# What is treatment success in cardiac resynchronization therapy?

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Cardiac resynchronization therapy (CRT) is an established treatment for symptomatic patients with heart failure, a prolonged QRS duration, and impaired left ventricular (LV) function. Identification of 'responders' and 'non-responders' to CRT has attracted considerable attention. The response to CRT can be measured in terms of symptomatic response or clinical outcome, or both. Alternatively, the response to CRT can be measured in terms of changes in surrogate measures of outcome, such as LV volumes, LV ejection fraction, invasive measures of cardiac performance, peak oxygen uptake, and neurohormones. This review explores whether these measures can be used in assessing the symptomatic and prognostic response to CRT. The role of these parameters to the management of individual patients is also discussed.

**Keywords**     Cardiac resynchronization therapy • Mortality • Responders

## Introduction

Cardiac resynchronization therapy (CRT) was unveiled as a new therapy by the pioneering work of Cazeau et al.[1] who, in 1994, reported the dramatic clinical improvement of a 54-year-old man in severe heart failure treated by four-chamber pacing. Later in an acute study, Leclercq et al.[2] showed that temporary CRT increases left ventricular (LV) stroke volume and reduces pulmonary capillary wedge pressure. Auricchio's group, further, showed that CRT increases LV dP/dt.[3] In 2001, the Multisite Stimulation in Cardiomyopathies (MUSTIC) study, in the first randomized controlled cross-over trial design in the field of resynchronization therapy, found that CRT dramatically reduced heart failure hospitalizations and improved NYHA class, as well as quality of life, exercise distance, and peak oxygen uptake (peak $VO_2$).[4] More recently, the Cardiac Resynchronization in Heart Failure (CARE-HF) trial indicated that CRT-pacing (CRT-P) led to a 36% relative reduction in total mortality compared with medical therapy.[5] The comparison of medical therapy, pacing, and defibrillation in heart failure (COMPANION) study showed that addition of a cardioverter defibrillator (CRT-D) to CRT also led to additional survival benefits compared with CRT-P.[6]

Response to CRT has become critically important as it is considered in a different way from that with drug therapy of heart failure. With drugs, patients are up-titrated to the doses used in major outcome trials without the need for measuring symptomatic response or predictors of outcome in routine clinical settings.

Possibly, the insistence on defining CRT response in the same settings reflects both the high initial cost of the pacing system and the need for a surgical procedure to implant it. If measurement of response and outcome in CRT is necessary, outcome variables must surely provide 'a valid and reliable measure of some clinically relevant and important treatment benefit in the patient population'.[7] Ultimately, the final objective must be to prolong survival and/or to alleviate symptoms as well as to improve quality of life. This review focuses on parameters that have so far been used to define a response to CRT. The relevance of these parameters to the management of individual patients is also discussed.

## Outcome and response

### Outcome

In order to estimate the effects of CRT on survival, patients' lifetimes must be considered rather than the follow-up period of a study. The 2007 United Kingdom National Institute of Clinical Excellence (NICE) Health Technology Appraisal (HTA) on CRT provided an extensive analysis of CRT-P, CRT-D, and optimum pharmacological therapy (OPT) alone over patients' lifetimes (Table 1).[8] According to these analyses, the median survival after device implantation is 4.62 years for CRT-P and 5.15 years for CRT-D. However, the additional life gained must be compared with OPT and amounts to a median of 0.85 years for CRT-P and 1.39 years for CRT-D.

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**Table I** Survival from CRT-P and CRT-D over a patients' lifetime

| Age[b] | Survival | | | Additional life[a] | |
|---|---|---|---|---|---|
| | OPT | CRT-P | CRT-D | CTR-P | CRT-D |
| 30 | 7.31 | 9.00 | 10.39 | 1.69 | 3.08 |
| 40 | 7.23 | 8.92 | 10.31 | 1.69 | 3.08 |
| 50 | 7.15 | 8.76 | 10.08 | 1.62 | 2.92 |
| 60 | 6.15 | 7.15 | 8.00 | 1.00 | 1.85 |
| 70 | 4.46 | 5.39 | 5.85 | 0.92 | 1.39 |
| 80 | 3.08 | 3.77 | 4.31 | 0.54 | 1.23 |
| 90 | 2.31 | 2.69 | 2.92 | 0.39 | 0.62 |
| Overall | 3.77 | 4.62 | 5.15 | 0.85 | 1.39 |

All values are expressed as medians (years).
Reproduced with permission from the Peninsula Technology Assessment Group.[8]
[a]Refers to survival advantage over optimum medical therapy alone (OPT).
[b]Age at the time of implantation.

The 2007 NICE HTA on CRT also showed that certain patient characteristics influence the outcome of CRT.[8] Age at the time of implantation, for example, has a significant impact: the additional life gained from CRT-P, compared with OPT alone, was a median of 1.69 years for 40 year olds and only 0.54 years for 80 year olds. The additional life gained from CRT-D was 3.08 and 1.23 years, respectively. The addition of a defibrillation capacity to the device makes an important difference at all ages.[8] For 50 year olds, the proportional increase in overall median survival was 23% for CRT-P and 41% for CRT-D, compared with OPT. Other studies have shown that outcome of CRT also depends upon the NYHA class prior to implantation,[9−11] the aetiology of the heart failure,[12] and the atrial rhythm.[13]

In observational studies, the criterion for survival with CRT has arbitrarily been set at 1 year of life following implantation.[14−16] Rather than adopting such arbitrary cut-offs, patients could be considered 'prognostic responders' to CRT if their actual survival matches that expected from modelling analyses, taking into account patient- and device-related variables. This methodology, which is yet to be applied, is anticipated to be more precise than using the same arbitrary cut-offs for all patients.

## Response

It is often quoted that CRT has a 'non-responder' rate of up to 30%, implying that a responder rate of anything lower than 100% is unsatisfactory. Similar figures, however, emerge for drug therapy if the same approach is adopted. In the results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), 46.7% of patients treated with enalapril improved by ≥1 NYHA class.[17] In the Cardiac Insufficiency Bisoprolol Study (CIBIS), 21% of patients treated with bisoprolol improved by ≥1 NYHA class.[18] In the Randomized Aldactone Evaluation Study (RALES), 41% of patients treated with spirinolactone improved by ≥1 NYHA class.[19] Accordingly, the 'non- responder' rates in these studies were 53.3% for enalapril, 79% for bisoprolol, and 59% for spironolactone. To quantify the true additional effect of

a treatment, it is necessary to compare the new therapy with controls. Adopting an improvement by ≥1 NYHA class as the definition of response, the 'responder' rate for placebo was 21.8% in the CONSENSUS study, 15% in the CIBIS study, and 33% in the RALES study. Accordingly, the response to treatment, compared with placebo, was 24.9% for enalapril, 6% for bisoprolol, and 8% for spironolactone.

The symptomatic response to CRT can be quantified in randomized, controlled trials, but what should be considered to be an adequate response to CRT in individual patients? With reference to the CARE-HF study, CRT was associated with a reduction in NYHA class from 3.06 at baseline to 2.1 at 90 days post-implantation.[5] With respect to quality of life, the COMPANION study showed an improvement by 8.8% with CRT-P, 9.3% with CRT-D, and 3.7% with medical therapy alone.[6] Therefore, a reduction by approximately one NYHA class and an improvement in quality of life by ∼5 to 6% is what should CRT-P or CRT-D be expected to achieve in the 'average' patient.

## Discordance between outcome and response

A favourable symptomatic response to a treatment does not necessarily parallel a favourable outcome. At one extreme, palliative treatments improve symptoms but do not prolong survival. At the other, chemotherapy for cancer prolongs survival, but causes symptoms and worsens quality of life. It should also be considered that, if given the choice, some patients prefer symptomatic benefit to prognostic benefit, particular if they are severely limited by symptoms.

As for most treatments for heart failure, symptomatic and prognostic benefits from CRT are not necessarily concordant. This was suggested by Yu et al.,[20] who found similar improvements in NYHA class, 6 min walk distance and quality of life at 3−6 months in survivors and non-survivors treated by CRT. These findings raise problems in clinical practice. For example, should CRT be modified or withdrawn in a patient who has improved symptomatically but in whom a surrogate measure of outcome predicts a shortened survival? So far, this question is unanswered.

## Surrogate markers of outcome

A surrogate endpoint should be a true predictor of disease, not reflection of a co-variable.[21] To be clinically useful, a surrogate measure of outcome must be measurable and reproducible by different observers and by different centres. It should be reliable, available, and easily quantifiable. The relationship between a surrogate and the true endpoint should be also validated internally,[22] within the population from which it is derived, and externally by other centres. In addition, P-values should not be considered to be the sole arbiter in a study. A $P < 0.05$ does not mean that the sample size is adequate, that the effect size is clinically meaningful, or that the parameter in question has discriminatory ability.[23] Diagnostic utility should be tested using Bayesian analyses. Cut-offs should be sensitive and specific (>90% for both), with a clear distinction between what is normal or abnormal.

In an ideal world, the surrogate endpoint is mechanistically linked to the true endpoint via a single pathway and the surrogate
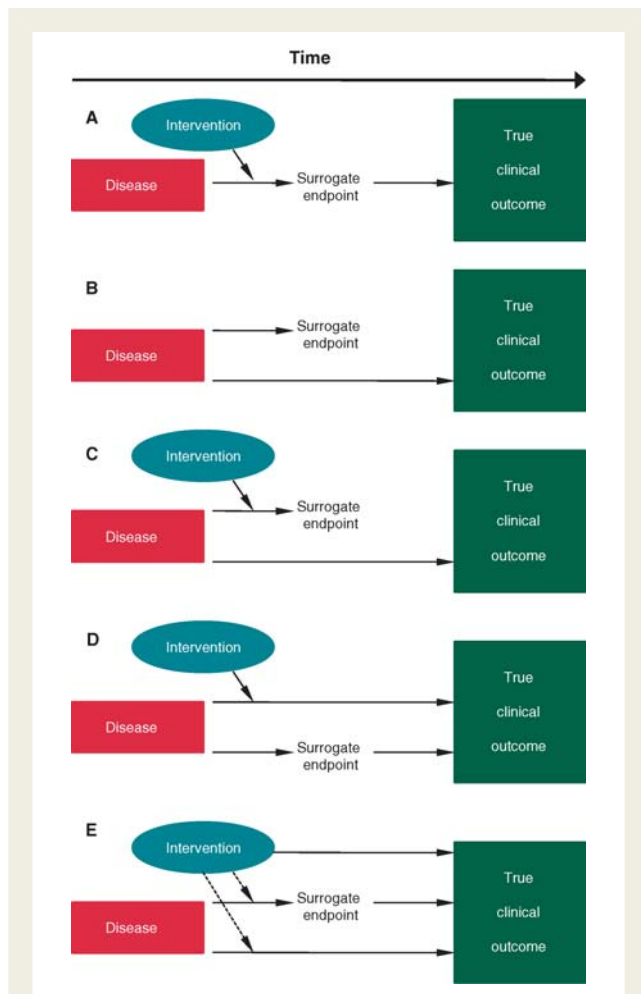
**Figure I** Relationship between disease processes, interventions, surrogate endpoints, and true clinical outcome. (*A*) The ideal situation, which offers the greatest potential for the surrogate to be valid; (*B*) the surrogate is not in the aetiological pathway of the disease; (*C*) the intervention affects only the pathway mediated through the surrogate, but there are other aetiological pathways; (*D*) the intervention does not affect the surrogate; (*E*) the mechanism of action of the intervention is independent of the disease process. Dotted lines represent other possible mechanisms of action. Adapted with permission from Fleming TR and DeMets DL.[84]

endpoint is the result of a single pathophysiological process, which is affected by the intervention. In practice, however, the pathophysiological processes linking the cause and the surrogate are manifold, as are the processes linking the surrogate endpoint and the true endpoint (*Figure 1*). These complex interactions between biological variables often underlie the difficulty in identifying reliable surrogate endpoints.

## Reverse left ventricular remodelling

Cardiac remodelling is the final common pathway of chamber dilatation and failure that occurs after myocardial infarction, pressure overload, inflammatory muscle disease, idiopathic dilated

cardiomyopathy, or volume overload.[24] Left ventricular remodelling has been linked to poor long-term prognosis in patients with heart failure.[24-26] Reverse LV remodelling, on the other hand, has been demonstrated with drugs that are known to benefit patients with heart failure, such as angiotensin converting enzyme (ACE) inhibitors[24,27-29] and beta-blockers.[29] Reductions in LV end-systolic volume (LVESV) appears to be the most useful measure of reverse remodelling.[26]

Numerous studies have shown significant reduction in LVESV after CRT.[20,30-32] Such reductions are evident as early as 1 month post-implantation,[33] and are sustained at 29 months.[5] Further support for a causative link between CRT and reverse LV remodelling is suggested by the finding of LV dilatation when CRT is withdrawn.[34] The value of reverse LV remodelling in discriminating prognostic 'responders' and 'non-responders' to CRT was explored in a study of 141 patients, in which a reduction in LVESV $\geq$9.5% 3 to 6 months post-implantation was identified as a predictor of all-cause ($P = 0.0003$) and cardiovascular ($P < 0.0001$) mortality.[20] There is, in addition, evidence to indicate that the magnitude of reverse LV remodelling relates to the clinical outcome. In this respect, Ypenburg *et al.*[35] found that in patients undergoing CRT, all-cause mortality was 3% in patients with a LVESV reduction of $\geq$30% and 21% in patients with a LVESV reduction between 0 and 14%. This goes some way towards satisfying another desirable characteristic of surrogate endpoints, namely, that they should relate linearly to the true endpoint.[36]

On the basis of the above, reverse LV remodelling is a promising surrogate measure of outcome after CRT. Cut-offs of reverse LV remodelling must, however, clearly differentiate between good and poor outcome. They must, therefore, withstand the rigour of Bayesian analyses. One of the few studies to employ this methodology showed that a reduction in LVESV $\geq$9.5% predicted all-cause mortality with a sensitivity of 70% and a specificity of 70%, and cardiovascular mortality with a sensitivity of 87% and a specificity of 69% (*Figure 2*).[20] While these figures compare favourably with other biomarkers, it must be noted that a sensitivity of 70% means that 30% of patients, who benefit prognostically from CRT, are wrongly classified as 'non-responders'. A specificity of 69% means that 31% of patients, who do not benefit prognostically, are wrongly classified as 'responders'. With this discriminatory ability, it would appear that reduction in LVESV is of limited value in discriminating between 'responders' and 'non-responders' after CRT. As a further limitation of studies of LV remodelling in relation to CRT, none has used the statistical methodology of internal and external validation.[22]

Although reverse LV remodelling relates to outcome, it does not relate to symptomatic response. In a study of 141 patients undergoing CRT, Yu *et al.*[20] found no relationship between reduction in LVESV and changes in NYHA class, 6 min walk distance, or quality of life score after CRT. Likewise, Ypenburg *et al.*[35] found similar improvement in NYHA class, quality of life score, and 6 min walk distance in patients exhibiting $\geq$15% reduction in LVESV compared with those exhibiting a reduction in LVESV of <14%. Lafitte *et al.*[37] showed that 63% of patients, who did not show a $\geq$15% reduction in LVESV following CRT, nevertheless made clinical improvement. A clinician may, therefore, encounter a patient, who has improved symptomatically after CRT,
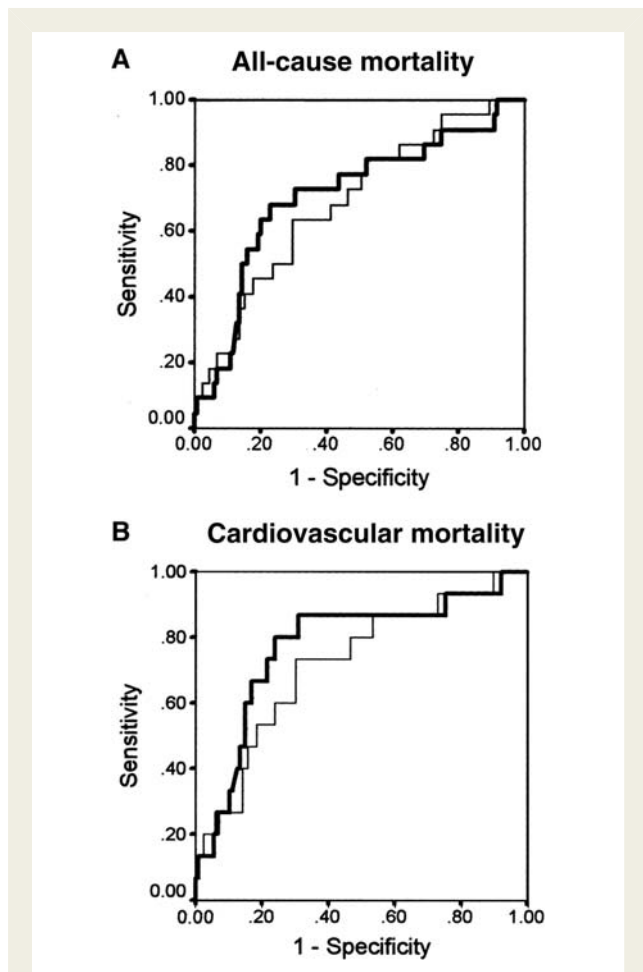
**Figure 2** Receiver-operating curves for predicting all-cause (*A*) and cardiovascular (*B*) mortality by LV reverse remodelling, as reflected by the reduction in LVESV (dark line) and LVEDV (light line). Reproduced with permission from Yu CM, *et al.*[20]



**Figure 3** Acute haemodynamic changes in patients with CRT-on and CRT-off. Changes pertain to patients with advanced decompensated heart failure who had undergone CRT implantation at least 3 months prior to testing. A significant worsening of haemodynammics was observed immediately after CRT was programmed off. Reproduced with permission from Mullens *et al.*[45]

but has no volumetric response. A reasonable question would be whether the absence of reverse remodelling, even on the background of clinical improvement, should prompt further intervention, e.g. atrioventricular and ventricular-ventricular optimization, lead repositioning or withdrawal of therapy.

The discordance between symptoms and reverse LV remodelling after CRT is not unexpected, given that CRT acts via multiple pathways. Diastolic ventricular interaction, which is demonstrable in patients with heart failure,[38] is relieved by CRT.[39] In addition, CRT reduces functional mitral regurgitation,[40] an effect which is not wholly dependent on reverse LV remodelling.[41] Blood flow,[42] heart failure aetiology,[43] location of myocardial scarring,[44] and atrial rhythm[13] may also influence the outcome of CRT. In addition, it has been shown that withdrawal of CRT in patients who had exhibited progressive LV remodelling was associated with a reduction in blood pressure and cardiac output[45] (*Figure 3*). This suggests that CRT confers a favourable haemodynamic profile, even on the background of progressive cardiac remodelling.

## Left ventricular ejection fraction

The notion that LV systolic function relates to the prognosis of heart failure is mechanistically attractive. In this respect, the Vasodilator-Heart Failure Trials (V-HeFT I and II) identified LVEF, measured using radionuclide imaging, as a predictor of mortality in male patients with heart failure.[46] Improvements in LVEF with
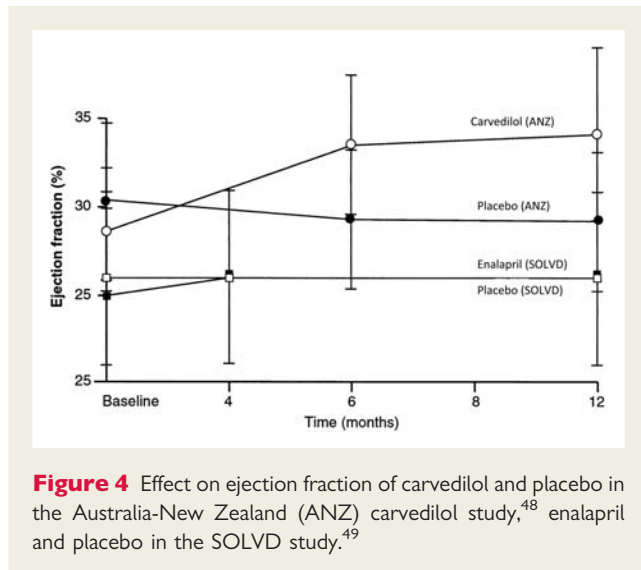
**Figure 4** Effect on ejection fraction of carvedilol and placebo in the Australia-New Zealand (ANZ) carvedilol study,[48] enalapril and placebo in the SOLVD study.[49]



**Figure 5** Receiver-operating curves for peak $VO_2$ in relation to 3 year survival. The area under the curve was significantly greater for peak $VO_2$ than for age and ejection fraction ($P < 0.05$). Reproduced with permission from Myers *et al.*,[58] EF, left ventricular ejection fraction.

treatment have also been linked to improved prognosis.[46,47] In some studies, however, drugs, which are known to prolong survival, such as carvedilol[48] and enalapril[49] do not significantly alter LVEF (*Figure 4*). Conversely, bucindolol does increase LVEF, but does not prolong survival.[50]
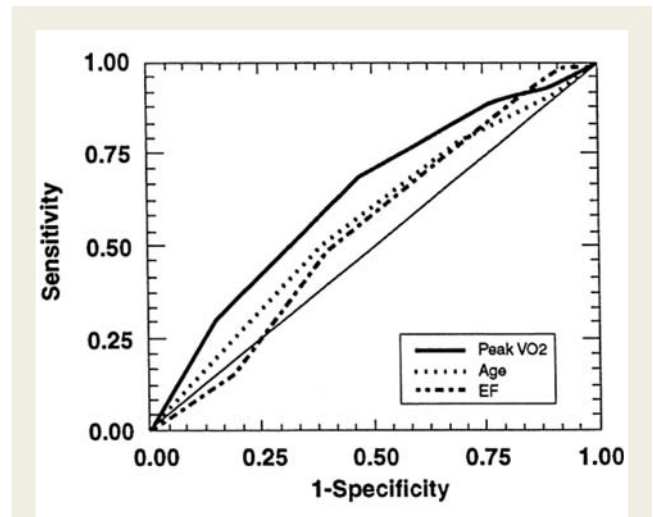
In the CARE-HF trial, LVEF at 3 months increased by 4.7% in the CRT-P arm, compared with 0.3% in OPT arm.[51] In multivariate analyses, however, improvements in LVEF did not emerge as an independent predictor of outcome. The demonstration of an increase in LVEF by CRT, therefore, does not endorse the use of LVEF as a predictor of benefit from CRT. It should also noted that, in patients with heart failure, LVEF relates poorly to symptoms.[52] Furthermore, the value of LVEF in monitoring patients with heart failure has not been addressed by randomized studies, nor has it been validated, with regard to CRT, nor any other treatment. On this basis, echocardiographically derived LVEF is an unlikely surrogate measure of outcome in CRT patients.

## Other echocardiographic variables

On the basis that cardiac dyssynchrony is the substrate for effective CRT, some echocardiographic studies have adopted dyssynchrony measures, such as the septal-to-posterior wall motion delay and the interventricular mechanical delay, as study endpoints.[53] Yet, these measures have been proven not to relate to clinical improvement after CRT.[54] No studies have validated whether correction of dyssynchrony translates into an improved response or outcome after CRT.

## Haemodynamics

As for LVEF, improvements in the haemodynamic profile should, intuitively, qualify as a measure of response and outcome after CRT. While, undoubtedly, CRT causes a haemodynamic improvement in the acute setting,[2,3] no studies have explored whether this is predictive of long-term response or outcome. Treatments, which improve cardiac function, do not necessarily lead to a prognostic benefit. A trial comparing hydralazine and nitrates with an

ACE-inhibitor showed that, despite similar haemodynamic effects, mortality was lower with the ACE inhibitor.[55] On this basis, haemodynamic variables cannot be used as predictors of long-term response or outcome after CRT.

## Peak oxygen uptake

Peak $VO_2$ is regarded as the gold standard prognostic marker in patients with heart failure. One of the earliest studies to analyse peak $VO_2$ in relation to outcome in patients with heart failure was that of Mancini *et al.*[56] According to the study protocol, patients with a peak $VO_2 > 14$ mL/kg/min were denied transplantation, whereas those with a peak $VO_2 \leq 14$ mL/kg/min were offered transplantation. The study demonstrated that peak $VO_2$ could be used to identify patients in whom cardiac transplantation could be safely delayed. However, as mortality and transplantation were influenced by the study protocol, the findings cannot be taken as validation of peak $VO_2$ as a predictor of mortality in patients with heart failure. In a similar study of patients referred for cardiac transplantation, Aaronson *et al.*[57] found that normalized peak $VO_2$ predicted survival, but the area under the receiver-operator characteristic curve (ROC) was only 0.66. In a study of 644 patients, Myers *et al.*[58] found that peak $VO_2$ predicted mortality, but the ROC area was only 0.64 (*Figure 5*). In addition, these authors could not identify an optimal cut-off point for predicting survival. Several studies have shown that peak $VO_2$ does not predict survival in patients with heart failure.[59–61] With regard to peak $VO_2$ in relation to symptoms, Wilson *et al.*[62] found no relation between peak $VO_2$ and quality of life, and only a weak correlation between peak $VO_2$ and a dyspnoea/fatigue index. In this study, up to 45% of patients with a peak $VO_2 < 14$ mL/kg/min had few or no exertional symptoms. It would appear, therefore, that peak $VO_2$ is not a reliable measure of

response or a predictor of outcome in unpaced patients with heart failure.

An increase in peak VO$_2$, ranging from 0.6[63] to 1.4 mL/kg/min has been reported in relation to CRT.[64] Although this confirms that CRT has an effect upon cardiopulmonary and metabolic status, it does not equate to validation of peak VO$_2$ as a surrogate measure of response or outcome. As a practical issue, temporal changes in peak VO$_2$ in individual patients are highly unpredictable.[65] This should be taken into account in interpreting the findings of studies such as RethinQ study, in which, interestingly, patients with narrow QRS complexes undergoing CRT exhibited an improvement in NYHA class, but not in peak VO$_2$.[66]

## Walk distance

The 6 min walk test (6-MWT) has been adopted as a measure of response to CRT in a number of studies. In a study of 1077 patients with heart failure, Ingle et al.[67] found a negative correlation ($r = -0.55$; $P = 0.0001$) between changes in symptoms and changes in 6-MWT distance (i.e. a reduced 6-MWT distance is associated with reduced symptom severity at follow-up). On this basis, the 6-MWT provides a reproducible[68] measure of symptomatic status in patients with heart failure. In a systematic review, the 6-MWT distance was shown to concur with changes in heart failure symptoms, particularly in the context of CRT.[69]

As well as providing an additional measure of symptomatic status, 6-MWT distance has been shown to relate to survival in unpaced patients with heart failure.[60,70] In patients undergoing CRT, pre-implant a 6-MWT distance <225 m has been shown independently to predict cardiovascular mortality.[71] Further studies are needed to validate that the absolute 6-MWT distance or change from baseline after implantation also translates into poor outcome.

## Neuroendocrine data

The observation that circulating natriuretic peptide levels change with drug treatment[72,73] raises the possibility that they may be good surrogate markers of outcome after CRT. In a study of 50 patients undergoing CRT, Pitzalis et al.[74] observed that at 1 month post-implantation, brain natriuretic peptide (BNP) was lower in patients who had experienced no progression of heart failure, compared with those who did. Further data from the CARE-HF study showed that N-terminal (NT)-pro-BNP 3 month post-implantation predicted long-term outcome (HR 5.7 for patients in the highest tertile compared with those in the lowest tertile).[51]

Although natriuretic peptides relate to the clinical outcome of CRT, their very high variability is likely to compromise their use as surrogate markers of outcome during clinical follow-up. In healthy individuals, serial changes of up to 92% for NT pro-BNP and up to 168% for BNP have been reported.[75] In patients with heart failure, the intraindividual coefficient of variation can be as high as 35% from week to week.[76] To be useful as a marker of response, one must define what reduction in natriuretic peptides post-implantation relates accurately to a future survival benefit in individual patients. To date, however, the magnitude of this reduction has not been determined, nor validated. Post-implant changes in natriuretic peptides, therefore, cannot be taken as reliable surrogate markers of long-term outcome after CRT.

## Ventricular arrhythmias

Ventricular ectopy was once considered a surrogate of prognostic benefit following a myocardial infarction. Drugs which reduce ventricular ectopy, such as flecainide,[77] however, were subsequently found to shorten survival. Similarly, amiodarone controls ventricular tachycardia, but has no effect on survival. Early studies showed that CRT reduces ventricular ectopy[78] and device delivered antitachycardia therapy.[79] These findings may be relevant to those of the CARE-HF extension study, in which reduction in sudden cardiac death following CRT was found.[80] Importantly, such an effect was not apparent after the initial 29 months' follow-up.[5] It follows, therefore, that even if ventricular arrhythmias were good predictors of sudden cardiac death after CRT, they would be unlikely to be predictors of survival benefit.

## Composite measures

As discussed earlier, single measures are unlikely to be reliable predictors of the outcome of CRT in the complex syndrome of heart failure. The rationale for using composite measures stems from the fact that heart failure has many effects: it causes death, hospitalization, exercise intolerance, breathlessness, and a worsening in quality of life. The attraction of a composite endpoint, or score, is that it allows the reduction of a disease's varied effects into a single, measurable parameter. By strengthening the capacity to pick out weaker signals from the background noise of sampling error, combined endpoints improve the decisiveness of a clinical trial.[23] In clinical practice, composite clinical scores[81] could include variables which, together, amount to a clinically meaningful measure. The difficulty lies in choosing what to measure and in deciding on the relative importance of each measure.[82] For example, should a reduction in LVESV be treated with equal importance (or weighting) as an improvement in NYHA class, or avoidance of hospitalization, or death? The 9th Clinical Trialists Workshop of the US National Institutes of Health and other regulatory bodies concluded that standards for weighting composite scores were needed; that consensus was needed to define a clinically meaningful effect of composite scores, and that the value of the 'trade-off' position between components of composite scores needs to be defined.[83] These issues are yet to be addressed in the field of CRT. Arguably, they should be a priority for regulatory bodies.

## Conclusions

In summary, CRT has revolutionized the treatment of selected patients with heart failure. Although reverse LV remodelling is a promising surrogate of outcome after CRT, one should consider that volumetric 'non-responders' may nevertheless experience symptomatic benefit. On the other hand, patients who benefit symptomatically may not necessarily derive a prognostic benefit. As for most heart failure therapies, reliable measures of response to CRT in individual patients are yet to emerge. Composite measures may hold the key. Such measures must be validated against the survival and symptomatic benefits that are to be

expected from therapy in individual patients, on the basis of randomized, controlled trials. In addition, composite clinical endpoints must reflect the relative importance of response and outcome benefits, as judged by patients, not doctors. Until this is established, the terms 'responder' and 'non-responder' to CRT have little meaning in clinical practice.

**Conflict of interest:** none declared.

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