Meta-analysis of symptomatic response attributable to the pacing component of cardiac resynchronization therapy

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Aims
Prognostic benefit from CRT compared with controls is well established. Symptomatic response rates, however, are controversial and have never been systematically evaluated with standard subtraction of control rates to establish the incremental symptomatic response effect of CRT pacing.

Methods and results
First, we identified 150 consecutive CRT papers and assessed researchers’ perceptions of the symptomatic response to CRT. The mean quoted response rate was 66%. Only 26 studies acknowledged the existence of response without the device. Secondly, we examined actual symptomatic response rates in the randomized trials (CARE-HF, COMPANION, CONTAK-CD, MIRACLE, MIRACLE-ICD, MIRACLE-ICD II, MUSTIC, and REVERSE) totalling 3904 patients. The NYHA status improved in 51% of those randomized to CRT vs. 35% of controls (incremental effect 16%). This incremental improvement was significantly greater in open studies (with no device for controls) than in blinded studies (control arm receiving a device but no CRT, such as a defibrillator or a CRT programmed off), 20% vs. 13%, P < 0.001.

Conclusions
Quoting CRT responder rates in isolation without recognizing spontaneous ‘response’ is common but unwise. The incremental symptomatic response rate from CRT pacing is ≏16%, much lower than widely reported. This value is similar to that for drugs in heart failure and should not be considered disappointing; they both exert powerful prognostic benefits. For scientific purposes, e.g. to explore potential improvements, symptomatic benefit from CRT should be quantified, like all other effects, by comparison with a control.

Introduction
Descriptions of the benefits of CRT on survival and hospitalization are rightly always described by comparison with randomized control groups who do not receive CRT. Large clinical trials and meta-analyses have consistently demonstrated prognostic benefits, with clear reductions in mortality,1–5 but understanding the symptomatic benefit from this therapy is less straightforward. Many patients symptomatically improve in clinical trials of CRT, even in the non-CRT arm.6 This might be due to natural history, placebo effects, or being part of a clinical trial.

In this study we set out to determine from the CRT literature whether the conventional scientific approach of subtracting this control arm improvement rate from the active arm rate is widely used, and what the incremental symptomatic response attributable to CRT actually is.

This distinction, between observed changes in symptoms with CRT and the net benefit truly attributable to CRT, is important for...
two reasons: (i) to allow clinicians to provide information to enable patients to give accurate informed consent; and (ii) to protect researchers, working to improve selection criteria and new methods of delivering CRT, from assuming that responder rates are already high and a small improvement might make it complete. If it is found that commonly quoted symptom response rates are overstated, the scientific fields of patient selection and advancement of methods for delivering CRT may be more open than we may assume, and researchers may become less satisfied with achieving symptomatic improvement.

This study is in two parts. First we analyse the heart failure community’s published perception both of what response rates to CRT are and of how the symptomatic response rate should be evaluated: do they recognize the possibility of ‘spontaneous symptomatic response’ to no CRT, i.e. the response rate in the control arm of a randomized controlled trial of CRT where a device is implanted but programmed not to deliver therapy? Secondly, we conduct a systematic review of randomized, controlled trials to establish a placebo-subtracted symptomatic response rate to CRT that eliminates bias using a range of established markers of heart failure symptoms such as NYHA score and Minnesota Living with Heart Failure (MLWHF) score. We then assess whether there is any difference between the symptomatic response rates in the non-CRT arm between blinded trials (where patients have CRT devices implanted which are programmed not to deliver therapy) and open trials (where patients in the non-CRT arm have no device).

Methods

Assessment of the published perception of the rates of symptomatic improvement due to cardiac resynchronization therapy

A Pubmed search using the terms (MeSH) ‘cardiac’ OR ‘heart’ AND ‘resynchronization’ AND ‘therapy’ OR ‘therapeutics’ was performed. A total of 150 consecutive papers in the English language (January 2006 to October 2011) were reviewed in order to gauge the scientific community’s current perception of the symptomatic effects of CRT. From each of these papers we extracted information concerning quoted response rates including the following: (i) whether symptomatic response or non-response with CRT has been mentioned at any stage in the paper; (ii) whether the symptomatic response with CRT was compared with a control arm response; and (iii) whether the authors give a number or word to describe the proportion of symptomatic non-response.

Systematic review of randomized controlled trials to calculate the symptomatic response truly attributable to cardiac resynchronization therapy

Selection of trials

We searched the Pubmed database for (MeSH) ‘Cardiac Resynchroniza-
tion Therapy’ activating the ‘Randomized Controlled Trials’ limit, and analysing papers in English (search performed 10 October 2011). Of the 158 papers listed under this category, only papers which compared a CRT arm with a non-CRT arm were included (total: 61). The non-CRT arm could be either no device (an open comparison study, where it was clear to both patients and investigators to which arm the patient was randomized) or a CRT device with the LV lead programmed off (blinded comparison study, whether the patients ± investigators were unaware of the group into which the patient had been randomized). Duplicate publications from the same trial were excluded, leaving a total of 12 studies. Of these 12 studies, the RethinQ trial was excluded as the selection criterion for CRT (narrow QRS) was quite different from that of all the other large trials included.

These 11 trials were then screened to search for both baseline and follow-up data on different measures of symptomatic response to CRT. These included: NYHA score, clinical composite score, 6 min walk test, measured peak VO2 on cardiopulmonary exercise testing, and MLWHF score. Such data were present in eight of the trials.

Analysis of symptomatic response

For NYHA score and clinical composite score which provide categorical variables, the number and proportion of participants who reported an improvement in response were recorded in both of the arms (CRT and non-CRT). For the MLWHF score, peak VO2, and 6 min walk test (which all provide continuous variables), the change in score was noted pre- and post-CRT. Analysis of results was divided according to the blinding methodology—blinded (CRT implanted in both groups, but switched off in the control arm) and open (no CRT implanted in the control arm). In COMPANION, the CRT-P arm was compared with the control arm.

Statistics

For each of the parameters listed above, a weighted average across the clinical trials was calculated for both the CRT arm and the control arm. The difference in response between the two groups is presented as the incremental benefit truly attributable to CRT. A three-way contingency table and $\chi^2$ test were performed to assess for the effect of blinding and CRT response for NYHA class. A Fisher’s exact test was performed for the clinical composite score. For the continuous variables, data on the standard deviations of the differences in responses were not available for all the trials, precluding calculation of a test statistic. Statistical analyses were performed on SPSS version 16 (IBM, New York).

Results

Assessment of the published perception of the rates of symptomatic improvement due to cardiac resynchronization therapy

Of the 150 publications identified from the Pubmed search, 119 mentioned a response rate. Symptomatic response rate was specifically mentioned in 84 (70.6%). Of these, only 26 (21.8%) mentioned this response in comparison with the response in the control arm (Figure 1). Six (23.1%) of these 26 papers did not provide a numerical value for response rate. Two papers (7.7%) provided values of responses to CRT only and did not mention the numerical value for response rate in the control group. Eighteen papers (69.2%) provided numerical values for responses to both CRT and control, and statistically compared these response rates. However, in no publication was an absolute difference between response rates in the two groups expressed as a single figure.

Forty-four (37.0%) of the 119 papers that mentioned response rate specifically described the presence of non-responders to CRT. A figure was quoted for the ‘non-response’ in 33 of these papers. Values for non-response rates with CRT given in the papers either gave a single value, minimum and maximum value, or a maximum or minimum value alone (e.g. ‘up to X% of patients do not respond’). If only the upper or lower limit for non-response was mentioned, averages were calculated for these (Table 1). For the studies
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where a single value for response rate was quoted, the values were averaged across the studies and the mean response rate was calculated to be 66%. Where maximum non-response was quoted, the minimum response rate was calculated to be 65%. Where a range of non-response was quoted, the average response rate range was calculated as 61–75%. For the purpose of our study, where both echocardiographic and clinical responses were quoted, only the clinical non-response rate was taken. Where papers mentioned response rather than non-response, the mean response rate was 65%.

**Composite clinical score**
The composite clinical score has been commonly used as a measure of heart failure response in a range of clinical trials. The score combines three separate markers of the symptomatic severity of heart failure: the first is hospitalization due to heart failure or death, the second is change in NYHA class, and the third is the patient’s perception of their symptoms using the Patient Global Assessment score. Based on these measures, the patient can be classified as better, the same, or worse. Improvements in the NYHA score and Global Assessment score categorize the participants in the ‘better’ group. Death, hospitalization, or a fall in the other two measures categorize the participants in the ‘worse’ group. All others come under the ‘unchanged’ category.

The clinical composite score at baseline and follow-up was available in three of the trials (Supplementary material, Table S1). In all three, the patients were blind to the treatment they had received.

Across all the groups, a mean of 54% of patients in the CRT arms of the trials had an improvement in the clinical composite score, compared with a 40% improvement in the control arm ($P < 0.001$). This suggests that based on this scoring system, 14 patients out of every 100 having CRT devices implanted will have incremental benefit from cardiac resynchronization (Supplementary material, Figure S1).

**Quality of life scores: Minnesota Living with Heart Failure questionnaire**
Quality of life scores are intended to provide a measure of the overall impact of heart failure on the patient’s life and can provide an insight into the impact of heart failure symptoms beyond exercise capacity and breathlessness. The MLWHF score is a widely used marker and was measured at baseline and follow-up in seven of the trials. A score of up to 105 is generated from a series of questions; the higher the score, the worse the estimated effect on quality of life. A 17-point improvement was seen in the MLWHF score with CRT. By deducting the effect seen in the control group, it became apparent that an 11-point improvement in the score is truly attributable to CRT pacing (Figure 3, Supplementary material, Table S2).

As with change in NYHA status, the incremental effect of CRT pacing (i.e. CRT minus control) was greater in the open than in the blinded trials (13.3 vs. 7.4). This difference was due to the greater improvement in the score in the control arm of the blinded trials compared with the control arm response of the open trials (9.5 vs. 3.9); responses in the CRT arms of the two types of trials were very similar (16.9 vs. 17.3). This suggests that there is a measurable placebo effect above and beyond the spontaneous improvement found in the open trials (Figure 3).

**Change in exercise capacity: improvements in 6 min walk distance and peak VO2 response truly attributable to cardiac resynchronization therapy**
Six of the trials had baseline and follow-up data for 6 min walk distances, and, of these, five had baseline and follow-up cardiopulmonary exercise test data (peak VO2) and four were blinded (Supplementary material, Table S3).
The 6 min walk distance improved in both the control and CRT arms of all trials. There was greater incremental effect of the CRT arm in the open studies, because of less control arm response than in the blinded studies.

In contrast, although there was an increase in peak VO2 in the CRT arm of all trials, both blind and open, participants in the control arms of both types of trial had a minimal response.

**Discussion**

While there is no doubt that CRT improves survival (vs. control) and improves symptoms, the symptomatic response rate reflected in the clinical research literature is arguably an overestimation of the incremental effect of CRT pacing itself. The actual incremental symptomatic improvement due to CRT pacing, as documented by large,
systematically conducted, externally monitored, and meticulously reported clinical trials, is 14–16%. Much of this overestimation is the result of failing to subtract the symptomatic improvement found in the control arm.

Defining response as improvement in NYHA, in these five major randomized clinical trials, the control arm response was 35%. In their counterparts in the treatment arm who received CRT pacing, the symptomatic response rate was 51%. The presence of CRT pacing therefore increased the response rate by 16 absolute percentage points.

**Symptomatic response as a goal of cardiac resynchronization therapy**

Symptomatic response rates arouse great interest despite the intrinsic difficulties and poor reliability of the methods available for measuring them. They are frequently mentioned in the clinical literature, and sessions at scientific conferences are dedicated to discussing ways to reduce non-responder rates. It is conceivable that real-world symptomatic response rates are even lower than calculated in this study, given the broadening of the indications for CRT in milder heart failure.17 In the trials we studied, 2.7% of subjects were in NYHA functional class I, 21.7% in NYHA II, 67.5% in NYHA III, and 8% in NYHA IV. In patients starting with milder symptoms, the symptomatic response rate attributable to CRT pacing might be even lower. In the REVERSE trial and MIRACLE ICD-II trial where patients had milder symptoms to start with (NYHA class I–II), symptomatic response rates were even lower (Supplementary material, Table S5). The presence of the REVERSE trial may give the impression that the overall improvements in NYHA class are lower in blinded studies than in open studies; without REVERSE, an opposite effect appears, with the weighted percentage improvement in blinded studies increasing to 65% and overall to 60%.

Nevertheless there is no doubt about mortality benefit from CRT, which has been well established by a randomized controlled trial against no CRT.1 This study does not contradict the excellent survival and hospitalization advantages conferred by CRT, nor does it contradict the clear symptomatic benefits. It only suggests that the oft-quoted responder rates are four-fold larger than the incremental effect delivered by CRT pacing. It also highlights the importance of taking into account the study design when relaying conclusions from studies using symptoms as an endpoint.

**Association between symptomatic benefits and improvements in markers of functional capacity (peak VO₂ and 6 minute walk test)**

Symptomatic improvement is desirable but can arise from sources other than genuine physiological improvement. Comparison of blinded with open studies can be illuminating. For peak VO₂, an objective measurement, the control arm has only one-fifth the response of the therapy arm, regardless of study design. For measurements...
such as 6 min walk distance and MLWHF score where patient’s attitudinal state may have a greater role, in open studies again the control arm has only about one-fifth the response of the therapy arm, but in blinded studies the control arm has more than half the response of the therapy arm (Figure 3; Supplementary material, Figure S2). Blinding enhances the response rates in the control arm for these variables.

Mortality vs. symptomatic benefits

It is not universally agreed whether CRT should be considered a treatment to reduce the risks of an event such as death, or to improve symptoms from heart failure. If its primary purpose is event risk reduction, a lack of detectable change in symptoms in an individual should not be perceived as a therapy failure, and individual patients should not be classified into ‘responder’ and ‘non-responder’. Prognostic and symptomatic improvements may not always be concordant; many patients benefit from reduced risk of events or deterioration, without any perceptible immediate symptomatic benefits. While in later disease the symptomatic goal may be a detectable improvement, in earlier disease the symptomatic goal may be prevention of deterioration: this is impossible to confirm in individuals since no comparator arm is available.

It may not be wise to expend effort describing symptomatic improvement rates in individual patients, or to focus attention and studies on ‘non-responders’, since the great majority of response has nothing to do with CRT pacing.

Comparison with a control arm is already standard for discussion of death and hospitalization benefits of CRT. In CARE-HF, mortality was 20% in the treatment arm vs. 29.7% in the control arm: 10 deaths prevented per 100 devices implanted. This large reduction in mortality compares very favourably with many cardiovascular treatments.

Does it matter whether the effect is caused by cardiac resynchronization therapy pacing or not?

In an individual patient, it is not possible to tell in normal clinical practice which of the three explanations (actual benefit of CRT pacing, placebo effect, or spontaneous improvement/variation) is the cause of an observed improvement in heart failure symptoms, just as it cannot be determined for drugs. If a patient believes their CRT implant has improved symptoms, it may be good medical practice to allow that belief to stand.

Figure 3

Comparison of symptomatic response in open vs. blinded studies measuring improvement in the Minnesota Living with Heart Failure score. Similar degrees of improvement are seen in the CRT arms of both open and blinded trials. In the blinded trials, a greater improvement is seen in the controls, indicative of a placebo response to device implantation.

Table 3

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<td>Weighted mean of all studies</td>
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such as 6 min walk distance and MLWHF score where patient’s attitudinal state may have a greater role, in open studies again the control arm has only about one-fifth the response of the therapy arm, but in blinded studies the control arm has more than half the response of the therapy arm (Figure 3; Supplementary material, Figure S2). Blinding enhances the response rates in the control arm for these variables.

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In scientific fora or scientific journals, however, we should avoid basing reasoning on effect sizes that include an extraneous added component, because (for example) it reduces our ability to compare two effect sizes, and thereby recognize subtle improvements in strategy. There are also costs to patients, to health services, and to research, of working from erroneous effect sizes of CRT pacing. The risk of long-term complications from implanting CRT devices is not trivial, with rates quoted between 4% and 28%. For heart failure physicians to make the decision to offer CRT, and
for patients to make an informed decision to proceed, they need reliable information on the actual effect of CRT pacing.\textsuperscript{21}

Comparison of the symptomatic benefits of cardiac resynchronization therapy with other heart failure treatments

Despite the symptomatic response rates attributable to CRT being significantly lower than those commonly quoted, the number needed to treat for CRT would be \( \approx 6 \). In the context of other recent innovations in cardiovascular medicine,\textsuperscript{22,23} CRT compares favourably. The benefits are greater than those of beta-blockers or aldosterone antagonists and second only to ACE inhibitors.\textsuperscript{24} (Figure 4, Supplementary material, Table S4).

Distinction between individual and group mean effects

Reliably assessing changes is vastly more difficult for individuals than for group mean effects. Averaged across a population, spontaneous changes within individuals (which can be in either direction) tend to average out, so that the underlying treatment effect becomes more evident. Clinical trials show benefits as a population average, not only for measurements, but also for hard endpoints since event rates too can be considered to be averages, counting 1 for event and 0 for no event.\textsuperscript{24}

However, we should not assume we can usefully quantify the effect of CRT in individual patients with routine approaches.\textsuperscript{25} Assessing symptomatic effects in individuals in the conventional way is mostly unreliable, because previous status is an unsound control. Reverse remodelling documented by reductions in LV volumes has consistently shown an association with improvements in mortality, more consistently than other echocardiographic parameters across populations.\textsuperscript{26–28} However, using these for individualized response prediction is difficult because of the unavoidable effect of chance.\textsuperscript{18,29} When analysing any change in a continuous variable such as a chamber dimension on an echocardiogram, if the intervention were to have no effect there remains a 50\% chance that when the measurement is repeated, it will be higher; and, likewise, a 50\% chance that it will be lower.

If individualized response quantification is needed for research purposes, it could instead be achieved by measuring a physiological marker with the device on and off, with the intraindividual error bar made as small as is needed by repeating the process enough times\textsuperscript{30,31} to quench the effect of noise. Just as the presence of a symptomatic response does not signify that the pacing is having any useful effect, the lack of symptomatic response does not signify that the pacing is not having any useful effect. Patients who do not describe a symptomatic response should not be denied access to interventions such as exercise therapy which have been shown to improve quality of life.\textsuperscript{32}

This analysis has highlighted that markers of symptom response are affected by very many more phenomena than just biventricular pacing itself. Using the symptomatic response, in a cohort without a control group, and without assessing differential response with pacing on and off, biases us to substantial overestimation of the pacing effect on symptoms. Cognitive and psychological status may influence this bias. If it is desired purely to increase the symptomatic response, as distinct from increasing the physiological benefits that lead to a symptomatic response, future research might focus on interventions that are explicitly psychological.

Clinical implications

The widely perceived rate of symptomatic response rate to biventricular pacing is shown by the randomized controlled trials to be an
overestimate of the CRT pacing effect itself. Even in trial populations who may be more optimistic than the general heart failure population, and even counting all causes of improvement in symptoms (spontaneous, placebo, and pacing mediated): (i) only half report a symptomatic improvement; and (ii) of that half, two-thirds would have reported improvement without pacing and only one-third (~16% of all recipients) are reporting it specifically because of pacing.

Discussing this openly might be uncomfortable, but it is a scientific starting point to developing better methods of judging which individuals are receiving advantage from pacing itself (Figure 5).

Multiple randomized controlled trials, in which individual variability is damped down by averaging, have demonstrated beyond doubt substantial symptomatic and survival improvements with CRT across groups of patients: clinicians can continue with confidence to recommend CRT implantation in the same way that they do drug therapy. However, symptomatic change should not necessarily be the focus of individual consultations.

Study limitations

We collated data from the large, carefully conducted clinical trials which reported them. However, some recent trials, such as RAFT and MADIT CRT, did not show these data. The trials in this systematic review used different methods to monitor symptomatic response. The NYHA data are not available for all the trials listed here, and the clinical composite score is only present for four of the trials for example.

We cannot exclude changes in symptoms smaller than the resolution of the methods: NYHA class, by definition, is a crude measure of symptom response. While another scale with more gradations might detect smaller improvements in symptoms caused by CRT, it would similarly detect smaller fluctuations arising for reasons other than the CRT. It is this presence of intercurrent variation in clinical state, and not failure of any individual index, that is the obstruction to useful determination of response to CRT in individuals. All of the markers of symptom response used in this study could all be classified as ‘soft endpoints’ which are very much influenced by the opinions of individual patients and physicians. The greater spontaneous improvement in the control arms of the blinded studies vs. the open studies demonstrates this (Figure 3).

Conclusions

The symptomatic response rate to the pacing element of CRT is distinctly less than the two-thirds currently perceived by the scientific community. Symptomatic improvement with CRT in the clinical trial setting is 51–54% depending on the measure used. Once the effect of spontaneous improvement is subtracted, the symptomatic improvement rate truly attributable to CRT pacing is only 14–16%. There are signs of a placebo effect in symptom endpoints: controls in blinded trials show improvements more nearly matching those of their CRT counterparts than do controls in unblinded trials. This analysis is not designed to detract from the clinical benefits or accomplishments of CRT as a discipline, or CRT research in general. It is designed only to analyse the components of reported rates of CRT response, and scientifically to put the pacing-mediated component into the context of response rates with other therapeutic modalities that have been similarly assessed. The ultimate purpose is to provide clinicians with information that can be comparable between device
and drug therapy, and to provide readers and researchers with a reliable frame of reference.

Supplementary material
Supplementary material is available at European Journal of Heart Failure online.

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