The importance of early evaluation after cardiac resynchronization therapy to redefine response: Pooled individual patient analysis from 5 prospective studies

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BACKGROUND Cardiac resynchronization therapy (CRT) reduces mortality and improves outcomes in appropriately selected patients with heart failure (HF); however, response may vary.

OBJECTIVE We sought to correlate 6-month CRT response assessed by clinical composite score (CCS) and left ventricular end-systolic volume index (LVESVi) with longer-term mortality and HF-related hospitalizations.

METHODS Individual patient data from 5 prospective CRT studies—Multicenter InSync Randomized Clinical Evaluation (MIRACLE), Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD), InSync III Marquis, predictors of response to cardiac resynchronization therapy (PROSPECT), and Adaptive CRT—were pooled. Classification of CRT response status using CCS and LVESVi were made at 6 months. Kaplan-Meier analyses were used to assess time to mortality. Cox proportional hazards regression models were used to compute hazard ratios (HRs) for the 3 levels of CRT response: improved, stabilized, and worsened. Adjusted models controlled for baseline factors known to influence both CRT response and mortality. HF-related hospitalization was compared between CRT response categories using incidence rate ratios.

RESULTS Among a total of 1603 patients, 1426 and 1165 were evaluated in the CCS and LVESVi outcome assessments, respectively. Mortality was significantly lower for patients in the improved (CCS: HR 0.22; 95% confidence interval [CI] 0.15–0.31; LVESVi: HR 0.40; 95% CI 0.27–0.60) and stabilized (CCS: HR 0.38; 95% CI 0.24–0.61; LVESVi: HR 0.41; 95% CI 0.25–0.68) groups than in the worsened group for both measures after adjusting for potential confounders.

CONCLUSION Patients with a worsened CRT response status have a high mortality rate and HF-related hospitalizations. Stabilized patients have a more favorable prognosis than do worsened patients and thus should not be considered CRT nonresponders.

KEYWORDS Cardiac resynchronization therapy; Heart failure; Response; Mortality; Remodeling; Heart failure hospitalization; Clinical composite score

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Introduction
Cardiac resynchronization therapy (CRT) is recommended for patients with mild-to-moderate heart failure (HF), reduced ejection fraction (EF), and ventricular electrical dysynchrony as demonstrated by prolonged QRS duration.\(^1,2\) As with most therapies, however, individual patient response traditionally evaluated after 6 months of CRT varies, with up to one-third of those treated categorized as nonresponders.\(^3\) This has traditionally encompassed all patients who do not realize full benefit, including both patients who progress (or worsen) and those who neither improve nor worsen (remain stabilized). For example, when response was defined using the clinical composite score (CCS)\(^4\) to measure clinical response at 6 months, 31% were categorized as not improved (“unchanged” or “worsened”).\(^5\) If structural reverse remodeling cardiac effects, such as left ventricular end-systolic volume index (LVESVi) are considered, the percentage of patients may be higher. However, the clinical course of patients with unchanged response compared with those who worsen is not well understood, so it may not be appropriate to group them together.

Gaining a better appreciation of the correlation between early response and longer-term outcomes could inform patient management strategies and subsequently improve outcomes. Accordingly, we performed an individual patient analysis of 5 large prospective trials to assess the relationship between CRT response 6 months after implantation and outcomes, including mortality and rate of HF-related hospitalizations.

Methods
Patient population
We pooled individual patient data from 5 multicenter prospective studies of CRT that had CCS allocation and echocardiographic evaluation at 6 months postimplantation. These studies included Multicenter InSync Randomized Clinical Evaluation (MIRACLE),\(^6\) Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD),\(^7\) InSync III Marquis,\(^8\) Predictors of response to cardiac resynchronization therapy (PROSPECT),\(^9\) and Adaptive CRT.\(^9\) Details of the trial designs have been published previously, and key characteristics of the trials are summarized in Table 1. All studies were approved by institutional review boards, and all enrolled patients provided written informed consent. The research reported in this article adhered to the human research protection protocol. The included studies had similar inclusion/exclusion criteria. Briefly, these consisted of New York Heart Association (NYHA) functional class III or IV, left ventricular EF ≤ 35%, and QRS duration ≥ 130 ms (>120 ms for Adaptive CRT) while on guideline-directed medical therapy. Patients with permanent atrial tachyarrhythmias were excluded from all trials. Follow-up duration varied by study and was a maximum of 24 months postimplantation. Only those trial participants who received CRT were included in this analysis.

Variables
There were 2 methods to determine CRT response at 6 months: CCS and change in LVESVi. CCS developed by Packer et al\(^4\) categorizes patients as “improved,” “unchanged,” and “worsened” on the basis of mortality, HF-related hospitalization, termination of treatment, including crossover to other study arm for randomized trials, NYHA classification, and patient global assessment.\(^4\) Patients were judged to be worsened if they died, were hospitalized for worsening HF, crossed over to or permanently discontinued double-blind treatment because of worsening HF, or demonstrated worsening in NYHA class or moderate-marked worsening of patient global assessment. Patients were judged to be improved if they had not worsened and demonstrated improvement in NYHA class and/or moderate-marked improvement in patient global assessment. Patients who were not worsened or improved were classified as unchanged, hereafter referred to as stabilized.\(^10\)

Echocardiograms were obtained at baseline and after 6 months of treatment with CRT and were analyzed in echocardiography core laboratories. LVESV was derived from the single plane 4-chamber view using Simpson’s rule. Patients were judged to be improved if they had a decrease of >15% in LVESVi. Patients were classified as stabilized if they had a decrease of 0%–<15% of LVESVi. Patients with any increase of LVESVi (>0%) from baseline to 6 months were classified as worsened. Patients without either baseline or 6-month LVESVi were excluded from the analysis involving LVESVi response.

The primary outcome was mortality for any cause, and the secondary outcome was HF-related hospitalization.

Statistical analysis
Descriptive statistics were performed by determining mean ± SD of continuous variables and proportions of categorical variables to summarize the characteristics of the study population. Time-to-event analyses (including mortality estimates at 12, 18, and 24 months postimplantation) used the Kaplan-Meier method. Cox proportional hazards regression models were used to compute hazard ratios (HRs) for mortality by levels of CRT response. Both unadjusted and covariate-adjusted models are presented. The adjusted models further control for factors at baseline known to influence both CRT response and mortality including age, gender, NYHA, left ventricular EF, QRS duration, etiology of HF, β-blockers, and angiotensin-converting enzyme/angiotensin receptor blocker medication use.

HF-related hospitalizations between 6 and 12 months postimplantation were collected in all 5 studies. HF-related hospitalizations per patient-year were compared between CRT response categories using Poisson regression and reported as incidence rate ratios. This included both univariate models and adjusted models, which controlled for the same covariates of CRT response by which the mortality models were adjusted.
### Table 1  Baseline demographics and characteristics of the study population by included study

| Characteristic                              | MIRACLE<sup>6</sup> (N = 233) | InSync III Marquis<sup>8</sup> (N = 238) | MIRACLE ICD<sup>7</sup> | PROSPECT<sup>5</sup> (N = 467) | Adaptive CRT<sup>9</sup> | Total patients (N = 1603) |
|---------------------------------------------|--------------------------------|------------------------------------------|-------------------------|-----------------------------|-------------------------|---------------------------|
| Patients                                    | NYHA class III–IV, QRS duration ≥ 130 ms, EF ≤ 35% | NYHA class III–IV, QRS duration ≥ 130 ms, EF ≤ 35% | NYHA class III–IV, QRS duration ≥ 130 ms, EF ≤ 35% | NYHA class III–IV, QRS duration ≥ 120 ms, EF ≤ 35% | NYHA class III–IV, QRS duration ≥ 130 ms, EF ≤ 35% | NYHA class III–IV, QRS duration ≥ 130 ms, EF ≤ 35% |
| Randomization                              | 1:1 (CRT-P vs VDI-30)         | 1:1 (CRT optimized vs CRT simultaneous) | 1:1 (CRT-D vs DDI-35)   | Not randomized              | 2:1 (Adaptive CRT vs echo optimization) |               |
| Median follow-up (mo)<sup>†</sup>          | 12                            | 17                                       | 15                      | 21                          | 14                         |               |
| Echocardiographic assessment                | Two-dimensional Doppler wave | Two-dimensional Doppler wave             | Two-dimensional Doppler wave | HF CCS and relative change in LVESV | Four-dimensional Doppler wave |               |
| Primary end point                           | NYHA, the quality-of-life score, and the distance walked in 6 min | HF CCS                     | NYHA, the quality-of-life score, and the distance walked in 6 min | CCS                        |                           |               |
| Age (y)                                     | 64.1 ± 10.7                   | 66.8 ± 10.4                              | 66.6 ± 11.3             | 67.5 ± 11.2                 | 65.7 ± 10.7               | 66.2 ± 10.9              |
| Male                                        | 160 (68.7)                    | 186 (78.2)                               | 142 (75.9)              | 331 (70.9)                  | 330 (69.0)                | 1149 (71.7)              |
| HF characteristics                          |                               |                                          |                         |                             |                          |                           |
| NYHA class III                              | 211 (90.6)                    | 225 (94.5)                               | 165 (88.2)              | 449 (96.1)                  | 453 (94.8)                | 1503 (93.8)              |
| NYHA class IV                               | 22 (9.4)                      | 13 (5.5)                                 | 22 (11.8)               | 18 (3.9)                    | 19 (4.0)                  | 94 (5.9)                 |
| Ventricular arrhythmia                      | 23 (9.9)                      | 170 (71.4)                               | 88 (47.1)               | 191 (40.9)                  | 194 (40.6)                | 666 (41.5)               |
| Ischemic cardiomyopathy                     | 118 (50.6)                    | 186 (78.2)                               | 119 (63.6)              | 251 (53.7)                  | 224 (46.9)                | 898 (56.0)               |
| LBBB                                        | 194 (83.3)                    | 141 (59.2)                               | 142 (75.9)              | 337 (72.2)                  | 368 (77.0)                | 1182 (73.7)              |
| RBBB                                        | 28.4 ± 6.6                    | 28.7 ± 5.5                               | 27.8 ± 6.1              | 28.0 ± 5.5                  | 29.4 ± 6.3                | 28.6 ± 6.0               |
| Body surface area (m<sup>2</sup>)           | 1.93 ± 0.25                   | 2.00 ± 0.22                              | 1.97 ± 0.28             | 1.93 ± 0.25                 | 1.99 ± 0.25               | 1.96 ± 0.25              |
| Baseline LVEF (%)                           | 23.9 ± 6.8                    | 25.0 ± 5.9                               | 24.2 ± 6.5              | 28.9 ± 9.1                  | 24.8 ± 6.6                | 25.6 ± 7.4               |
| LVESVI (mL/m<sup>2</sup>) at baseline       | 123.6 ± 52.7                  | 113.1 ± 36.4                             | 129.3 ± 51.4            | 87.9 ± 43.9                 | 74.6 ± 30.4               | 96.7 ± 46.1              |
| QRS duration at baseline (ms)               | 167.4 ± 20.5                  | 155.9 ± 20.9                             | 165.5 ± 21.9            | 158.2 ± 26.7                | 154.8 ± 21.1              | 159.0 ± 23.3             |
| Baseline medications                        |                               |                                          |                         |                             |                          |                           |
| ACE inhibitor or ARB                        | 215 (92.3)                    | 214 (89.9)                               | 173 (92.5)              | 391 (83.7)                  | 417 (87.2)                | 1410 (88.0)              |
| β-Blocker                                   | 144 (61.8)                    | 213 (89.5)                               | 116 (62.0)              | 425 (91.0)                  | 435 (91.0)                | 1333 (83.2)              |

Values are presented as mean ± SD or n (%) unless specified otherwise.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCS = clinical composite score; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; EF = ejection fraction; HF = heart failure; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; NYHA = New York Heart Association; RBBB = right bundle branch block; MIRACLE = Multicenter InSync Randomized Clinical Evaluation; MIRACLE ICD = Multicenter InSync ICD Randomized Clinical Evaluation; PROSPECT = Predictors of response to cardiac resynchronization therapy.

*The original MIRACLE ICD trial included patients with NYHA class II–IV, but this analysis includes only those with NYHA class III or IV.

†The follow-up times are from implant to exit/death of the subjects included in this analysis (assigned to CRT or NYHA class III or IV).
Survival curves and HF-related hospitalization rate plots by CRT response categories were created using the R statistical software platform, version 3.4.3 (R Project for Statistical Computing, Vienna, Austria). All other statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). The statistical significance was based on the P value less than .05.

Results

Patient demographics and baseline characteristics
There were 1603 patients assigned to CRT therapy included in the response assessment who were followed up for a mean of 14.8 months (range 0–31 months after implant). Table 1 presents demographics and characteristics of the study population at baseline stratified by trials. The patients were, on average, in their mid-60s, and most often were males. Most had left bundle branch block, which was more common in the trials that had a higher proportion of nonischemic HF etiology.

CRT response

CCS
The distribution of patients across the CCS categories 6 months post-CRT implantation was 1087 (67.8%) improved, 237 (14.8%) stabilized, and 279 (17.4%) worsened. Baseline patient characteristics by CCS category are presented in Online Supplemental Table S1. Worsened patients were more likely to have NYHA class IV and right bundle branch block (RBBB) at baseline and less likely to be taking angiotensin-converting enzyme/angiotensin receptor blocker or β-blockers. Improved patients were more likely to have LBBB and less likely to have RBBB, ventricular arrhythmia, and ischemic cardiomyopathy. Stabilized patients were more likely to have NYHA class III, ischemic etiology, and higher body mass index/body surface area and less likely to have LBBB.

Of the 279 patients in the worsened group, 59 patients (21.1%) died within the first 6 months of implantation and were excluded from the outcome assessment. Of the remaining patients, 167 (59.9%) were classified as such because of 1 (or more) HF-related hospitalization during the initial 6-month period post-CRT device implantation, 11 (3.9%) were allocated to worsened because of study exit or crossover due to worsening HF, 18 (6.4%) because of worsening NYHA class, and 24 (8.6%) because of worsening patient global assessment. In the improved group, all of whom, by definition, were still alive at 6 months and had not experienced HF-related hospitalization, 965 of 1087 patients (88.8%) were classified improved because of improved NYHA class status. The remaining 122 patients (11.2%) were improved because of a better patient global assessment. Further details on reasons for patient classification by included study are provided in Online Supplemental Table S2.

LVESVi
Of the 1603 patients included, 1165 (72.7%) had adequate echocardiograms for LVESVi measurements both at baseline and at 6 months follow-up. Of these subjects, 538 (46.2%) were improved, 251 (21.5%) were stabilized, and 376 (32.3%) were worsened. The clinical characteristics of patients assessed by LVESVi are presented in Online Supplemental Table S3. Worsened patients were more likely to have ischemic etiology, RBBB, lower baseline LVESVi, and smaller QRS duration. Improved patients were more likely to have LBBB and less likely to have ventricular arrhythmias or ischemic etiology at baseline. Stabilized patients were more likely to be male and had higher baseline LVESVi.

Clinical outcome assessment cohort
Of the 1603 patients, 59 (3.68%) patients died before the 6-month visit and an additional 118 (7.36%) patients exited the study before the 6-month visit, leaving 1426 (88.96%) patients for outcome assessment based on 6-month CCS (Figure 1). In 261 patients, adequate echocardiograms for LVESVi measurements at either baseline or the 6-month visit were missing, leaving 1165 patients for outcome assessment based on 6-month LVESVi. In these 1165 patients, CRT response classifications of patients at 6 months by CCS and LVESVi measurements showed modest, but still statistically significant, agreement. The Spearman rank correlation between the 2 classification schemes was 0.102 (P = .0005).

Mortality
The estimated mortality rates at 24 months were highest in the worsened group for both measures (CCS: 30.5% vs 20.2% for stabilized and 10.1% for improved; LVESVi: 18.3% vs 14.1% for stabilized and 9.7% for improved).
Estimated mortality rates at various time points (12, 18, and 24 months) are presented in Table 2. The unadjusted mortality rates were lower in improved and stabilized groups than those in the worsened group for both response measures across time ($P < .0001$ and $P = .0005$ for CCS and LVESVi, respectively). Survival curves by the 2 CRT response measures are presented in Figures 2A and 2B, which demonstrate that the curves separate early and continue to diverge over the course of follow-up.

Table 3 presents unadjusted and multivariate adjusted mortality hazard rates by CCS and LVESVi response. Multivariate modeling found that improved and stabilized CCS statuses relative to worsened predicted reduced mortality (improved vs worsened: unadjusted HR 0.24; 95% confidence interval [CI] 0.16–0.37; $P < .0001$; stabilized vs worsened: unadjusted HR 0.43; 95% CI 0.26–0.73; $P = .003$). Improved vs stabilized CCS also predicted reduced mortality at 24 months (unadjusted HR 0.56; 95% CI 0.34–0.91; $P = .011$). Similar findings were observed after adjusting for covariates.

Similarly, improved and stabilized LVESVi statuses predicted reduced mortality (improved vs worsened: unadjusted HR 0.42; 95% CI 0.27–0.66; $P = .0002$); stabilized vs worsened: unadjusted HR 0.58; 95% CI 0.34–0.98; $P = .042$). In contrast, improved vs stabilized LVESVi status did not predict reduced mortality (HR 0.73; 95% CI 0.41–1.29; $P = .27$). After adjusting for covariates, stabilized vs worsened LVESVi no longer predicted reduced mortality across 24 months. The 261 patients with missing LVESVi status were not significantly different from other groups in terms of baseline characteristics (Online Supplemental Table S3).

HF-related hospitalization

The annual adjusted HF-related hospitalization rates based on 6-month CCS were 0.19 (95% CI 0.15–0.25) per subject-year for the improved group, 0.39 (95% CI 0.27–0.57) for the stabilized group, and 1.06 (95% CI 0.85–1.33) for the worsened group (Figure 3). Slightly different rates were found when 6-month outcomes were stratified by LVESVi, although the overall pattern of reduced admits for the improved and stabilized groups relative to the worsened group remained the same: 0.20 (95% CI 0.15–0.28) HF admits per subject-year for the improved group, 0.23 (95% CI 0.15–0.36) for the stabilized group, and 0.62 (95% CI 0.50–0.77) for the worsened group. Table 4 presents the unadjusted and adjusted annualized incidence rates of HF-related hospitalization by CCS and LVESVi response status. Overall, patients classified as improved or stabilized had a much lower risk of HF-related hospitalizations than did those classified as worsened.

Discussion

The main finding of this study is that a formal assessment of CRT response at 6 months stratifies patients’ longer-term risk that should inform allocation of clinical resources. Specifically, patients with worsening within 6 months of CRT identifies a group of patients with extremely poor outcomes. Importantly, the clinical course of the stabilized group (neither worsened nor improved) tracks closely with the improved group; thus, the definition of response should be refined to reflect this observation. These data should form the basis for a protocolized approach to CRT follow-up in which CRT response is assessed routinely at 6 months.

It has been established that HF hospitalization confers a 1-year mortality of $\sim 30%$. We found, in our study, 60% of the worsened group (on the basis of CCS) were classified as such because of HF-related hospitalization; additionally, 21% of patients in the worsened group died before 6 months and were excluded from the clinical outcome analysis. Therefore, it should follow that the worsened group will have a poor prognosis. However, further identification and clarification of high risk should raise the urgency of closer assessment and management. While prior reports have demonstrated the feasibility of systematic multidisciplinary methods of intensification of care after CRT implantation, a recent report from the ADVANCE CRT registry showed that intensification of resources for site-defined “nonresponders” remained minimal. Specifically, 44% of site-defined nonresponders received no additional treatment and the frequency and duration of hospitalizations and death was much higher for nonresponders than for responders. Advancements in mechanical support for severe systolic HF
as well as increasing numbers of heart transplants\textsuperscript{17} and left ventricular assist devices mandate that viable high-risk patients be identified and assessed earlier. Short of advanced therapies, there are earlier interventions that should be evaluated in such patients, including medical adjustments, implantable hemodynamic monitors, and CRT optimization.

Conversely, in patients who have an improved CCS, clinical resources could be reduced and perhaps patients may be discharged from HF programs back to clinical cardiologists’ care. Follow-up care could be less frequent, and some replaced by telemanagement. Our study corroborates this finding and shows that patients with an improved CCS had an 82\% lower incidence rate for HF-related hospitalizations than did those classified as worsened.

Those patients with neither an improved nor a worsened CCS, previously termed “unchanged,” and traditionally categorized with the nonresponder group, should be labeled as “stabilized.” These would be patients who are alive at 6 months, without HF-related hospitalization, but without improvement in NYHA class or global patient assessment. HF is a progressive disease, and stable clinical status should be interpreted as a favorable impact of CRT. In support is our observation that these stabilized patients had a 63\% reduction in the incidence of HF-related hospitalizations than did those

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure2.png}
\caption{A: Mortality curve by CCS for subjects studied at least 6 months post-CRT device implantation. B: Mortality curve by LVESVi response class for subjects studied at least 6 months post-CRT device implantation. CCS = clinical composite score; CRT = cardiac resynchronization therapy; LVESVi = left ventricular end-systolic volume index.}
\end{figure}
classified as worsened. In addition, 1-year survival for the stabilized group was similar to the improved group, although longer-term outcomes appear to be somewhere in between improved and worsened. Therefore, management of these patients will need to be individualized.

Various criteria have been used to define response to CRT in the literature. Echocardiographic response has typically been assessed by LVESVi reduction and clinical response by CCS categorization. However, agreement between the 2 measures for determining improved response has been reported to be only modest. CCS, as a combination of clinical factors, is more readily measured, with lower cost, less technical and interpretive expertise, and likely greater reproducibility. For the patient, the relative value of a favorable clinical response may also be greater than an echocardiographic volume change. As seen in our study, different rates of response to CRT have been reported when the 2 definitions of response are used within the same population with less extent of response for LVESVi. It is observed that 1087 of 1603 (67.8%) were classified as improved on the basis of CCS while only 568 of 1229 (46.2%) were considered as improved on the basis of LVESVi. This might be because echocardiographic response was evaluated by using a continuous variable. Patients might have a small percentage of increase in LVESVi and/or their baseline LVESVi values were relatively small, but these patients may still have subjective improvements in NYHA class or patient global assessment. In addition, the study cohort included a large percentage of patients with ischemic cardiomyopathy, which has previously been shown to impact reverse remodeling and which in CRT studies has been linked to smaller baseline LVESVi and QRS duration. Specifically, patients with ischemic cardiomyopathy have demonstrated reduced capacities for reverse

### Table 3
Unadjusted and multivariate adjusted mortality hazard rates by various CRT response measures

| Variable                      | CCS                  |          |                   |                   |                   | LVESVi              |          |                   |                   |                   |
|-------------------------------|----------------------|----------|-------------------|-------------------|-------------------|---------------------|----------|-------------------|-------------------|-------------------|
|                               | Unadjusted           | Adjusted | Unadjusted        | Adjusted          |                   | Unadjusted          | Adjusted |                   |                   |                   |
| Improved vs stabilized        | 0.53 (0.33–0.87)     | 0.55     | (0.33–0.93)       | 0.73 (0.41–1.29)  | 0.77 (0.43–1.38)  |                     |          |                   |                   |                   |
| Improved vs worsened          | 0.24 (0.16–0.36)     | 0.25     | (0.16–0.37)       | 0.42 (0.27–0.66)  | 0.46 (0.29–0.73)  |                     |          |                   |                   |                   |
| Stabilized vs worsened        | 0.45 (0.27–0.76)     | 0.45     | (0.26–0.77)       | 0.58 (0.34–0.98)  | 0.60 (0.35–1.02)  |                     |          |                   |                   |                   |
| Gender: female vs male        | 0.79 (0.50–1.23)     |          | 0.79 (0.50–1.23)  | 0.85 (0.54–1.33)  |                   |                     |          |                   |                   |                   |
| NYHA class IV                 | 1.20 (0.55–2.58)     |          | 1.20 (0.55–2.58)  | 1.14 (0.52–2.46)  |                   |                     |          |                   |                   |                   |
| LVEF at baseline              | 0.98 (0.95–1.01)     |          | 0.98 (0.95–1.01)  | 0.98 (0.95–1.01)  |                   |                     |          |                   |                   |                   |
| Age (per year)                | 1.03 (1.01–1.05)     |          | 1.03 (1.01–1.05)  | 1.03 (1.01–1.05)  |                   |                     |          |                   |                   |                   |
| Ischemic cardiomyopathy       | 1.00 (0.66–1.49)     |          | 1.00 (0.66–1.49)  | 1.05 (0.70–1.57)  |                   |                     |          |                   |                   |                   |
| β-Blockers                    | 0.72 (0.46–1.14)     |          | 0.72 (0.46–1.14)  | 0.72 (0.46–1.13)  |                   |                     |          |                   |                   |                   |
| ACE inhibitors/ARBs           | 0.64 (0.40–1.02)     |          | 0.64 (0.40–1.02)  | 0.63 (0.40–1.02)  |                   |                     |          |                   |                   |                   |
| Baseline QRS duration         | 0.99 (0.99–1.00)     |          | 0.99 (0.99–1.00)  | 1.00 (0.99–1.00)  |                   |                     |          |                   |                   |                   |

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCS = clinical composite score; CRT = cardiac resynchronization therapy; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index; NYHA = New York Heart Association.

Figure 3  HF-related hospitalizations per patient-year by CCS and LVESVi response class. CCS = clinical composite score; HF = heart failure; LVESVi = left ventricular end-systolic volume index.
remodeling; however, their propensity for reduced mortality and HF hospitalizations with CRT is similar to that of patients with nonischemic cardiomyopathy.\textsuperscript{19,20}

Although CCS and LVESVi may differ in terms of CRT response rates, the overall impact of CRT response on health outcomes are similar. Both measures show that improved and stabilized patients have reduced mortality relative to worsened patients. Significant reductions in HF-related hospitalizations were also observed for improved and stabilized patients relative to worsened patients for both CRT response measures. Thus, stabilized portends a better clinical course than worsened and should not be considered nonresponse to CRT. Figure 4 further establishes the fact that the broad classification of CRT outcomes as \textit{response or nonresponse} underestimates the clinical benefit of CRT. When the clinical benefits of HF stabilization such as reduced HF-related hospitalization and mortality are acknowledged, we realize that between 14.8\% and 21.5\% more patients derived clinical benefit from CRT than when CRT outcomes were reported as response vs nonresponse. Our findings build on those recently reported in a different cohort of patients from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction trial. This was a study of mild HF that demonstrated that stabilized patients have a prognosis similar to improved patients but much better than worsened patients.\textsuperscript{21} Collectively, these data support the notion that the

\begin{table}
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\begin{tabular}{lllll}
\hline
\textbf{Variable} & \multicolumn{2}{c}{\textbf{CCS}} & \multicolumn{2}{c}{\textbf{LVESVi}} \\
& \textbf{Unadjusted} & \textbf{Adjusted} & \textbf{Unadjusted} & \textbf{Adjusted} \\
\hline
Improved vs stabilized & 0.50 (0.32–0.79) & 0.56 (0.35–0.91) & 0.88 (0.51–1.52) & 0.97 (0.56–1.69) \\
Improved vs worsened & 0.18 (0.13–0.26) & 0.22 (0.15–0.31) & 0.33 (0.22–0.49) & 0.40 (0.27–0.60) \\
Stabilized vs worsened & 0.37 (0.24–0.57) & 0.38 (0.24–0.61) & 0.37 (0.23–0.61) & 0.41 (0.25–0.68) \\
\hline
\end{tabular}
\caption{Unadjusted and multivariate adjusted incidence rate ratios of HF-related hospitalization rates at 12 mo by various CRT response measures}
\end{table}

\textit{CCS} = clinical composite score; \textit{CRT} = cardiac resynchronization therapy; \textit{HF} = heart failure; \textit{LVESVi} = left ventricular end-systolic volume index.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4}
\caption{Proposed and historic classification of CRT response by CCS and LVESVi for subjects studied at least 6 months post-CRT device implantation. CCS = clinical composite score; CRT = cardiac resynchronization therapy; LVESVi = left ventricular end-systolic volume index.}
\end{figure}
terms “responder” and “nonresponder” are obsolete and CRT response should instead be reclassified as improved, stabilized, or worsened regardless of the severity of HF with a reduced EF. In addition, both our study and the findings of the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction trial support a systematic clinical evaluation and rigorous follow-up of post-CRT implant patients.

Limitations
There are several limitations to consider when interpreting the results of this analysis. Although our study population comprised those of 5 prospective trials, 4 of the trials were performed over a decade ago and CRT technology as well as guideline indicated HF medication has since evolved, which may improve outcomes. However, the findings of this pooled analysis are important to inform future clinical trial design and management. Patients in this analysis had advanced HF (mostly NYHA class III); thus, the findings may not be applicable to other patient populations. LVESVi data either at baseline or at the 6-month visit were missing for 23% of the patient population. However, even an inability to attain an LVESVi response class between baseline and 6 months carries some prognostic value toward patient outcomes up to 18 months later, with missing LVESVi values at either time point associated with increased mortality. Additionally, HF-related hospitalization data at 1 year were missing from 193 patients in the Adaptive CRT trial; however, this is unlikely to impact the annual HF-related hospitalization rates. Further, HF-related hospitalization estimates reflect some degree of survivorship bias for subjects who died outside the hospital. However, it appears that this effect may be small, as models adjusted for the same covariates that died outside the hospital. However, it appears that this effect may be small, as models adjusted for the same covariates

Conclusion
In this pooled patient-level analysis from 5 prospective trials, patients with an improved or stabilized CRT response status at 6 months have reduced mortality and incidence of HF-related hospitalizations relative to those with a worsened status. Stabilized CRT response status represents a unique response classification and should not be considered nonresponse to CRT. The results of this analysis suggest that earlier identification of patient prognosis can be used to both inform patients and tailor clinical management.

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Appendix

Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2021.11.030.

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