Cardiac resynchronization therapy and its role in the management of heart failure

ABSTRACT

The prevalence of heart failure is increasing and it is associated with significant mortality and morbidity. Optimal medical therapy improves outcome, but heart failure continues to have a substantial impact on both the individual patient and wider society. Over the last two decades, cardiac resynchronization therapy has revolutionized the treatment of selected patients who have heart failure. Cardiac resynchronization therapy significantly reduces mortality and hospitalization through reverse cardiac remodelling. This review informs non-specialists about cardiac resynchronization therapy and for which patients it should be considered.

The burden of heart failure on both the individual patient and wider society continues to increase despite optimal medical therapy. Cardiac resynchronization therapy has become established therapy for selected patients with heart failure who are refractory to optimal medical therapy.

Heart failure is defined as an abnormality in cardiac structure and function that leads to the inability of the heart to deliver adequate levels of oxygen to match the metabolic demand of the tissues (McMurray et al, 2012). Patients commonly suffer from a plethora of symptoms including breathlessness, ankle oedema and fatigue (McMurray et al, 2012). Heart failure affects approximately 800 000 people in the UK (McMurray et al, 2012), about half of whom have heart failure with reduced ejection fraction. The mortality from heart failure is estimated at 30–40% within a year of diagnosis (Cowie et al, 2000), a rate that surpasses that of many malignancies. Several pharmacological agents, specifically angiotensin-receptor blockers (Swedberg and Kjekshus, 1988), beta-blockers (Packer et al, 1996), mineralocorticoid receptor antagonists (Pitt et al, 1999) and angiotensin receptor neprilysin inhibitors (Packer et al, 2015), significantly improve morbidity and mortality. Despite advances in medications the incidence and prevalence of heart failure continues to rise and confers a poor prognosis (McMurray et al, 2012). Cardiac resynchronization therapy has revolutionized management of patients with heart failure and improved outcomes.

Dr Christopher J McAloon, Cardiology Research Fellow, Department of Cardiology, University Hospitals Coventry and Warwickshire NHS Trust, Coventry CV2 2DX and Translational & Experimental Medicine, University of Warwick Medical School, Coventry

Dr Mark D Theodoreson, Core Medical Trainee Year One, Department of Cardiology, University Hospitals Bristol NHS Trust, Bristol Heart Institute, Bristol

Dr Sajad Hayat, Consultant Cardiologist and Electrophysiologist, Department of Cardiology, University Hospitals Coventry and Warwickshire NHS Trust, Coventry

Dr Faizel Osman, Consultant Cardiologist and Electrophysiologist, Department of Cardiology, University Hospitals Coventry and Warwickshire NHS Trust, Coventry and Translational & Experimental Medicine, University of Warwick Medical School, Coventry

Correspondence to: Dr CJ McAloon (christopher.mcaloon@doctors.org.uk)

Heart failure with reduced ejection fraction and cardiac dyssynchrony

Many patients with heart failure with reduced ejection fraction develop dyssynchronous contractions of the heart as a result of damage to the underlying conduction tissue causing inefficient cardiac contraction that leads to symptoms. Cardiac dyssynchrony is a complex and multifactorial process that impacts function (Brignole et al, 2013). Prolongation of atrioventricular conduction encroaches on the starting of systole and filling of early diastole. With delayed ventricular contraction, the left ventricular diastolic pressure exceeds left atrial pressure during passive filling, leading to development of functional mitral regurgitation (Brignole et al, 2013). The impact of reducing ventricular pre-load leads to reduced left ventricular contractility, by the Starling mechanism. Moreover, the occurrence of intra- and inter-ventricular conduction delay causes asynchronous left ventricular contraction (so-called mechanical dyssynchrony) leading to reduced stroke volume, left ventricular ejection fraction and systolic blood pressure (Brignole et al, 2013). Ventricular dyssynchrony leads to dis-coordinated papillary muscle contraction and further contributes to development and progression of functional mitral regurgitation, with the whole process contributing to left ventricular adverse remodelling (Brignole et al, 2013).

Cardiac resynchronization therapy

Cardiac resynchronization therapy or 'biventricular pacing' involves implanting pacing leads into the heart via the transvenous route to the right and left ventricles (the latter through the coronary sinus) to resynchronize ventricular contraction. A lead is implanted to the right atrium to achieve atrioventricular synchrony (*Figure 1*) unless the patient has permanent atrial fibrillation. Cardiac resynchronization therapy can 'resynchronize' cardiac contraction through restoration of inter-/intra-

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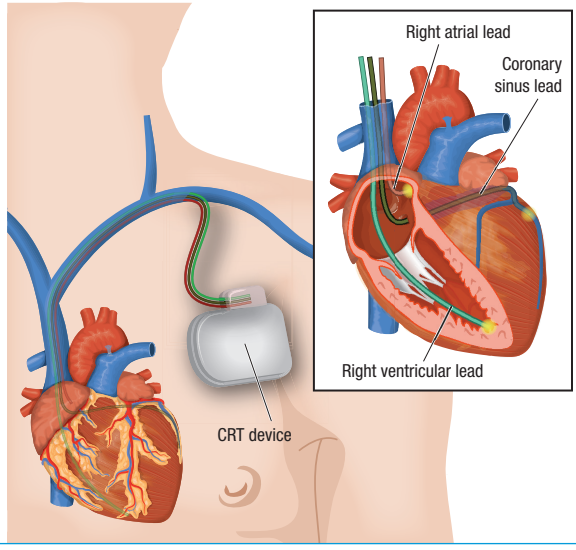
ventricular and atrioventricular dyssynchrony (Brignole et al, 2013). Cardiac resynchronization therapy improves left ventricular ejection fraction, left ventricular contractility, left ventricular filling time and reduces functional mitral regurgitation, which in turn can induce reverse left ventricular remodelling (Brignole et al, 2013). Cardiac resynchronization therapy can also be combined with a defibrillator function in selected patients. Implantable cardioverter defibrillators are designed to reduce the risk of sudden cardiac death caused by ventricular arrhythmias, by delivering anti-tachycardia pacing or shock therapy. This can be performed for those identified at high risk (primary prevention) or those who have had a malignant ventricular arrhythmia and survived (secondary prevention) (Goldenberg et al, 2011). Cardiac resynchronization therapy devices that have defibrillator functionality are referred to as cardiac resynchronization therapy-defibrillators and those without as cardiac resynchronization therapy-pacemakers.

Figure 1. Cardiac resynchronization therapy (CRT) device.



Who benefits from cardiac resynchronization therapy?

Over the last 20 years cardiac resynchronization therapy has become one of the most effective treatments for heart failure and is appropriate for ~25–30% of heart failure patients (Daubert et al, 2012). Cazeau et al (1994) showed that a cardiac resynchronization therapy-pacemaker in a 54-year-old patient with advancing heart failure improved New York Heart Association (NYHA) symptoms. Since then multiple randomized controlled trials have demonstrated the resounding benefit of cardiac resynchronization therapy for patients with heart failure with reduced ejection fraction who have mechanical dyssynchrony, with reduced mortality and hospitalization (Bristow et al, 2004; Cleland et al, 2005) alongside improved quality of life (Cleland et al, 2005; Moss et al, 2009; Tang et al, 2010), symptoms (Abraham et al, 2002), functional performance (Abraham et al, 2002) and left ventricular volumes (Linde et al, 2008). *Table 1* summarizes the largest randomized controlled trials examining cardiac

Table 1. Randomized control trials evaluating cardiac resynchronization therapy in sinus rhythm

Trial (reference)	No	Study design	Inclusion	Outcome	Main findings
COMPANION (Bristow et al, 2004)	1520	Double-blinded, randomized – optimal medical therapy *vs* CRT-d or CRT-p, 15 months	NYHA III–IV, left ventricular ejection fraction <35%, QRS >120 msec	Primary – all-cause mortality or hospitalizations, secondary – all-cause mortality, cardiac mortality	CRT-d and CRT-p reduced all-cause mortality and hospitalization
CARE-HF (Cleland et al, 2005)	813	Double-blinded randomized – optimal medical therapy *vs* CRT-p, 29.4 months	NYHA III–IV, left ventricular ejection fraction <35%, QRS >120 msec	Primary – all-cause mortality or hospitalizations, secondary – all-cause mortality, NYHA, quality of life	CRT-p reduced all-cause mortality, hospitalizations and improved NYHA, quality of life
REVERSE (Linde et al, 2008)	610	Double-blinded, randomized – CRT-ON *vs* CRT-OFF, 12 months	NYHA I–II, left ventricular ejection fraction <40%, QRS >120 msec	Primary – % worsened heart failure clinical composite, secondary – left ventricular end systolic volume index, heart failure hospitalizations, all-cause mortality	CRT-p/CRT-d did not change the primary endpoint, reduced left ventricular end systolic volume index, heart failure hospitalizations
MADIT-CRT (Moss et al, 2009)	1820	Single-blinded, randomized – CRT-d *vs* internal cardiac defibrillator, 12 months	NYHA I–II, left ventricular ejection fraction <30%, QRS >130 msec	Primary – all-cause mortality or heart failure hospitalizations, secondary – all-cause mortality, left ventricular end systolic volume	CRT-d reduced the primary endpoint and left ventricular end systolic volume, CRT-d did not reduce all-cause mortality
RAFT (Tang et al, 2010)	1798	Double-blinded, randomized – CRT-d *vs* internal cardiac defibrillator, 40 months	NYHA II–III, left ventricular ejection fraction <30%, QRS >120 msec	Primary – all-cause mortality or heart failure hospitalizations, secondary – all-cause mortality and cardiovascular death	CRT-d reduced primary endpoint CRT-d (NYHA III) reduced all-cause mortality

CRT-d = cardiac resynchronization therapy-defibrillator; CRT-OFF = cardiac resynchronization therapy – turned OFF; CRT-ON = cardiac resynchronization therapy – turned ON; CRT-p = cardiac resynchronization therapy-pacemaker; NYHA = New York Heart Association. Adapted from Brignole et al (2013).

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> QRS duration is one of the most powerful predictors of benefit from cardiac resynchronization therapy.

resynchronization therapy in specific patients with heart failure with reduced ejection fraction and sinus rhythm.

Unfortunately, not all patients who have heart failure benefit from cardiac resynchronization therapy. Multiple randomized controlled trials have informed and refined implantation criteria of national and international guidelines. Benefit has consistently been demonstrated in patients with severe left ventricular systolic dysfunction (left ventricular ejection fraction ≤35%). Those with moderate impairment (left ventricular ejection fraction 35–45%) can be offered cardiac resynchronization therapy if they have a bradycardia pacing indication and are likely to require >40% pacing (Curtis et al, 2013).

New York Heart Association classification

NYHA symptom classification as a criterion initially favoured more symptomatic patients in class III or IV (*Table 1*). Interestingly, these trials consistently recruited a substantially lower proportion of patients with NYHA IV symptoms (representing 7–15%) (Brignole et al, 2013). More recent randomized controlled trials have included patients with milder heart failure symptoms (NYHA I–II) and demonstrated improvement in cardiovascular outcomes and reverse left ventricular remodelling. However, NYHA class I patients represented a small proportion of the participants in all trials and no benefit was specifically seen for these in sub-group analyses (Linde et al, 2008; Moss et al, 2009).

QRS duration

QRS duration is one of the most powerful predictors of benefit from cardiac resynchronization therapy. Sub-group analyses of MADIT-CRT (Moss et al, 2009; Hsu et al, 2012), REVERSE (Linde et al, 2008) and RAFT (Tang et al, 2010) consistently demonstrated that patients with QRS durations ≥150 msec on resting 12-lead electrocardiogram have the greatest reduction in cardiovascular outcomes.

Cleland et al (2013) performed a large meta-analysis (n=3782) from five Medtronic Ltd (Minneapolis, USA) sponsored randomized controlled trials comparing cardiac resynchronization therapy with no active treatment or cardiac resynchronization therapy-defibrillator with implantable cardiac defibrillators. Several pre-defined variables were evaluated to identify if they predicted a composite outcome of all-cause mortality and/or first heart failure hospitalization (Cleland et al, 2013). Patients with atrial fibrillation and NYHA I symptoms were excluded from analysis as they only comprised a small proportion of patients. Cleland et al (2013) accounted for the influence of having cardiac resynchronization therapy and treated it as a fixed effect variable in the prediction models. Incremental increase in QRS duration on pre-implant electrocardiogram showed a magnitude of benefit for improving cardiovascular outcomes after cardiac resynchronization therapy implant for every additional millisecond. Definitive benefit was observed from 140 msec onwards and plateaued beyond 180 msec for composite outcome alone (Cleland et al, 2013). This meta-analysis has been an important milestone in reviewing the evidence behind the recommendations on QRS durations.

Patients with narrower QRS duration (120–130 msec) do not benefit from cardiac resynchronization therapy implantation (Cleland et al, 2013). The Cardiac Resynchronization Therapy in Heart Failure with a Narrow QRS Complex (EchoCRT) trial (Ruschitzka et al, 2013) enrolled patients (n=855) across 115 centres. These patients met standard implantation criteria having a QRS complex ≤130 msec with evidence of cardiac dyssynchrony on echo to CRT-ON (cardiac resynchronization therapy capability turned on) or CRT-OFF (cardiac resynchronization therapy capability turned off) following implantation. The primary outcome was a clinical composite of all-cause mortality and heart failure hospitalization. The EchoCRT trial demonstrated CRT-ON had a higher rate of composite primary end-point occurrence compared with CRT-OFF (28.7% *vs* 25.2%, P=0.15). However, all-cause mortality was significantly higher in the CRT-ON group compared with CRT-OFF (11.1% *vs* 6.4%, P=0.02) (Ruschitzka et al, 2013). The greatest benefit of cardiac resynchronization therapy was seen in those with the widest QRS duration.

QRS morphology: bundle–branch block

QRS morphology is important in determining response to cardiac resynchronization therapy. Sub-group analyses of MADIT-CRT (Moss et al, 2009), RAFT (Tang et al, 2010) and REVERSE (Linde et al, 2008) trials all identified complete left bundle–branch block as having better outcome on all-cause mortality and hospitalization compared with right bundle–branch block and non-specific intraventricular conduction delay. A meta-analysis by Cunnington et al (2015), including 6914 patients, analysed those with and without left bundle–branch block. Participants across all included trials had NYHA I–IV symptoms, left ventricular ejection fraction ≤30–40% and QRS duration ≥120–130 msec. The study demonstrated no benefit from cardiac resynchronization therapy for patients with non-left bundle–branch block QRS morphology for pooled outcome of all-cause mortality and heart failure hospitalization (hazard ratio 1.09, 95% confidence interval 0.85–1.39). It should be noted that Cunnington et al (2015) only studied cardiovascular end-points and did not examine symptom, functional or echocardiographic outcomes. It was also acknowledged that NYHA classes I and IV were under represented and observations were driven by those with NYHA class II–III symptoms.

The MADIT-CRT trial (Moss et al, 2009) of NYHA I–II patients (n=536), followed over 7 years, demonstrated increased risk of mortality for non-left bundle–branch block patients (hazard ratio 1.57, 95% confidence interval 1.03–2.39).

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Separating QRS duration from bundle–branch block morphology remains a challenge for cardiac resynchronization therapy. Both variables are important for selecting suitable candidates. Different bundle–branch block patterns have been demonstrated on activation mapping studies to have heterogeneous patterns and should be considered as different entities (Varma, 2009). In the meta-analysis by Cleland et al (2013) left bundle–branch block was associated with broader QRS durations, suggesting the power of increasing QRS duration to infer better cardiovascular outcomes was confounded by bundle–branch block morphology; it also observed that non-left bundle–branch block had an increased trend towards higher mortality. However, when QRS duration was removed from the multivariable prediction model, little difference was noted between left bundle–branch block and non-left bundle–branch block in terms of impact on mortality (Cleland et al, 2013). Together these observations suggest that bundle–branch block and QRS duration are intertwined variables, which may need to be considered together when reviewing a patient for cardiac resynchronization therapy.

Atrial fibrillation

Atrial fibrillation commonly co-exists in patients with heart failure and its presence can reduce the success of cardiac resynchronization therapy (Wilton et al, 2011). Understanding the true influence of atrial fibrillation on the success of cardiac resynchronization therapy is difficult as patients with atrial fibrillation tend to be older, have more comorbidities and be more unwell. Comparison between sinus rhythm and atrial fibrillation is influenced by these confounding factors, which often infer worse prognosis (Brignole et al, 2013). Atrial fibrillation is underrepresented in randomized controlled trials of cardiac resynchronization therapy and so meta-analysis is needed. Patients with atrial fibrillation receiving cardiac resynchronization therapy have a similar improvement in left ventricular ejection fraction to those in sinus rhythm, but have worse symptom and functional response (Wilton et al, 2011). In a large (n=7495) meta-analysis of 33 observational studies, Wilton et al (2011) compared those with atrial fibrillation (22.5%) to those with sinus rhythm receiving cardiac resynchronization therapy and observed a significantly higher all-cause mortality and non-responder rate in the atrial fibrillation group. Evidence on the precise recommendations for cardiac resynchronization therapy in patients with atrial fibrillation remains weak and is based on limited evidence and expert opinion. However, implantation is favoured if >99% biventricular pacing percentage can be achieved (Brignole et al, 2013).

Cardiac resynchronization therapy implantation criteria

The current implantation criteria have been significantly modified over the last 15 years as more evidence has been produced and collated. The previous sections have discussed the evolution and refinement of the current evidence, which reflects the current international guidelines (Daubert et al, 2012). These have changed to incorporate the most recent evidence, including patients with atrial fibrillation and bradycardia pacemaker indications (Brignole et al, 2013). In June 2014 in the UK, the National Institute for Health and Clinical Excellence revised guidance on cardiac resynchronization therapy implantation that reflected updated international guidelines (National Institute for Health and Clinical Excellence, 2014) (*Table 2*). Current indications are heart failure with reduced ejection fraction (left ventricular ejection fraction ≤35%) with NYHA II–IV symptoms on optimal medical therapy and with QRS duration on resting electrocardiogram of either: 120–149 msec with left bundle–branch block morphology or ≥150 msec duration (this includes NYHA class I patients). Patients in atrial fibrillation who can be rate controlled (by medication or atrioventricular node ablation) and fulfil cardiac resynchronization therapy implant criteria can be considered too. Patients with impaired left ventricular

Table 2. National Institute for Health and Clinical Excellence indications for implantable cardiac defibrillator and cardiac resynchronization therapy in patients with left ventricular ejection fraction ≤35%

	NYHA class			
QRS interval	**I**	**II**	**III**	**IV**
<120 msec	Internal cardiac defibrillator if there is a high risk of sudden cardiac death		Internal cardiac defibrillator and cardiac resynchronization therapy not clinically indicated	
120–149 msec without left bundle–branch block	Internal cardiac defibrillator	Internal cardiac defibrillator	Internal cardiac defibrillator	CRT-p
120–149 msec with left bundle–branch block	Internal cardiac defibrillator	CRT-d	CRT-p or CRT-d	CRT-p
>150 msec	CRT-d	CRT-d	CRT-p or CRT-d	CRT-p

Adapted from National Institute for Health and Clinical Excellence (2014). CRT-d = cardiac resynchronization therapy-defibrillator; CRT-p = cardiac resynchronization therapy-pacemaker; New York Heart Association.

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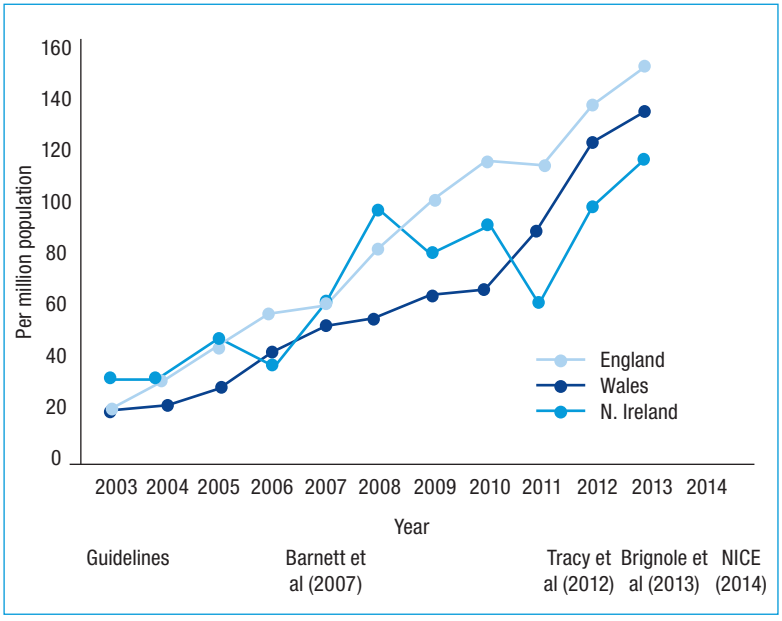
Figure 2. Total cardiac resynchronization therapy implant rates 2003–13 and release of national and international implantation criteria. Adapted from Cunningham et al (2014). NICE = National Institute for Health and Clinical Excellence.



function who are anticipated to require ventricular pacing >40% of the time should also be considered for cardiac resynchronization therapy (Brignole et al, 2013).

The European Society of Cardiology introduced new recommendations for cardiac resynchronization therapy implantation in August 2016 (Ponikowski et al, 2016). Referring to the issues raised by the strength of evidence about implanting cardiac resynchronization therapy into patients with a low QRS 120–130 msec raised by Cleland et al (2013) and the ECHO CRT study (Ruschitzka et al, 2013), these guidelines recommended that cardiac resynchronization therapy should now be implanted in patients with a QRS ≥130 msec. The National Institute for Health and Clinical Excellence (2014) guidance still remains as in *Table 2*, but will possibly change when guidelines are updated in August 2018.

Cardiac resynchronization therapy implantation in the UK

Over the last decade several hundred thousand cardiac resynchronization devices have been implanted worldwide (Daubert et al, 2012). In 2013 the UK was the fourth highest total cardiac resynchronization therapy implanter within western Europe (Cunningham et al, 2014). *Figure 2* demonstrates the increasing year-on-year implantation rate within the home nations of the UK, over the last decade. Figures for Scotland are not presented because the data are incomplete (Cunningham et al, 2014). These figures demonstrate the establishment of cardiac resynchronization therapy as a cornerstone of heart failure management. Implantation rates continue to increase with broadening of implantation guidelines and more centres starting to implant.

Health economics of cardiac resynchronization therapy

Despite recent revision of international guidelines and more focused studies on cardiac resynchronization therapy response, evidence suggests a non-response rate of 20–30% (Bristow et al, 2004; Cleland et al, 2005; Moss et al, 2009). There is a strong focus on trying to predict and minimize this non-response rate. Cardiac resynchronization therapy implantation is a costly intervention with a large up-front cost of an estimated £3411 for a cardiac resynchronization therapy-pacemaker and £12 293 for a cardiac resynchronization therapy-defibrillator (National Institute for Health and Clinical Excellence, 2014). The up-front cost is larger than for many other medical devices, and there are also ongoing costs of monitoring and replacing these devices (Boriani et al, 2009).

Randomized controlled trials have been used to model the quality-adjusted life year costs of a cardiac resynchronization therapy device. It is widely accepted that this falls below $50 000 per quality-adjusted life year, which is the accepted cost of an intervention in the USA (Boriani et al, 2009). Efforts have focused on minimizing this cost by better defining the heart failure population who will benefit, streamlining implantation and using remote monitoring to reduce patient visits to hospital (Boriani et al, 2009). However, the burden of cost to health-care systems will continue to rise with the growing population of patients with heart failure who might benefit from cardiac resynchronization therapy. More accurately defining the non-response rate will minimize this burden of cost.

The challenge of non-response

Despite two decades of large randomized controlled trials, detailed meta-analyses and observational studies, there remains an unchanging minority (20–30%) of heart failure patients meeting cardiac resynchronization therapy implant criteria who fail to respond (Bristow et al, 2004; Cleland et al, 2005; Moss et al, 2009). QRS duration and morphology have consistently been shown to be the strongest predictors of cardiovascular outcomes. Cleland et al (2013) clearly demonstrated the pooled magnitude of strength of ever-increasing QRS duration beyond >140 msec to predict benefit. QRS morphology does not demonstrate such clear strength to predict response (Cleland et al, 2013), although it is clear that non-left bundle–branch block morphology favours poorer response (Cunnington et al, 2015).

Questions still remain around the benefit of cardiac resynchronization therapy in patients with QRS durations 120–140 msec and the additional benefit that left bundle–branch block morphology offers (Cunnington et al, 2015). Calls have been made for randomized control trials of patients with cardiac resynchronization therapy already in-situ, who have narrow native QRS with non-left bundle–branch block morphology on electrocardiogram, to have their devices deactivated for a period of observation, given the question over benefit

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(Cleland and Freemantle, 2015). Moreover the apparent influence of bundle–branch block morphology on QRS duration >150 msec remains unclear.

Beyond current indications for cardiac resynchronization therapy and QRS durations and morphology many other predictors have been identified. Sub-studies of the large cardiac resynchronization therapy randomized controlled trials have identified multiple variables that improve morbidity and mortality. In a sub-study of the MADIT-CRT trial, Hsu et al (2012) performed a best-subset regression on patients who had paired echocardiograms at 12 months and had been assigned to have cardiac resynchronization therapy-defibrillator (n=752) to examine for predictors of echo super-responders (top quartile of left ventricular ejection fraction change). Six predictors were identified as being associated with left ventricular ejection fraction super-response: female gender (odds ratio 1.96, P=0.001), no prior myocardial infarction (odds ratio 1.80; P<0.01), QRS duration ≥150 msec (odds ratio 1.79, P<0.01), left bundle–branch block (odds ratio 2.05, P<0.01), body mass index <30 kg/m^2 (odds ratio 1.51, P=0.035), and smaller baseline left atrial volume index (odds ratio 1.47, P=0.001). The impact of cardiac resynchronization therapy was not accounted for in this analysis (Hsu et al, 2012); furthermore this sub-study required paired echocardiograms, thereby favouring patients who had survived 12 months, creating a selection bias.

Cleland et al (2013) examined multiple predefined potential predictor variables (age, gender, NYHA class, heart failure aetiology, QRS morphology, QRS duration, left ventricular ejection fraction and systolic blood pressure) and only QRS duration could predict cardiac resynchronization therapy outcomes. Cleland and Freemantle (2015) consistently argued that much of the evidence for predictors is based upon sub-group analyses. Moreover, in these subset studies and meta-analyses based upon the cardiac resynchronization therapy randomized controlled trials the impact of the device was not accounted for and confounded the results observed.

Many observational studies have been performed to examine the potential of different variables to predict cardiac resynchronization therapy response and outcome. These observational studies tend to be of limited value, often being under-powered, having flawed methodology, not accounting for cardiac resynchronization therapy implantation and using a variety of different response and outcome definitions. Their value shadows that of the often quoted cardiac resynchronization therapy randomized controlled trial sub-studies and more importantly meta-analyses. However, observational studies tend to emphasize the value of response in terms of patient-centred criteria (symptoms, function and quality of life) compared with the composite cardiovascular outcomes of most cardiac resynchronization therapy trials (*Table 1*). Well-conducted observational studies often generate new lines of hypothesis and investigation, so they still have value in the investigation of non-response. *Table 3*

Table 3. Observational studies assessing predictors of non-response

Study	Patients	Study design	Inclusion	Response criteria	Main findings
Shanks et al (2011)	581	Observational study, single centre (Holland), 6 months	Not clear which NYHA, left ventricular ejection fraction ≤35%, QRS ≥120 msec	Clinical and echocardiographic: ↓NYHA ≥1 and survival and no heart transplantation ↑>15% left ventricular end systolic volume	Predict non-response: ischaemic aetiology, shorter 6-minute walk distance at baseline, less baseline cardiac dyssynchrony and left ventricle lead position
Lin et al (2014)	193	Retrospective observational study (China), single centre, all consecutive cardiac resynchronization devices, 12 months	NYHA II–IV, left ventricular ejection fraction ≤35%, QRS ≥120 msec	Echocardiographic: ↑≥5% left ventricular ejection fraction and survived and being free from heart failure hospitalization	Predicts non-response: non-left bundle–branch block and non-optimal left ventricle lead position
Rinkuniene et al (2014)	82	Retrospective observational study, single centre (Lithuania), 12 months	NYHA III–IV, left ventricular ejection fraction ≤35%, QRS ≥120 msec, left bundle–branch block	Clinical: ↓≥1 NYHA and ↑>15% 6-minute walk distance echocardiographic: ↑≥15% left ventricular end systolic volume	Predicts response: non-ischaemic aetiology (clinical) and left ventricular end diastolic diameter (≤75 mm) (echo)
Sassone et al (2015)	243	Retrospective observational study, all consecutive cardiac resynchronization devices, majority cardiac resynchronization therapy-defibrillator, single centre (Italy), 6 months, left bundle–branch block in predictor analysis	NYHA II–IV, left ventricular ejection fraction <35%, QRS >120 msec	Echocardiographic: ↑>15% left ventricular end systolic volume. Clinical composite: heart failure hospitalization, mortality and first sustained ventricular tachycardia	Predict non-response: ischaemic aetiology and QRS duration (≥178 msec). Clinical composite: non-left bundle–branch block ↑ rate events

NYHA = New York Heart Association

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KEY POINTS

- Cardiac resynchronization therapy should be considered in all patients with severe left ventricular systolic dysfunction with evidence of electrical dyssynchrony on resting 12-lead electrocardiogram refractory to optimal medical therapy.
- Cardiac resynchronization therapy significantly reduces mortality and hospitalizations in heart failure patients with broad QRS.
- Cardiac resynchronization therapy resynchronizes both atrioventricular and inter-/intra-ventricular dyssynchrony thereby promoting reverse cardiac remodelling. This improves left ventricular ejection fraction and reduces left ventricular end systolic volume and functional mitral regurgitation.
- The benefit of cardiac resynchronization therapy increases incrementally with increasing QRS duration (with benefit beginning at QRS duration >130 msec).
- Patients with at least moderate left ventricular impairment and bradycardia pacing indication and likely to require >40% ventricular pacing should be offered cardiac resynchronization therapy.
- A significant challenge of cardiac resynchronization therapy remains the 20–30% non-response rate.

summarizes important observational studies evaluating clinical predictors.

Responder definition

The consistent issue when examining the response to cardiac resynchronization therapy is the variety of different definitions used in the literature. This makes comparing and pooling data for comparison difficult because of the heterogeneity of criteria used for response. Fonwalt et al (2010) performed a seminal systematic review of the 26 most cited papers on predicting cardiac resynchronization therapy response and extrapolated 17 different criteria. Fifteen criteria (clinical and echocardiographic) were all applied to the PROSPECT trial cohort (two criteria could not be calculated). The application of these different definitions to the same cohort demonstrated a response rate variation between 32% and 91% (Chung et al, 2008; Fornwalt et al, 2010). Agreement was poor (105 combinations) between 79 (75.2%) pairs of definitions (Fornwalt et al, 2010). Moreover, a strong association of agreement was only observed in four (3.8%) pairs of definitions. All echocardiographic and clinical definition combinations had a poor association. Removal of definitions applied in short-term follow up (<3 months) made no significant change to the analysis. Agreement between definitions is poor, even between similar categories of criteria (Fornwalt et al, 2010).

In a paper on heart failure composite scores, Packer (2001) identified the pitfalls of using one individual metric to measure response; composite scores can minimize this problem. No universal response definition has yet been agreed upon, but the consensus is that a combination of composite criteria is required. Criteria should not combine clinical or echocardiographic variables (Fornwalt et al, 2010).

Conclusions

Cardiac resynchronization therapy has revolutionized the treatment and outcomes for selected heart failure patients who are refractory to optimal medical therapy and exhibit evidence of dyssynchrony on resting 12-lead electrocardiogram. In the correct patient, cardiac resynchronization therapy reverses adverse cardiac remodelling; the process that underpins the development and progression of heart failure with reduced ejection fraction. Refinement of evidence over the last 15 years has led to changes in national and international guidelines for cardiac resynchronization therapy. QRS duration on electrocardiogram remains the most important factor determining response to cardiac resynchronization therapy. Emerging evidence suggests that QRS durations 120–130 msec do not confer any benefit. Unfortunately, despite refinements in implant criteria, a significant cardiac resynchronization therapy non-response remains (20–30%). Research continues on being able to better identify and stratify patients before cardiac resynchronization device implantation. Cardiac resynchronization therapy remains one of the greatest advances in the last 20 years for the management of heart failure with reduced ejection fraction. All patients who have a significant reduction in left ventricular ejection fraction and have broad QRS duration on resting electrocardiogram should be considered for implantation of cardiac resynchronization therapy. **BJHM**

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