≥75 years (HR = 0.57 and HR = 0.59, respectively), while no significant benefit in patients aged <60 years (HR = 0.81) was observed. Other smaller observational studies have supported this finding.[67,92] Recently it was however shown that among elderly patients (>75 years),(N=208) implanted with CRT the cause of death was mainly non-cardiac (29% in the elderly versus 19% in non-elderly; P<0.001). Diabetes, impaired renal function and reduced 6-minute walk distance were independently associated with all-cause mortality in the elderly patients.[93] Competing risk of non-cardiac death could indicate an overall reduced efficacy of a CRT device among the elderly. Currently patient selection for CRT considering age relies on individual physician judgement. Expected lifespan <1 year is considered a contraindication for CRT-D or ICD. Current evidence does not support that high age alone should be regarded as a limiting factor or a contraindication for CRT implantation.

Conclusion

Physicians implanting CRT should take into account several clinical factors when selecting patients for this therapy. Aside from the guidelines recommended cardiac criteria of disease severity (NYHA class), the magnitude of left ventricular dysfunction, QRS width and morphology as well as rhythm and life-expectancy it is important to evaluate important comorbid factors. Further data is needed to help guide clinicians in future patient selection by setting the right cut-off of risk/benefit and co-morbidity burden where we cannot expect the device to have an overall positive effect.

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