Many response criteria are poor predictors of outcomes after cardiac resynchronization therapy: validation using data from the randomized trial

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Aims
The aim of the study was to assess the predictive value for outcomes of various response criteria currently used in patients undergoing cardiac resynchronization therapy (CRT).

Methods and results
Data from TRUST CRT randomized trial in patients with New York Heart Association (NYHA) III–IV class, QRS ≥ 120 ms, ejection fraction ≤ 35%, and mechanical dyssynchrony was analysed. Ninety-seven subjects who survived 6 months after implantation of CRT-defibrillator were classified as responders or non-responders depending on 15 criteria used in most of the previous trials. Blindly adjudicated data on major adverse cardiac events (MACEs) within 1 year after classification were used to calculate the predictive value of response criteria. After adjustment for baseline confounding variables only eight criteria were significantly predictive for future MACEs. Sensitivity and specificity ranged substantially for clinical (32–94% and 26–63%) and echocardiographic criteria (40–93% and 22–70%, respectively). The most powerful clinical predictor was a NYHA class reduction ≥ 1 [adjusted relative risk (RR) 4.41 for non-responders; 95% confidence interval (CI) 1.75–11.04, P = 0.002], while the strongest echocardiographic predictor was a reduction in the left ventricular end-systolic index by ≥ 15% (RR 3.49; 95% CI 1.59–7.64, P = 0.002). A combination of these two criteria did not improve the predictive value of a single parameter. Both criteria showed multiple significant interactions with baseline patients’ characteristics.

Conclusion
Only some of the commonly used response criteria predict outcome in patients undergoing CRT. The predictive value varies substantially across different criteria, with a higher sensitivity observed for the clinical parameters and a higher specificity observed for echocardiographic parameters. Combining various criteria adds little to their prognostic value. The predictive accuracy of various criteria can be different in various subgroups due to multiple interactions with baseline characteristics.

ClinicalTrials.Gov Identifier
NCT00814840.

Keywords
Response criteria • Cardiac resynchronization • Pacing • Response • Predictors • Randomized trial

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What’s new?
- The most commonly used criteria of response to cardiac resynchronization were studied for their predictive value for future major adverse events. To our knowledge, it is the first attempt to compare the predictive power of multiple parameters currently used to assess the efficacy of resynchronization therapy.
- The data on adverse events used in this analysis was derived from a randomized trial with blinded adjudication of all events by independent experts.
- Interactions between the most powerful criteria and patients’ baseline characteristics were analysed to determine whether various criteria may have a different predictive power in different populations.

Introduction
Cardiac resynchronization therapy (CRT) has been proposed as an effective and life-saving method of treatment in a subset of patients with moderate to severe symptoms due to left ventricular systolic dysfunction who present with signs of electrical dyssynchrony. Recent trials have shown, that this form of therapy can be beneficial in heart failure (HF) patients with less severe symptoms, which has led to a broadening of indications for CRT implantation. The effectiveness of CRT has been evaluated in numerous trials; however, these studies used different criteria for a positive response to resynchronization. This contributes to differences encountered while comparing the results of these trials. Moreover, to the best of our knowledge, there has been no data on the predictive value of different response criteria. The aim of the study was to assess the predictive value of various response criteria currently used in patients undergoing CRT.

Methods
Patients
Data on patients included in the Triple-Site Versus Standard Cardiac Resynchronization Therapy Trial (TRUST CRT) was used to validate the response criteria. TRUST CRT was a single-centre, prospective, randomized trial to assess the effectiveness of triple-site pacing vs. standard resynchronization. The trial was conducted in the second biggest tertiary referral cardiology centre in the Upper Silesia—a region of Poland inhabited by a population of over 4.6 million. The study included patients with symptomatic HF in New York Heart Association (NYHA) functional class III–IV despite optimal medical treatment, with sinus rhythm and QRS \( \geq 120 \) ms, left ventricular ejection fraction (LVEF) \( \geq 35\% \), and significant (\( \geq 40\) ms) inter- or intraventricular mechanical dyssynchrony. Patients were randomized in a 1 : 1 ratio to conventional or triple-site resynchronization therapy. Resynchronization systems with implantable defibrillator-cardioverter and automatic monitoring of fluid status InSync Sentry Model 7298 (Medtronic) were implanted in every patient participating in the trial. Standard, commercially available leads were used to pace/sense the atrium, right- and left ventricle. A bipolar Y-connector (Lead Adaptor 2827, Medtronic) was employed to connect two left-ventricular leads in the triple-site group. Atrioventricular and interventricular delays were optimized between the first and the third post-operative day under the echocardiographic guidance to obtain consistent ventricular capture, the most favourable diastolic filling and to reduce septal-to-lateral and anterior-to-inferior wall motion delays. The study protocol and procedural outcomes have been published elsewhere.

The enrolment began in February 2008 and was accomplished in January 2010, when 100 consecutive patients were included in to the trial. Two patients were excluded within 3 months after randomization and were not included into analysis. One patient died within 6 months after inclusion. Data from 97 patients, who survived during the 6 month observation period after randomization, have been used for the purpose of this analysis. The study complies with the Declaration of Helsinki, the research protocol was approved by the locally appointed ethics committee. Written informed consent has been obtained from all study participants.

Response criteria evaluation
Seventeen response criteria extracted by Fornwalt et al. from 26 most cited studies on CRT were analysed. In brief, Web of Science ‘Science Citation Index Expanded’ database was searched for two topics: patient baseline characteristics were analysed to determine whether various criteria may have a different predictive power in different populations.

Table 1 Analysed response criteria

<table>
<thead>
<tr>
<th>Clinical</th>
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</tr>
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<tbody>
<tr>
<td>1. ↓ NYHA ≥ 1 class</td>
<td>9–12</td>
</tr>
<tr>
<td>2. ↓ NYHA ≥ 1 class and ↑ 6MWD ≥ 25%</td>
<td>13</td>
</tr>
<tr>
<td>3. ↑ 6MWD &gt; 10%, no heart transplant, did not die of progressive HF within 6 months</td>
<td>14</td>
</tr>
<tr>
<td>4. ↓ NYHA ≥ 1 class or ↑ VO2 max &gt; 10% or ↑ 6MWD &gt; 10% and alive, no hospitalization for decompensated HF</td>
<td>15</td>
</tr>
<tr>
<td>5. Two of three:</td>
<td></td>
</tr>
<tr>
<td>↓ NYHA ≥ 1 class</td>
<td></td>
</tr>
<tr>
<td>↑ 6MWD &gt; 50 m</td>
<td></td>
</tr>
<tr>
<td>↓ QOL ≥ 15</td>
<td></td>
</tr>
<tr>
<td>6. Clinical composite score improved</td>
<td>17</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Echocardiographic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>7. ↑ LVEF ≥ 5% (absolute)</td>
<td>9,18</td>
</tr>
<tr>
<td>9. ↓ LVEDV ≥ 15%</td>
<td>9</td>
</tr>
<tr>
<td>10. LVEF &lt; 115% of baseline</td>
<td>21</td>
</tr>
<tr>
<td>11. ↓ LVESV &gt; 15%</td>
<td>9,16,17,22,–25</td>
</tr>
<tr>
<td>12. ↓ LVESV &gt; 10% and did not die of progressive HF within 6 months</td>
<td>26,27</td>
</tr>
<tr>
<td>13. ↓ LVESV &gt; 15%</td>
<td>28</td>
</tr>
<tr>
<td>14. ↑ Stroke volume ≥ 15%</td>
<td>20,29,30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combined</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>15. [↑ LVEF ≥ 5% (absolute) or ↑ 6MWD ≥ 30 m] and (↓ NYHA &gt; 1 class or ↓ QOL ≥ 10)]</td>
<td>31</td>
</tr>
</tbody>
</table>

HF, heart failure; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVESVI, LVESV index by body surface area; 6MWD, 6-minute walk distance; NYHA, New York Heart Association functional class; QOL, quality-of-life score; VO2 max, oxygen consumption at peak exercise; ↑, increase; ↓, decrease.

Clinical composite score was considered improved if: (i) patient survived, (ii) without interim hospitalization for decompensated HF, with (iii) ≥1 point decrease in NYHA functional class or; if NYHA was unchanged, shown a >10% increase in peak VO2 in the distance covered during a 6-minute walk, or in both.
Many current response criteria are poor predictors of further outcomes after CRT

‘cardiac resynchronization’ and ‘response.’ The 50 top cited publications were reviewed and after exclusion of four review articles and 20 publications that did not report response criteria, 17 response criteria were considered.8 Two criteria have been excluded as they overlap with at least one another criterion in patients who survived (criterion ‘decrease of NYHA class ≥ 1 and did not die of progressive HF within 6 months’, and ‘decrease of NYHA class ≥ 1 and increase of 6-minute walk distance and did not die of progressive HF within 6 months’). The remaining 15 response criteria were included into analysis. These included six clinical, eight echocardiographic, and one combined criterion (Table 1).

### Data collection and classification of adverse events

Post-baseline assessment visits were scheduled at 1 week, 1, 3, and 6 months, and every 6 months thereafter. To assess the predictive value of subsequent response criteria, data on major adverse cardiac events (MACEs), which occurred within 1 year after classification (the time period between the 6th and 18th months after inclusion), were analysed. Major adverse cardiac events included hospitalization for HF, heart transplantation, or all-cause death. Only the first event was taken into consideration in a particular patient.

Hospitalization for exacerbated HF was defined as at least one overnight hospitalization with increasing symptoms and signs of congestive HF, which were confirmed by objective measures and which initiated treatment with intravenous inotropic drugs or diuretics, increased doses of oral diuretics, or the institution of an additional oral diuretic. Data on any potential adverse events were collected continuously throughout the entire study during scheduled and unscheduled visits, via telephone calls, fax, as well as other media from patients, relatives, witnesses, death certificates, hospital records, outpatient notes, letters, device memory, and all other available sources. All events were assessed by the endpoint and adverse events adjudication board, which consisted of two local blinded investigators. The classification was made based upon the consensus opinion of the board members.

### Statistical analysis

Continuous parameters were expressed as median (range). Categorical variables were presented as numbers and percentages. Comparison between the groups was performed with the χ² test or the Mann–Whitney U test for dichotomous and continuous parameters, as appropriate. Predictive values for every response criterion which separated significantly patients with and without MACE were calculated using a multivariate Cox proportional hazard model after adjustment for baseline NYHA functional class and creatinine values. The results were expressed as relative risks (RRs) with 95% confidence intervals (CIs). The predictive power of combined criteria was determined with the use of receiver-operating curves characteristics using RRs as independent variables. The RRs were calculated for every patient in four Cox regression models, separately for each tested criterion. Two most predictive criteria—clinical and echocardiographic—were combined in two ways. First, every patient has been classified as a responder or non-responder depending on clinical AND echocardiographic criteria (both criteria had to be fulfilled simultaneously to classify patient as responder). Secondly, classification has been repeated for clinical OR echocardiographic criteria (at least one out of the two criteria had to be fulfilled). To compare the predictive power of these two combinations with clinical or echocardiographic criteria alone, pairwise comparisons of the areas under the curve (AUC) were conducted, following the DeLong method. A P value of < 0.05 was considered statistically significant. All statistical analyses were conducted using the Statistica Software (version 6.0, StatSoft Inc.).

### Table 2 Baseline characteristics and medication in patients with and without major adverse events

<table>
<thead>
<tr>
<th></th>
<th>Patients with MACE (n = 27)</th>
<th>Patients without MACE (n = 70)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female n (%)</strong></td>
<td>5 (18)</td>
<td>16 (23)</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>62 (57–69)</td>
<td>61 (55–71)</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>NYHA IV</strong></td>
<td>7 (26)</td>
<td>6 (8.6)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Ischaemic HF</strong></td>
<td>19 (70)</td>
<td>40 (57)</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>QRS (ms)</strong></td>
<td>164 (156–177)</td>
<td>171 (151–185)</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>24 (21–25)</td>
<td>24 (21–26)</td>
<td>0.76</td>
</tr>
<tr>
<td><strong>Creatinine (µmol/L)</strong></td>
<td>96 (84–115)</td>
<td>90.5 (74–108)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>NT pro-BNP (pg/mL)</strong></td>
<td>2804 (857.3–5853)</td>
<td>1441 (849–2449)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>6MWD (m)</strong></td>
<td>284 (221–357)</td>
<td>353 (300–409)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>VO₂ max (mL/kg/min)</strong></td>
<td>11.2 (9.6–13.7)</td>
<td>13.7 (11.5–15.9)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Medication at discharge n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BB</td>
<td>27 (100)</td>
<td>69 (98)</td>
<td>0.53</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>27 (100)</td>
<td>69 (98)</td>
<td>0.53</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>25 (92)</td>
<td>68 (97)</td>
<td>0.31</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>27 (100)</td>
<td>63 (90)</td>
<td>0.09</td>
</tr>
<tr>
<td>Digoxin</td>
<td>7 (26)</td>
<td>3 (4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>2 (7)</td>
<td>4 (6)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Continuous variables are presented as median (range) and compared with non-parametric tests.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BB, beta-block; HF, heart failure; LVEF, left ventricular ejection fraction; 6MWD, 6-minute walk distance. NT pro-BNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association functional class; VO₂ max, oxygen consumption at peak exercise.
Results

Studied population

Median age of the 97 patients who survived 6 months after implantation was 61 years, 78% were men. Median QRS duration was 168 ms and LVEF was 24%. Ischaemic aetiology was responsible for HF in 61% of cases.

Patients with and without major adverse events

Within 1 year, MACE occurred in 27 patients (28%): 12 patients died, 15 were hospitalized for HF; 70 remained free of major cardiovascular events. Patients with MACE had had lower peak oxygen consumption (11.2 vs. 13.7 mL/kg/min, \(P = 0.003\)) and a shorter 6-minute walking distance (284 vs. 353 m, \(P = 0.002\)) at baseline and were taking digoxin more often than subjects without MACEs (26 vs. 4%, \(P = 0.002\)). Furthermore, a trend towards higher baseline NYHA functional class, higher levels of serum creatinine and N-terminal pro B-type natriuretic peptide (NT pro-BNP), and more frequent use of loop-diuretics was observed in the MACE group. The baseline characteristics of patients with and without MACE events are presented in Table 2.

Predictive strength of various response criteria

The sensitivity (range 32–94% and 40–93%) and specificity (range 26–63% and 22–70%, respectively) of clinical and echocardiographic criteria differed considerably among the analysed criteria (Table 3). Only 8 out of 15 analysed criteria differentiated between patients who developed MACE and those who remained free of adverse events (Table 4). After adjustment for baseline confounder, a reduction of NYHA by at least one class was the most predictive criterion and the absence of response was associated with 4.4-fold higher probability of MACE within the next year (adjusted RR 4.41; 95% CI 1.75–11.04, \(P = 0.002\)) (Table 4).

Clinical responders (exhibiting \(\geq 1\) NYHA class reduction) were significantly \((P < 0.05\) for all) more often males (81 vs. 54%), non-smokers (84 vs. 45%), and had higher left ventricular end-systolic (201 vs. 139 mL) and end-diastolic volumes (268 vs. 197 mL) as well as lower LVEF (24 vs. 27%). They also presented with a longer 6-minute walking distance (346 vs. 285 m) and a borderline higher oxygen consumption at peak exercise (VO\(_2\) max) at peak exercise.
baseline (13 vs. 11.7 mL/kg/min, P = 0.07). On the other hand, echocardiographic responders (with >15% reduction in LVEF) had significantly (P < 0.05 for all) less frequently ischaemic aetiology of HF (52 vs. 75%), lower NT pro-BNP (1471 vs. 2788 pg/mL), less advanced mitral incompetence (2 vs. 3 grade), lower VO2 max at baseline (14 vs. 12 mL/kg/min).

**Combination of response criteria**

The combination of the decrease in NYHA class ≥ 1 and in LVESV I by >15%) increased the specificity of to 70%, but decreased its sensitivity to 72%. The presence of either clinical or echocardiographic criterion, increased the sensitivity of the combination to 98%, however, at the cost of specificity which decreased to 15%. The combination of clinical and echocardiographic criteria was not more predictive than the reduction in NYHA class alone (difference in AUC 0.049, P = 0.34) or the reduction in LVESV I > 15% (difference in AUC 0.046, P = 0.11). Similarly, the combination of clinical or echocardiographic criterion was not more predictive than any of the two criteria alone (Figure 2).

**Table 4 Response rates in patients with and without major cardiac adverse events**

<table>
<thead>
<tr>
<th>Response criterion</th>
<th>Response rates</th>
<th>Predictive value&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With MACE (n = 27)</td>
<td>Without MACE (n = 70)</td>
</tr>
<tr>
<td>NYHA ↓ ≥ 1 class</td>
<td>20 (74)</td>
<td>66 (94)</td>
</tr>
<tr>
<td>NYHA ↓ ≥ 1 class and 6MWD ↑ ≥ 25%</td>
<td>9 (37.5)</td>
<td>22 (32)</td>
</tr>
<tr>
<td>6MWD ↑ &gt; 10%, no heart transplant, did not die of progressive HF within 6 months&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15 (62.5)</td>
<td>44 (64.7)</td>
</tr>
<tr>
<td>(↓ NYHA ≥ 1 class or ↑ VO2 max &gt;10% or ↑6MWD &gt;10%) and alive, no hospitalization for HF&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17 (70.8)</td>
<td>64 (94.1)</td>
</tr>
<tr>
<td>Two of three: ↓ NYHA ≥ 1 ↑6MWD ≥ 50 m ↓QOL ≥ 15&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14 (58.3)</td>
<td>53 (77.9)</td>
</tr>
<tr>
<td>Clinical composite score improved&lt;sup&gt;c&lt;/sup&gt;</td>
<td>17 (70.8)</td>
<td>64 (94.1)</td>
</tr>
<tr>
<td>Echocardiographic criteria, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF ↑ ≥ 5%</td>
<td>21 (78)</td>
<td>59 (84)</td>
</tr>
<tr>
<td>LVEF ↑ ≥ 15%</td>
<td>17 (63)</td>
<td>55 (78.6)</td>
</tr>
<tr>
<td>LVEF ↓ &gt; 15%</td>
<td>11 (40.7)</td>
<td>52 (74)</td>
</tr>
<tr>
<td>LVEF &lt; 115% of baseline</td>
<td>8 (29.6)</td>
<td>40 (57)</td>
</tr>
<tr>
<td>LVEF ↓ &gt; 15%</td>
<td>21 (77.8)</td>
<td>65 (92.8)</td>
</tr>
<tr>
<td>LVEFSI ↓ &gt; 15%</td>
<td>11 (40.7)</td>
<td>53 (75.7)</td>
</tr>
<tr>
<td>Stroke volume ↑ ≥ 15%</td>
<td>11 (40.7)</td>
<td>52 (76.5)</td>
</tr>
<tr>
<td>Combined criteria, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF ↑ ≥ 5% (absolute) or 6MWD ↑ ≥ 30 m AND NYHA ↓ ≥ 1 class or QOL ↓ ≥ 15&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19 (79.2)</td>
<td>63 (93)</td>
</tr>
</tbody>
</table>

CI, confidence interval; HF, heart failure; LVEDV, left ventricular end-diastolic volume; LVEF, ejection fraction of the left ventricle; LVEFSI, left ventricular end-systolic volume; LVEFSI, LVEFSI index by body surface area; MACE, major adverse cardiac event; NYHA, New York Heart Association functional class; RR, relative risk; VO2 max, oxygen consumption at peak exercise; ↑, increase; ↓, decrease.

<sup>a</sup>Measurements made for 24 patients with MACE and 68 patients without MACE events.

<sup>b</sup>Clinical composite score was considered improved if: (i) patient survived, (ii) without interim hospitalisation for decompensated HF, with (iii) ≥1 point decrease in NYHA functional class or, if NYHA was unchanged, shown a >10% increase in peak VO<sub>2</sub>, in the distance covered during a 6 min walk, or in both.

<sup>c</sup>Calculation made for non-responders vs. responders using multivariate Cox proportional hazard models after adjustment for baseline NYHA functional class and creatinine values. This analysis was performed for 8 variables which separated significantly patients with and without MACE events.

**Subgroup analysis**

The predictive effect of two most powerful criteria was influenced by baseline characteristics of patients (Table 5). The reduction of NYHA class significantly predicted future adverse events in older patients (>61 years), with narrower QRS complexes (≤168 ms) and higher LVEF (>24%). On the contrary, this criterion did not predict MACE in younger CRT recipients, with broad QRS complexes and low EF (Figure 3). The effect of LVEFSI reduction has also been influenced by several baseline parameters, but the interactions were different from those for changes in NYHA class. The reduction in LVEFSI was more predictive in younger patients (RR 0.19, P = 0.007) with broad QRS (RR 0.16, P = 0.007) than in older subjects (RR 0.32, P = 0.03), with narrow ventricular complexes (RR 3.4, P = 0.03). Moreover, this criterion predicted future MACE more powerfully in those with higher LVEF (RR 0.21, P = 0.01) than in those with severely impaired LVEF (RR 0.30, P = 0.02). The reduction in LVEFSI had a greater predictive power in patients with higher (>94 μmol/L) baseline creatinine levels (RR 0.23, P = 0.01) than in those with lower serum creatinine levels (RR 0.29, P = 0.03). The effects of clinical and...
echocardiographic criteria were not significantly modified by the presence of triple-site resynchronization pacemakers.

Discussion

The main findings of our study are that only some of the commonly used response criteria are predictive for MACE that occur within 1 year after evaluation. Moreover, we have shown that the accuracy varies considerably across different criteria, with higher specificity of clinical and higher sensitivity of echocardiographic parameters. Our data indicate also that relatively simple measures—NYHA class and LVESVI—are indeed very powerful predictors of future MACE events. On the other hand, a combination of these parameters adds little to the predictive power, at most increasing specificity at a cost of sensitivity, or vice versa. Moreover, we have found that the effect of various criteria can interfere significantly with baseline characteristics of the patient, with substantial inter-parameter variability of the strength or direction of the interactions.

Many different response criteria have been previously used in CRT clinical trials with significant differences in response rates. The multiplicity of criteria defining success of intervention makes it difficult to compare and interpret the results. In a recent study, patients involved in PROSPECT trial have been used to verify the agreement between the most commonly used response criteria. The results of this study indicate that 99% of patients may have been classified as ‘responders’ according to at least one of the 15 criteria, but concurrently 94% may have been classified as ‘non-responders’ by at least one criterion.8

A uniform consensus on definition of the response to CRT has not yet been established. What is more, there is still a great uncertainty in our understanding of mechanisms and determinants of the response. The most common definition of CRT response is that the patient has fewer symptoms and/or better clinical outcomes with this therapy than without it.32 However, many patients who gained better quality of life due to CRT did not gain additional years of life, while in others better outcomes were not necessarily associated with an increase in ‘well-being’ after CRT.33,34 What complicates the problem even more is that perception (and definition) of the response to CRT may depend on the patient or physician’s point of view. From the patients standpoint, the relief of symptoms and improved quality of life are probably the most important representatives of response to therapy. However, these characteristics are multifactorially influenced and are the most subjective indices of CRT response, which may alter on a day-to-day basis and may even depend on a single additional dose of a loop-diuretic. The physician’s opinion on the efficacy of CRT therapy tends to rely on more objective, quantifiable criteria such as 6-minute walk distance, oxygen consumption, and echocardiographic parameters. This on a doctor’s belief, that an improvement in a single parameter will be an appropriate surrogate of a better outcome. Moreover, this approach usually dichotomizes patients into two categories: ‘responders’ and ‘non-responders’, what can lead to oversimplification, as many patients actually worsen, some remain stable, and only some improve after CRT.17 In addition, the most appropriate cutoff-point which has to be reached to fulfill the response criterion has in fact never been validated for any of the most commonly used criteria (e.g. is the absolute 5% increment in LVEF a ‘better’ predictor than a 15% relative increment?). Recently published data suggest some methods that may be used to validate appropriate cut-off points.35

By assessing the value of echocardiographic ‘surrogate endpoints’ in predicting the ‘hard end-points’ in CRT recipients, our data can provide some further insights into the PROSPECT Trial findings.17 PROSPECT investigators showed that none of the baseline echocardiographic parameters of dyssynchrony can serve as a sensitive, specific, and reproducible predictor of response to CRT. Nevertheless, improvement in some, relatively simple echocardiographic indices due to CRT pacing seems to be a strong predictor of favourable future outcome.

Our study demonstrated that composite response criteria were not prognostically better than single ones and that combination of the two most powerful parameters added little to their predictive characteristics. Composite criteria are commonly used in CRT.
trials due to their ability to combine various unfavourable effects of disease into one, measurable endpoint and thus increasing the statistical power. However, the disadvantage of such combined composite criteria lies in the difficulty of assessing the relative importance of each measure and consequently in uncertainty which parameter should be included. Furthermore, interventions may influence single components in an opposite direction leading to difficulties in the interpretation of their combination.

We have shown that the most powerful response criteria have a different predictive power in different patient subgroups depending on baseline characteristics. Similar relations have been observed previously.\textsuperscript{36,37} It seems that in certain groups of patients changes of only some specific parameters are associated with improved outcomes, while others are not. These findings are very difficult to be interpreted. However, taking as an example the interaction between the effect of NYHA class improvement and age, one can assume that in younger patients HF is the main reason for functional impairment. Therefore, improvement in NYHA class due to CRT reflects primarily the improvement in cardiac function. On the contrary, older patients often suffer from many exercise-limiting comorbidities (chronic pulmonary disease, neuro-muscular, or rheumatologic disorders).

\begin{table}[h]
\centering
\caption{Effect of sex, age, etiology, QRS duration, ejection fraction, creatinine, and pacing mode on prognostic strength of criteria}
\begin{tabular}{lccccccc}
\hline
Response criteria & \multicolumn{6}{c}{\textit{P} for interaction} \\ 
 & Sex & Age & Etiology & Creatinine & QRS & LVEF & CRT mode \\
\hline
\textdagger NYHA $\geq$ 1 class & 0.65 & 0.009 & 0.83 & 0.17 & 0.001 & 0.005 & 0.75 \\
\textdaggerdown LVESVI $>$ 15\% & 0.07 & 0.002 & 0.26 & 0.002 & 0.001 & 0.001 & 0.62 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a}\textit{P} value was calculated for interactions between the effect of particular criterion and gender (female vs. male), etiology (ischaemic vs. non-ischaemic), mode of resynchronization (triple-site vs. conventional), and age, baseline serum creatinine, QRS width, and left ventricular ejection fraction (introduced as continuous variables).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Receiver-operating curves comparing predictive values of the strongest response criteria and their combinations. (A) Comparison of NYHA class decrease alone to NYHA class decrease AND LVESVI reduction. (B) Comparison of LVESVI reduction alone to NYHA class decrease AND LVESVI reduction. (C) Comparison of NYHA class decrease alone to NYHA class decrease OR LVESVI decrease. (D) Comparison of LVESVI reduction alone to NYHA class decrease OR LVESVI reduction. LVESVI, left ventricular end-systolic volume index; NYHA, New York Heart Association; SE, standard error.}
\end{figure}
and it is much harder to expect any significant reduction in NYHA class in the elderly, even if their cardiac function improved as a result of CRT. Therefore, a marked functional improvement in older patients implanted with CRT indicates not only that this patient benefited from pacing, but also suggests the absence of severe comorbidities. Thus, the prognostic effect of improvement in NYHA class may be stronger in older than in younger patients.

Our data indicate that a significant effort is urgently needed to define the most appropriate CRT response criteria. As proposed previously, the ideal criterion should be an easily available, true predictor of disease progression. It ought to be measurable and reproducible in different settings. It must be mechanistically linked to the outcome and should result from a pathophysiological process that can be modified by the intervention. It should undergo a strict process of internal and external validation to confirm its predictive value. Taking into account interactions between prognostic effects of different criteria and patient characteristics, we believe that no single ‘universal’ response criterion exists. This implies rather than ‘globally oriented’, a patient-tailored approach, with optimal criteria developed for specific groups of CRT recipients, should be used. Until such criteria have been developed and validated, true and ‘hard’ endpoints (death, hospitalization) should be used instead of endpoint surrogates.

Figure 3  Kaplan–Meier curves of cumulative survival without MACEs in responders and non-responders depending on baseline characteristics. Criterion of NYHA class reduction > 1 was used to dichotomize patients into responders and non-responders. Median values of age, QRS width and EF were calculated to define the subgroups. Survival free of adverse events in patients aged > 61 years (panel A left) and ≤ 61 years (panel A right), with QRS duration > 168 ms (panel B left) and QRS ≤ 168 ms (panel B right), and EF > 24% (Panel C left) and EF ≤ 24% (panel C right). Solid lines represent survival curves in responders and dotted line in non-responders. NYHA, New York Heart Association; EF, ejection fraction.
In summary, only some of the commonly used response criteria predict outcome in patients undergoing CRT. The predictive power varies substantially across different criteria. Combining various criteria adds little to their prognostic value. The predictive accuracy of various criteria can be different in patient subgroups due to multiple interactions with baseline characteristics.

**Study limitations**

The study sample was relatively small and the observation period was 1 year only. Therefore, our results did not provide data on the predictive characteristics of various criteria in the longer perspective. Our trial was not designed to assess different response criteria, and is based on a group of patients included into the randomized trial. Therefore, the studied population may differ from the population treated with CRT in everyday practice. However, the advantage of such studies is a very meticulous follow-up and reliable data on adverse events. Taking into account aforementioned limitations, our study does not provide a definitive solution of the problem, but should be considered as hypothesis generating and indicating the need for further research.

**Conflict of interest:** O.K., A.S., and R.L. have received consultant fees from Medtronic and Biotronik. B.S. has received consultant fees from Medtronic. All other authors have no conflict of interest to declare.

**References**


**EP CASE EXPRESS**

tunnelling defibrillator leads from the chest to the abdomen for chronic pain

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Chronic pain can be a complication of device implantation. Repositioning to another anatomical location can solve chronic pain.

We describe a novel approach to allow the safe passage of delicate pacemaker or implantable cardioverter defibrillator (ICD) leads and their connectors through the body wall tissues without risk of damage, using a chest drain as a tool.

A pre-pectoral and small sub-mammary crease incision was made, with a second incision in the lower abdominal wall through which a pre-peritoneal ICD pocket was fashioned. To aid tunnelling of the leads a large bore 36 French soft pliable PVC chest drainage catheter (Rocket Medical) was prepared by removing its distal portion and placing the defibrillator leads into its open end. The pre-pectoral incision was then connected to the sub-mammary pocket by blunt dissection with Roberts’ forceps. The chest drain catheter containing the ICD lead was then pulled through to the sub-mammary crease incision. The procedure was repeated, inserting an ICD lead extension into the catheter and pulling this from the sub-mammary crease incision to the abdominal pocket (Figure 1). The extension leads were then connected to the ICD leads in the sub-mammary incision. The extension leads were then connected to the original ICD which was re-implanted in the newly created abdominal pocket and the incisions sutured.

This is a novel, quick, simple, and safe method for tunnelling pacemaker or ICD leads to distant sites. It avoids the risk of damage to delicate leads and connectors. It also avoids extensive tissue dissection, reducing trauma.

The full-length version of this report can be viewed at: http://www.escardio.org/communities/EHRA/publications/ep-case-reports/Documents/tunnelling-defibrillator-leads-for-chronic-pain.pdf

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