Current Evidence and Recommendations for Cardiac Resynchronisation Therapy

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Abstract

The number of people in Europe living with symptomatic heart failure is increasing. Since its advent in the 1990s, cardiac resynchronisation therapy (CRT) has proven beneficial in terms of morbidity and mortality in selected heart failure (HF) patient populations, when combined with optimal pharmacological therapy. We review the evidence for CRT and the populations of HF patients it is currently shown to benefit, and those in which more research needs to be performed.

Keywords

Cardiac resynchronisation therapy, complex devices, heart failure, guidelines, recommendations

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Approximately 2 % of the adult population in high-income countries has clinical heart failure (HF),¹ and almost the same percentage again has impaired left ventricular (LV) function without symptoms.² The incidence and prevalence of HF rises steeply with age; the mean age at first diagnosis being 76 years,³ with about half of these patients having a left ventricular ejection fraction (LVEF) of <50 %.¹ The prevalence of HF is expected to rise because of an ageing population, improved survival of patients with ischaemic heart disease and more effective pharmacological treatments for HF.⁴ Prognosis from HF is poor, with a one-year mortality rate in those admitted to hospital with clinical HF of up to 40 % in those aged >75 years.⁵ However, there is already evidence of increased survival of HF patients, with one study showing a reduction in six month mortality over the 10 years between 1995 and 2005 from 26 % to 14 %.⁶ This has coincided with improved medical therapies and co-ordinated multidisciplinary care, but is likely to improve further since the advent of widespread use of cardiac resynchronisation therapy (CRT). Based on current guideline criteria from the European Society of Cardiology (ESC),⁷ CRT is only indicated in 5–10 % of HF patients, but this is still a large number of patients. It has been estimated that up to 400 patients per million population per year in Europe may be suitable for CRT;⁸ but even in Italy and Germany where the highest number of implants takes place, the implant rate is currently just over 200 per million.⁹

Cazeau and Bakker published the first case reports on LV pacing in 1994.^{10,11} They described the beneficial effects of biventricular pacing for New York Heart Association (NYHA) III/IV HF patients with a prolonged QRS, describing case series of thoracoscopically placed epicardial LV leads. The feasibility of biventricular pacing was furthered in 1998 when Daubert published the results of a fully transvenous permanent biventricular pacing system using a unipolar Medtronic lead.¹² Since then, there have been several large international multicentre studies extolling the virtues of CRT, which

this article will review. We will suggest populations where we know the evidence to be strong for being a CRT 'responder', other populations where the data are not so strong, and unresolved issues with regard to who may benefit from CRT and what decision tools are available to clinicians in order to decide who will be most likely to benefit.

Patients in Sinus Rhythm and New York Heart Association III-IV

The evidence is fairly convincing for the benefits of CRT in patients who are in sinus rhythm with severely impaired LV function, who have NYHA class III HF symptoms. Earlier studies suggested a benefit in terms of symptoms, exercise capacity and LV function.^{13–17} More recently, two large randomised controlled trials have shown benefit in terms of all-cause mortality and HF hospitalisations.^{18,19} The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial¹⁸ showed statistically significant reductions in the combined primary endpoint of death or hospitalisation from HF by 34 % in the cardiac resynchronisation therapy with pacemaker (CRT-P) arm and 40 % in the cardiac resynchronisation therapy with pacemaker-defibrillator (CRT-D) arm, versus optimal pharmacological therapy. It also showed reduction in all-cause mortality by 24 % ($p=0.059$) in the CRT-P group and by 36 % ($p=0.003$) in the CRT-D arm. The Cardiac Resynchronization – Heart Failure (CARE-HF) study¹⁹ reported a hazard ratio (HR) of 0.63 ($p<0.001$) for the primary combined endpoint of time to death from any cause or hospitalisation for any cardiovascular cause for CRT-P versus medical therapy. The HR for all-cause mortality was 0.64 ($p<0.001$) in the CRT-P group.

The evidence for patients in NYHA class IV is more limited. A substudy of COMPANION²⁰ suggested benefit in so-called 'ambulatory class IV' patients (i.e. those without a HF hospitalisation in the preceding month) in terms of a significant reduction in the primary endpoint

as above, and a trend towards reduction in all-cause mortality and HF deaths.

Patients in Sinus Rhythm and New York Heart Association I-II

The Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy (MADIT-CRT)²¹ looked at 1,820 patients with predominantly NYHA class II HF symptoms randomised 1:1 to either CRT-D or implantable cardioverter defibrillator (ICD). There was a statistically significant 34 % ($p=0.001$) reduction in the combined primary endpoint of all-cause mortality or any HF event in the CRT-D group versus the ICD group. However, the endpoint was driven by a 41 % reduction in HF events, and the annual mortality rate of 3 % did not differ between the two groups. The Resynchronization Defibrillation for Ambulatory Heart Failure Trial (RAFT)²² took 1,798 predominantly NYHA class II patients and showed a HR of 0.75 for the primary outcome of death from any cause or HF hospitalisation with CRT-D versus ICD. This time the result was not driven by just HF; a statistically significant reduction in all-cause mortality alone was shown (HR 0.75, $p=0.003$). Two other smaller randomised trials confirm the benefit in NYHA II patients.^{23,24}

CRT does not seem to reduce mortality or HF events in NYHA class I patients, according to subgroup analyses of the small percentage of NYHA I patients making up the Resynchronization Reverses Remodeling In Systolic Left Ventricular Dysfunction (REVERSE)²⁴ (15 %) and MADIT-CRT²¹ (18 %) trials, and thus CRT in NYHA class I patients is currently not recommended.

QRS Duration and Morphology

HF patients with a broad QRS have a worse prognosis than those with a narrow QRS, with three-year mortality rates in the MADIT-CRT trial for inter-ventricular conduction delay, right bundle branch block (RBBB) and left bundle branch block (LBBB) being 4, 7 and 8 %, respectively.²⁵ Meta-analyses suggest that the most benefit from CRT is gained, regardless of NYHA class (II-IV), if the QRS duration is ≥ 150 ms²⁶ and in patients with complete LBBB.²⁷ This benefit was a composite of all-cause mortality and HF hospitalisations, and it remains unclear as to whether there is benefit on all-cause mortality alone. Furthermore, in MADIT-CRT, those patients with non-LBBB had a 24 % (non-significant) increased risk of the primary outcome with CRT.²⁵

Atrial Fibrillation

It is apparent, despite how common atrial fibrillation (AF) is in HF patients, that there is a paucity of randomised controlled trial data in patients with a CRT indication and persistent or permanent AF. The evidence of benefit is small, and restricted to those in NYHA class III-IV in whom biventricular pacing can be maximised. The Multisite Stimulation in Cardiomyopathy – Atrial Fibrillation (MUSTIC-AF) trial²⁸ looked at CRT in patients with severe left ventricular systolic dysfunction (LVSD), NYHA III-IV and permanent AF. In those achieving >85 % biventricular pacing, there was a small but statistically significant improvement in functional status at six and 12 months. In the subgroup of 229 AF patients in the RAFT study,²⁹ there were no significant differences shown in patients treated with CRT-D versus ICD, with only trends towards reduced HF hospitalisations and improvements in Minnesota Living with HF Score found. However, results are slightly more encouraging in trials including patients undergoing atrioventricular (AV) node ablation. Both the Ablation for Paroxysmal Atrial Fibrillation (APAF)³⁰ and Post AV Nodal Ablation

Evaluation (PAVE)³¹ trial showed, in patients with AF undergoing AV node ablation and concurrent CRT implant with severe LVSD, NYHA III-IV and QRS ≥ 120 ms, a significant reduction in the primary composite endpoint of death from, or hospitalisation for, or worsening of, HF.

One of the most important factors determining the response to CRT is maximisation of biventricular pacing, and AF has been shown to be a major determinant in loss of biventricular pacing in large registries.^{32–34} Competing AF rhythm, be that by spontaneous conduction or fusion and pseudofusion beats, reduces biventricular pacing. Holter monitoring may be required to detect fusion and pseudofusion, as this will often be registered as biventricular pacing by device algorithms.³⁵ Biventricular pacing between 93 and 100 % has been shown to reduce all-cause mortality and HF hospitalisation by 44 % compared with 0–92 %, with the greatest magnitude of mortality reduction in patients achieving >98 % biventricular pacing.³³ In AF patients who cannot achieve this with AV nodal blocking agents alone, AV node ablation is the next appropriate step.

Ischaemic Versus Non-ischaemic Cardiomyopathy

A substudy of MADIT-CRT³⁶ has suggested that in mildly symptomatic patients (predominantly NYHA II), those with non-ischaemic cardiomyopathy tend to derive more benefit than those with ischaemic cardiomyopathy. CRT-D versus ICD therapy was associated with a 34 % and 44 % reduction in risk of HF or death in ischaemic and non-ischaemic patients, respectively. There was also greater benefit derived in terms of reduction in end-systolic and diastolic volumes of the left ventricle in non-ischaemic patients versus ischaemic patients. Patients in the ischaemic cardiomyopathy group were also noted to have greater benefit if they had a QRS ≥ 150 ms, systolic blood pressure <115 mmHg or LBBB, and likewise in the non-ischaemic group if they were female, diabetic or had LBBB.

For those with more significant symptoms (predominantly NYHA III), the same appears to be true in terms of non-ischaemic patients deriving greater benefit. In fact, in the COMPANION trial,¹⁸ the HR for all-cause mortality was 0.50, which was significant ($p=0.015$) for CRT-D versus ICD in non-ischaemic cardiomyopathy patients, while in those with ischaemic cardiomyopathy there was a trend to reduced mortality (HR 0.73), but this reduction was non-significant ($p=0.082$).

Cardiac Resynchronisation Therapy Pacemaker Device or Cardiac Resynchronisation Therapy Defibrillator Device?

Data from the Contak Italian Registry on 620 patients with an ESC IA recommendation for CRT randomised to either CRT-P or CRT-D suggests that there is a significant mortality benefit with CRT-D, and is the first randomised controlled trial to do so.³⁷ After a median follow-up of 55 months, mortality rates were significantly lower in the CRT-D group (6.6 % per year) versus the CRT-P group (10.4 % per year) ($p=0.020$). Following adjustment for the fact that the CRT-P group were predominantly older, female, had no history of life-threatening ventricular arrhythmias, had longer QRS durations and worse renal function, the only independent predictor of death from any cause was the use of CRT-P (HR 1.97, $p=0.007$). This data confers with observational data from other large trials not powered to look specifically at differences between CRT-P and CRT-D. Data from the three groups in COMPANION (optimal medical therapy, CRT-P and CRT-D)¹⁸ suggested that at one-year, only the CRT-D group had a significant reduction in all-cause mortality ($p=0.003$). While the CRT-P

Figure 1: Decision Aid Flowchart for Selecting Patients Suitable for Cardiac Resynchronisation Therapy

Pink = strong evidence-based recommendation likely to gain benefit; Purple = evidence present that may gain benefit, but not strong; Green = little/no evidence of benefit and/or potential for harm. AF = atrial fibrillation; AV = atrioventricular; AVN = atrioventricular node; BiV = biventricular pacing; CHB = complete heart block; CRT = cardiac resynchronisation therapy; EF = ejection fraction; LBBB = left bundle branch block; NSIVCD = non-specific interventricular conduction delay; NYHA = New York Heart Association Class; RBBB = right bundle branch block; SR = sinus rhythm.

group also showed a reduction, this was not significant ($p=0.059$). It took 16 months of follow-up for the reduction in sudden cardiac death with the CRT-D arm to become significant, hence suggestions in the current guidelines that the patient should be expected to live

for at least a year from time of implant to benefit.⁸ CARE-HF was the first trial to show a reduction in all-cause mortality for CRT-P, but did not initially show a reduction in the risk of sudden cardiac death.¹⁹ However, the extension study with a mean of 37.4 months follow-up

showed a significant 5.6 % reduction in sudden cardiac death.³⁸ These data suggest that the reduction in death seen initially with CRT-P is likely due to a reduction in HF-related deaths, and that only with the beneficial effects of CRT on LV reverse remodelling over time does one get a reduction in sudden cardiac death. Therefore, the argument is made that to help prevent sudden death in the initial period, CRT-D is the better modality. A recent meta-analysis of 12 randomised controlled trials showed no significant difference in survival between CRT-D and CRT-P (odds ratio [OR] 0.85, 95 % confidence interval [CI] 0.60–1.22) or CRT-D and ICD (OR 0.82, 95 % CI 0.57–1.18), but also looked at ‘probabilities’ of best therapy, finding a 75 % chance that CRT-D was the best therapy to reduce overall mortality (versus CRT-P 14 % and ICD 10 %).³⁹

While CRT-D may show a trend towards being the optimum therapy to reduce risk of death, this must be countered by the appropriateness of defibrillator therapy, as well as taking into account the physical and psychological effects of appropriate and inappropriate shock therapy, and potential problems with lead longevity.

Role of Imaging and Evidence of Mechanical Dyssynchrony

The benefit of imaging to help decide which patients will benefit from CRT remains uncertain. A subanalysis of CARE-HF data suggested an echocardiographic interventricular conduction delay of ≥ 49.2 ms was an independent predictor of CRT response.⁴⁰ Other imaging techniques have shown several measures of mechanical dyssynchrony to be predictive of response.^{41–45} However, The Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) trial,⁴⁶ which was a large multicentre study, showed only modest ability of dyssynchrony measures to predict response to CRT. The large differences in sensitivity, and specificity and heterogeneity in results between centres has in some areas been criticised, and further studies are needed in this area.

Left Ventricular Lead Position and Multi-site Pacing

The posterolateral position is the current recommended area for LV lead placement as it is often associated in patients with LBBB with the latest mechanical contraction. Data from REVERSE⁴⁷ and COMPANION⁴⁸ support this in terms of improvement in survival and clinical status, but the COMPANION data also suggest no difference in benefit between posterior, lateral and anterior lead placement. MADIT-CRT data show that basal or mid-ventricular positions of the LV lead are superior to apical placements,⁴⁹ as the closer to the apex the lead is, the closer to the right ventricular (RV) lead it is likely to be. Data are emerging suggesting benefit of a more technical approach in terms of placing the LV lead in positions of latest activated areas measured by speckle tracking echocardiography,⁵⁰ or by haemodynamic response of rate of rise of LV pressures (dP/dt) measured invasively by a pressure wire in the LV.⁵¹ While this may be an optimal solution, often the implanter is faced with limited options in terms of coronary venous anatomy and target veins.

With regard to multi-site LV pacing, there is a paucity of data at the current time. Most of the studies are small, but do show promise for multi-site pacing in terms of haemodynamic⁵² and functional^{53,54} benefit, or in patients with significant posterolateral scar.⁵⁵ Further study is needed to confirm the benefit, and it is important to balance this out with the potential complications associated with leaving an extra LV lead *in situ*.

Heart Failure Patients with Atrioventricular Block

Long-term right ventricular pacing is documented as causing adverse remodelling and deterioration in LV function. Up until recently, only small randomised trials suggested the benefit of *de novo* CRT implants versus standard RV pacing in patients with moderate-to-severe LV dysfunction and a bradycardia pacing indication. However, the Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK-HF) study,⁵⁶ randomised 691 patients with an ejection fraction (EF) ≤ 50 % (mean EF 40 %) and a pacing indication with AV block to either CRT or RV pacing. The primary outcome was a composite of death from any cause, an urgent care visit for HF requiring intravenous therapy, or ≥ 15 % increase in LV end-systolic volume index. The study reported a significantly lower incidence of the primary outcome in the CRT group versus RV pacing group (HR 0.74, 95 % CI 0.6–0.9), and this benefit persisted when excluding LV end-systolic volume index from analysis (HR 0.73, 95 % CI 0.57–0.92). However, the Kaplan–Meier curve suggests all the benefit appears to be in the first 12 months, with the lines running fairly parallel following that. In addition, there was the 6.4 % complication rate associated with LV lead placement. At this point in time, decisions regarding *de novo* CRT implants for patients with a reduced LV function and AV block should be individualised.

In terms of upgrading devices to CRT from the conventional pacemaker or the defibrillator, the evidence is encouraging but restricted to small trials^{57–60} and observational data.^{61–67} Reasons for upgrading are likely to be moderate-to-severe LV dysfunction combined with significant HF symptoms. This is reflected in the studies to date that have mainly been in NYHA III–IV patients, and have reported reductions in hospitalisations for HF. The decision to upgrade should not be taken lightly given a recently reported 18.7 % peri-procedural complication rate.⁶⁸

Patients with a Narrow QRS

While up to 50 % of patients with HF and a narrow QRS show evidence of echocardiographic dyssynchrony⁶⁹ the Echocardiography Guided Cardiac Resynchronization Therapy (Echo-CRT) study⁷⁰ showed no benefit to CRT-D over ICD in 809 patients with an EF < 35 %, narrow QRS and evidence of mechanical dyssynchrony, in terms of death or hospitalisation, and may actually increase mortality. This serves as a reminder that CRT is not without its challenges.

Cardiac Resynchronisation Therapy Complications

When considering CRT in a patient, complication rates are significantly higher than with simple pacemaker implants. Complication rates are higher in low volume centres, with a relative risk of complications of 1.6 for operators with fewer than 25 CRT implants. Lead complications are the most common reason for re-operation, with the presence of a CRT device being an important factor (OR 3.3) in re-intervention, with 4.3 % of LV leads needing to be re-operated on.⁷¹ A meta-analysis of 25 CRT trials (9,082 patients) suggested peri-procedural complications of mechanical complications (such as coronary sinus dissection, pneumothorax, haemothorax) in 3.2 %, lead problems in 6.2 % and infections in 1.4 %. The same study reported success in LV lead placement of 94.4 % and peri-implant deaths at 0.3 %.⁷²

Haematomas are common, and are usually managed conservatively. Evacuation is required in 0.3–2.0 % of implants and associated with a 15 times higher infection rate compared with the original implant. Aspirin doubles haematoma risk, and dual antiplatelet therapy quadruples

it.⁷³ Heparin bridging has also been shown to increase bleeding risk, with recent data suggesting that continuing warfarin therapy peri-procedurally is a safer option (OR of clinically significant haematoma 0.19).⁷⁴ No data are currently available with respect to bleeding risk with the novel oral anticoagulants.

Infection remains one of the most worrying post-operative complications. In one study looking at CRT infections, the prevalence was 4.3 % overall, with risk factors for infection being increased procedure time, requirement of re-intervention, haematoma, lead dislodgement, patient on dialysis and type of device (CRT-D devices being more likely to get infected than CRT-P).⁷⁵

Patient Selection Criteria for Cardiac Resynchronisation Therapy

Clearly, selection for CRT and certainly CRT-D therapy, should be made on an individual basis based on a number of clinical, physical and psychological factors. From the evidence presented, electrocardiographic criteria are still the most useful in deciding whether a patient is likely to benefit from CRT. It seems that

the presence of LBBB and QRS duration of ≥ 150 ms remain the strongest predictors of response to CRT. Patients with non-ischaemic cardiomyopathy and females are the next most likely to benefit, with men and those with ischaemic cardiomyopathies slightly less likely to benefit, with narrower QRS durations and non-LBBB pattern patients the least likely to derive benefit. *Figure 1* details a decision aid to decide whether an individual patient may be suitable for CRT, and the likelihood of them benefitting from CRT.

Conclusions

Certain subgroups have been delineated as likely to respond, and other subgroups await more evidence from larger randomised controlled trials. The decision to implant CRT should not be taken lightly given the complication rates, but neither should it be denied patients solely based on these concerns. CRT has been shown to reduce mortality and morbidity in several populations of HF patients. The most favourable outcomes with CRT require astute patient selection, effective LV lead placement, optimisation of device programming and active ongoing medical management of HF with optimal pharmacological therapy. ■

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