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CLINICAL RESEARCH

Impact of a Novel Adaptive Optimization Algorithm on 30-Day Readmissions

Evidence From the Adaptive CRT Trial

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ABSTRACT

OBJECTIVES This study investigated the impact of the Medtronic AdaptivCRT (aCRT) (Medtronic, Mounds View, Minnesota) algorithm on 30-day readmissions after heart failure (HF) and all-cause index hospitalizations.

BACKGROUND The U.S. Hospital Readmission Reduction Program, which includes a focus on HF, reduces Medicare inpatient payments when readmissions within 30 days of discharge exceed a moving threshold based on national averages and hospital-specific risk adjustments. Internationally, readmissions within 30 days of any discharge may attract reduced or no payment. Recently, cardiac resynchronization therapy (CRT) devices equipped with the aCRT algorithm allowing automated ambulatory device programming were introduced. The Adaptive CRT trial demonstrated the algorithm's safety and comparable outcome against a rigorous echocardiography-based optimization protocol.

METHODS We analyzed data from the Adaptive CRT trial, which randomized patients undergoing CRT defibrillation on a 2:1 basis to aCRT (n = 318) or to CRT with echocardiographic optimization (Echo, n = 160) and followed up these patients for a mean of 20.2 months (range: 0.2 to 31.3 months). Logistic regression with generalized estimating equation methodology was used to compare the proportion of patients hospitalized for HF and for all causes who had a readmission within 30 days.

RESULTS For HF hospitalizations, the 30-day readmission rate was 19.1% (17 of 89) in the aCRT group and 35.7% (15 of 42) in the Echo group (odds ratio: 0.41; 95% confidence interval [CI]: 0.19 to 0.86; p = 0.02). For all-cause hospitalization, the 30-day readmission rate was 14.8% (35 of 237) in the aCRT group compared with 24.8% (39 of 157) in the Echo group (odds ratio: 0.54; 95% CI: 0.31 to 0.94; p = 0.03). The risk of readmission after HF or all-cause index hospitalization with aCRT was also significantly reduced beyond 30 days.

CONCLUSIONS Use of the aCRT algorithm is associated with a significant reduction in the probability of a 30-day readmission after both HF and all-cause hospitalizations. (Adaptive Cardiac Resynchronization Therapy Study [aCRT]; NCT00980057) (J Am Coll Cardiol HF 2015;3:565–72) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

aCRT = AdaptivCRT

AV = atrioventricular

CMS = Centers for Medicare and Medicaid Services

CRT = cardiac resynchronization therapy

Echo = echocardiographic optimization

HF = heart failure

HRRP = Hospital Readmissions Reduction Program

LV = left ventricle

NYHA = New York Heart Association

RV = right ventricle

Cardiac resynchronization therapy (CRT) is an established therapy for patients with heart failure (HF) symptoms, left ventricular (LV) systolic dysfunction, and a wide QRS (1,2). CRT has been shown to improve functional capacity and quality of life (1), reduce mortality and hospitalization (3,4), reverse the cardiac remodeling process (1), and be cost-effective (5–7). However, not all patients respond to CRT (8), resulting in a failure to realize maximal potential reductions in the incidence of HF and repeated hospitalizations.

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In the United States, the introduction of the Affordable Care Act added to the Social Security Act, and the Hospital Readmissions Reduction Program (HRRP) was established (9). This program reduces all Medicare inpatient payments when readmissions within 30 days of discharge from an "index admission" exceed a moving threshold based on national averages and hospital-specific risk adjustments. Inpatient admissions for HF were one of the first hospitalization types identified in the rules of this program as relevant "index admissions." Although the United States and other countries have different modes of implementation (10), reducing early readmissions to the hospital is becoming an international policy priority aimed at reducing costs and improving the quality of health care (11).

The Adaptive CRT clinical trial (12) demonstrated that a novel algorithm for delivering CRT was at least as effective as protocol-driven echocardiographic optimization. The time to first HF admission was found to be similar for aCRT patients and patients who underwent traditional echocardiographic optimization; the initial report that was published did not include the overall number of admissions per patient (HF or otherwise). The AdaptivCRT (aCRT) algorithm (Medtronic, Inc., Mounds View, Minnesota) automatically adjusts atrioventricular (AV) and interventricular delays on the basis of frequent evaluation of the patient's underlying conduction (13). Specifically, the algorithm provides LV-only pacing synchronized to right ventricular (RV) activation when intrinsic AV conduction is normal or biventricular pacing when AV conduction is prolonged.

Whellan et al. (14) studied patients with CRT devices and an HF hospitalization. These investigators reported that risk of readmission within 30 days of the index hospitalization was increased when certain device-derived diagnostic criteria, such as high atrial fibrillation burden with poor rate control, were present 7 days after the index hospitalization. Of note, Martin et al. (15) also have reported a reduction in atrial fibrillation with use of the aCRT algorithm. Despite the high volume of research in the risk of HF hospitalization in general, we are not aware of any other studies that evaluated the risk of readmission within 30 days among patients with a CRT defibrillator. In the present study, we evaluated the impact of the aCRT algorithm on 30-day hospital readmission rate compared with conventional CRT optimized by echocardiography. We examined readmissions after either HF or all-cause index hospitalization.

METHODS

The design and primary results of the Adaptive CRT trial have been previously published (12,13). Briefly, the Adaptive CRT trial was a prospective, multicenter, randomized, double-blind clinical trial comparing aCRT with therapy dynamically adjusted by the algorithm to standard biventricular pacing with AV and interventricular settings optimized through use of a standardized, rigorous, echocardiographic protocol (Echo arm). The trial enrolled patients who did not have permanent atrial tachyarrhythmias and had clinical indications for implantation of a de novo CRT defibrillator system. The clinical indication at the time of enrollment was New York Heart Association (NYHA) functional class III or IV HF symptoms, LV ejection fraction of $<35\%$, and QRS duration of ≥ 120 ms while receiving optimal medical therapy. Primary objectives were met, demonstrating the algorithm's safety and effectiveness of improving patient 6-month response rate at a rate similar to that of the Echo arm.

OUTCOME MEASURES. Data regarding all hospitalizations were collected prospectively during the trial. Readmission within 30 days was assessed by identifying "index hospitalizations" that could fall under the HRRP or other international rules and determining for each one whether any subsequent hospital readmission occurred >1 day and ≤ 30 days after discharge. These readmissions would have been counted toward financial penalties. In alignment with the manner in which the Centers for Medicare and Medicaid Services (CMS) is measuring hospitals in the United States, our analysis specified an index hospitalization as having at least 30 days of patient follow-up after discharge, and no hospitalization was counted as both an index hospitalization and a readmission. Both all-cause and HF-related index hospitalizations were assessed. Hospitalizations for device implants were included only if investigators

considered them to be related to HF. For hospitalizations lasting at least 24 h, relatedness to HF was evaluated by a blinded event adjudication committee, with the remaining hospitalizations evaluated by the study investigator.

STATISTICAL ANALYSIS. Index hospitalizations were the unit of analysis. Because of the aims of our analyses, patients could contribute multiple index hospitalizations and readmissions. All patients included in the initial reporting of the Adaptive CRT Trial (12) were looked at for these analyses. However, some patients did not contribute any events because they were never hospitalized during follow-up. The proportion of index hospitalizations that resulted in a readmission within 30 days were compared between study arms using the generalized estimating equations logistic regression model. This analysis accounted for the fact that the same patient may be hospitalized more than once and that hospitalizations for the same patient may have exhibited correlation in the likelihood of readmission. The within-patient correlation was modeled with a compound symmetry working correlation. The generalized estimating equations logistic regression model was also used for subgroup analysis by assessing the interaction between study arm and subgroup variable. In addition, time to readmission that extended beyond 30 days of follow-up was described with Kaplan-Meier curves, with study exit or death as censoring events, to assess sensitivity to the readmission window. Time from discharge to readmission was compared between arms using a recurrent event proportional hazards regression with a robust sandwich estimator of the covariance to estimate the hazard ratio and 95% confidence interval (CI) while accounting for within-patient correlation. A score test using this proportional hazards model was performed to assess statistical significance. All analyses were performed with SAS software (version 9.2, SAS Institute, Cary, North Carolina).

RESULTS

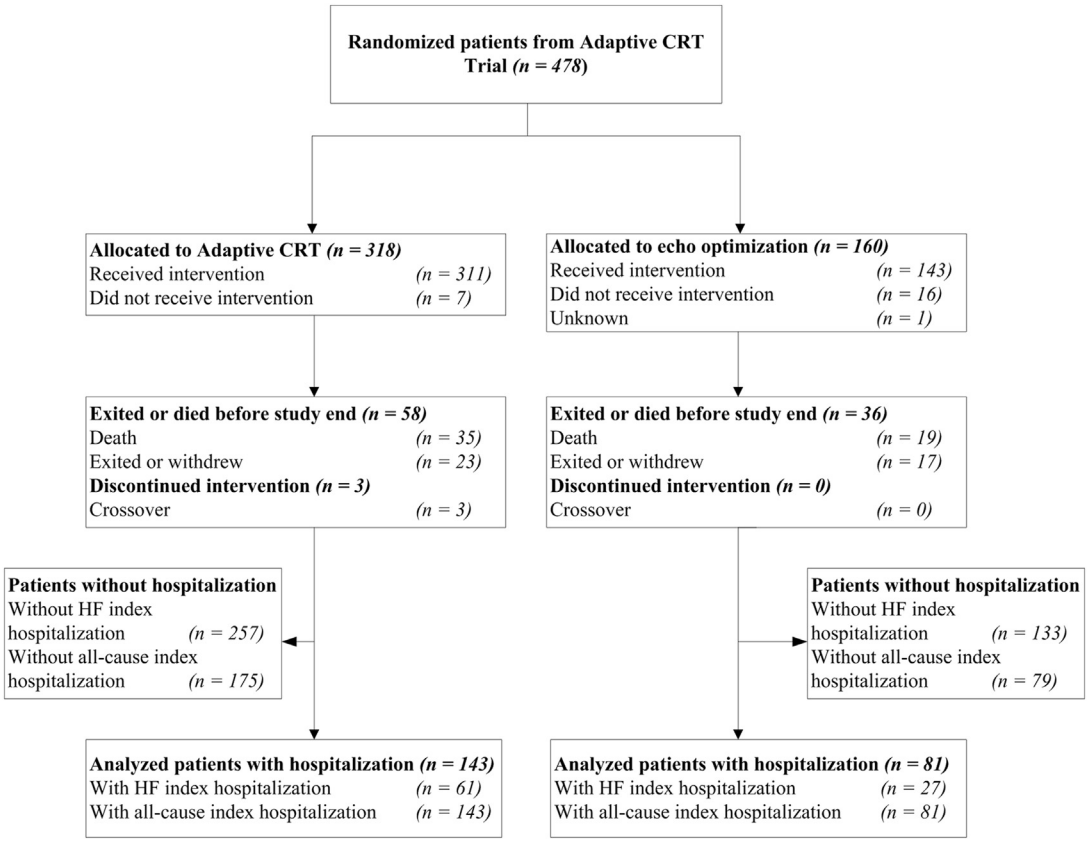
The Adaptive CRT trial randomized 478 patients (318 aCRT and 160 Echo) (Online Table 1). Patients were followed up for an average of 20.2 months (range: 0.2 to 31.3 months). During that period, a total of 570 hospitalizations occurred (337 aCRT and 233 Echo); 488 (290 aCRT and 198 Echo) of those lasted at least 24 h and were adjudicated.

Of all 488 hospitalizations, 84 (56 aCRT and 28 Echo) were not considered index hospitalizations because fewer than 30 days of follow-up were available after the hospitalization. The remaining 486 hospitalizations were either index hospitalizations or readmissions. Patients who had one or more index hospitalizations during follow-up were included in this analysis of 30-day readmissions (**Figure 1**). The proportion of patients with at least one index hospitalization did not differ between arms for all-cause hospitalizations (45.0% aCRT vs. 50.6% Echo; chi-square test $p = 0.24$) or HF-related hospitalizations (19.2% aCRT vs. 16.9% Echo; chi-square test $p = 0.54$). Study baseline characteristics for patients who had an index hospitalization are presented in **Table 1**. Patients were on average 65 ± 12 years of age and 72% male. They had advanced heart failure with 94% NYHA functional class III, LV ejection fraction of 24.3 ± 6.7%, and QRS interval of 153 ± 22 ms. A high percentage of these patients were taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (86%) and beta-blockers (90%). Patients who were hospitalized were similar in the 2 arms, with the exception of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, which was higher in the Echo arm (93.8% vs. 81.8% aCRT; $p = 0.01$).

The rate of readmission within 30 days after an all-cause index hospitalization was 14.8% in the aCRT arm versus 24.8% in the Echo arm. For HF-related index hospitalizations, the aCRT arm had a 30-day readmission rate of 19.1% versus 35.7% in the Echo arm (**Table 2**). The rate was significantly lower in the aCRT arm than in the Echo arm for both all-cause hospitalization (odds ratio [OR]: 0.54; 95% CI: 0.31 to 0.94; $p = 0.03$) and HF-related index hospitalization (OR: 0.41; 95% CI: 0.19 to 0.86; $p = 0.02$). This reduction was robust to the amount of time over which readmission was assessed. Kaplan-Meier curves in **Figure 2** show that the reduction is maintained over up to 1 year of follow-up, with borderline statistical significance for all-cause index hospitalizations ($p = 0.051$) and statistical significance for HF-related index hospitalizations ($p = 0.02$), without any signal of the impact attenuating over the period of follow-up.

Because previously published analyses from the trial examining improvement in Packer Clinical Composite Score and time to first HF hospitalization or death showed significant differences only in patients with normal AV conduction (16), we examined the reduction in 30-day readmissions within the normal and prolonged AV subgroups. An interaction test was used to compare the ORs between the normal and prolonged AV subgroups, examining whether the degree of risk reduction for a 30-day readmission seen in the aCRT arm differs between these subgroups. The interaction tests (**Table 3**) demonstrated

FIGURE 1 Patients Analyzed



Flow diagram of patients analyzed. CRT = cardiac resynchronization therapy; HF =heart failure.

that the ORs were not statistically different between the normal and prolonged AV subgroups either for HF-related (p = 0.25) or for all-cause index hospitalizations (p = 0.15). Similar analyses were performed to assess possible differences in persons with and without renal dysfunction and in different geographic regions (Online Tables 2 and 3). No significant differences in 30-day readmission rates were observed in these subgroups.

DISCUSSION

The aCRT algorithm is intended to safely replace other forms of CRT optimization while leveraging normal physiological conduction, when present. Martin et al. (12) demonstrated that the primary endpoint was reached in the pivotal trial (12). The principal finding of this analysis is a striking and robust relative reduction in both all-cause 30-day readmissions (46%) and HF 30-day readmissions (59%). Other studies have shown the impact of CRT on readmissions over a 6-month period, but this study is the first to demonstrate a reduction in the 30-day readmission rate with CRT and to specifically utilize a novel algorithm to optimize resynchronization therapy. These analyses, which include longer follow-up and are based on outcome measures different from the ones used in previous publications (12), were not expected to produce the same metrics. These findings are timely because the United States and many other countries have defined 30-day readmissions as an important metric related to reimbursement, financial incentives, and quality outcomes.

Acute readmissions have attracted heightened attention lately, not least because of the HRRP wherein CMS reduces all hospital inpatient reimbursement when readmissions within 30 days of discharge for predetermined hospitalizations exceed a threshold based on national averages and hospital-specific risk adjustments. Effective October 1, 2014, CMS expanded this list of predetermined

hospitalizations to include chronic obstructive pulmonary disease and total hip/knee arthroplasties in addition to the previous list of HF, acute myocardial infarction, and pneumonia hospitalizations. The maximum penalty was also increased from 2% to 3%. Many persons have questioned the appropriateness of the rate of readmission within 30 days as a quality metric (17), whereas others have suggested that an increased rate is associated with better outcomes (18). Despite the ongoing discussion, economic incentives are currently in place with the goal of reducing readmissions. Internationally, similar incentives exist. The English National Health Service is not providing reimbursement for any readmission within 30 days of any discharge (10). England also established a quality metric on HF mortality. However, a measure specific to HF readmissions has not been implemented (19). Germany will not pay for any readmission within 30 days of a hospitalization in the same "major diagnostic category" (20). With "cardiology" being such a category, the incentive is broad and perhaps harsh because it forces hospitals to absorb the full cost of additional care that may be needed.

CRT has been demonstrated to reduce morbidity and mortality and has the ability to reduce LV volumes and improve ejection fraction (1–4,21,22). The aCRT algorithm may have the ability to further enhance the benefits of CRT through reduced RV pacing and frequent ambulatory optimization (12,15,16,23). The current trial showed that aCRT is at least as effective as echocardiography-optimized CRT, reduces the need for manual optimization, and may lower all-cause and HF 30-day readmissions. A large global trial has now been launched and aims to determine if the aCRT algorithm can reduce the combined endpoint of all-cause mortality and intervention for HF decompensation compared with standard CRT (24). The 30-day readmissions after HF hospitalization is a secondary endpoint. Further studies will determine if enhanced LV pacing and reduced RV pacing will maximize the benefit of CRT and reduce the small, yet important, group of nonresponders.

Although the present trial does not provide evidence to determine why aCRT is associated with a striking reduction in readmissions, we propose several hypotheses. The lack of difference in index hospitalization rates between the 2 groups, for both all-cause and HF-related index hospitalizations, points to the possibility that aCRT may have a time-dependent, physiological effect. Martin et al. (15) have shown that patients with aCRT have a reduced atrial fibrillation burden, particularly after 12 months of follow-up. In addition, persons with a decrease in left atrial size had the largest reduction in atrial fibrillation (15). These data suggest that LV-only pacing and frequent interval optimization over time is associated with beneficial remodeling and a reduction in atrial fibrillation. Both of these factors likely contribute to the reduction in 30-day readmissions. Generally, a reduced atrial fibrillation burden would result in a greater percentage of time with resynchronization pacing therapy, which has been shown to improve outcomes. Reduced RV pacing should retard ventricular remodeling, annular dilation, tricuspid regurgitation, and right atrial enlargement and hence delay atrial fibrillation. The importance of maximizing the dose of beta-blockers is dogma, and we expect reduced RV pacing to facilitate up-titration of medical therapies. Finally, the algorithm's frequent interval optimization may provide a benefit during increased demand at exercise or over the course of cardiac remodeling or CRT-induced reverse remodeling.

Although it is agreed that reducing readmissions is an important objective, defining the best way to reduce readmissions has been elusive. Ultimately, one might speculate that a disease-modifying therapy would reduce readmissions. A CMS population

TABLE 1 Baseline Patient Characteristics

	aCRT	Echo	p Value
Age, yrs	143 (64.3 ± 12.7)	81 (66.1 ± 10.4)	0.30
LV ejection fraction, %	143 (24.1 ± 6.6)	81 (24.7 ± 6.8)	0.54
LV end systolic volume, ml	135 (145.6 ± 56.2)	72 (157.9 ± 84.8)	0.21
QRS interval, ms	141 (152.7 ± 21.2)	81 (154.4 ± 22.8)	0.57
6-min hall walk distance, m	138 (256.5 ± 136.3)	78 (254.9 ± 132.7)	0.93
Minnesota Living With Heart Failure Score	128 (54.4 ± 22.9)	69 (49.4 ± 23.5)	0.15
Left bundle branch block	143 (71.3)	81 (77.8)	0.29
Male	143 (72.7)	81 (70.4)	0.71
Ischemic cardiomyopathy	143 (49.0)	81 (56.8)	0.26
NYHA functional class III	143 (92.3)	81 (97.5)	0.11
Taking an ACE inhibitor/ARB	143 (81.8)	81 (93.8)	0.01
Taking a beta-blocker	143 (89.5)	81 (90.1)	0.89

Values are n (mean ± SD) or n (%).

ACE = angiotensin-converting enzyme; aCRT = AdaptivCRT; ARB = angiotensin II receptor blocker; Echo = echocardiographic optimization; LV = left ventricular; NYHA = New York Heart Association.

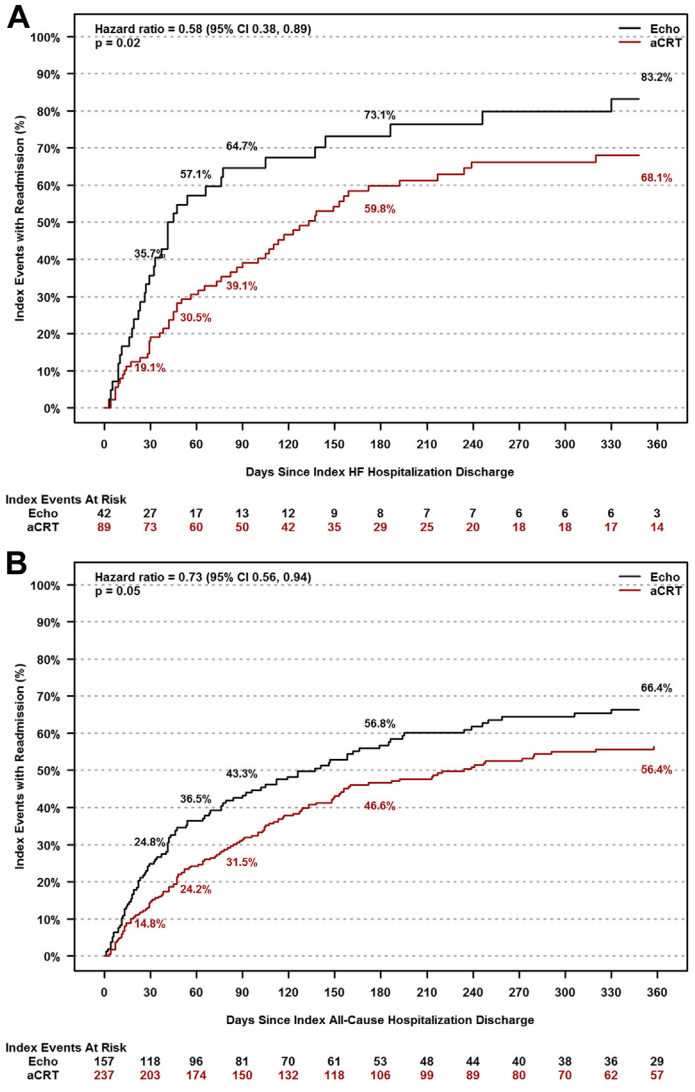
TABLE 2 Hospital Readmissions Within 30 Days After Discharge

	30-Day Readmission Rate			
Index Event Type	aCRT	Echo	OR (95% CI)	p Value
Heart failure	19.1 (17/89)	35.7 (15/42)	0.41 (0.19–0.86)	0.02
All cause	14.8 (35/237)	24.8 (39/157)	0.54 (0.31–0.94)	0.03

Values are % (# with readmission/# index).

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

FIGURE 2 Kaplan-Meier Curves of Hospital Readmissions



Time from heart failure hospitalization to all-cause readmission **(A)**. Time from all-cause hospitalization to all-cause readmission **(B)**. aCRT = AdaptivCRT; Echo = echocardiographic optimization; HF = heart failure.

TABLE 3 Subgroup Analysis of Hospital Readmissions Within 30 Days After Discharge

Index Event Type Subgroup	30-Day Readmission Rate		OR (95% CI)	Interaction p Value
	aCRT	Echo		
Heart failure				0.25
Normal AV	14.3 (4/28)	38.5 (10/26)	0.21 (0.05–0.86)	
Prolonged AV	21.3 (13/61)	31.3 (5/16)	0.62 (0.24–1.62)	
All cause				0.15
Normal AV	10.3 (10/97)	26.5 (22/83)	0.33 (0.14–0.79)	
Prolonged AV	17.9 (25/140)	23.0 (17/74)	0.76 (0.36–1.62)	

Values are % (# with readmission/# index).
AV = atrioventricular; other abbreviations as in Tables 1 and 2.

database study examined 3 areas that might have an impact on readmissions and showed that care transitions might have the greatest impact (25). In a study group of elderly persons with heart failure decades ago, Rich et al. (26) demonstrated that a multidisciplinary team approach to patients with HF would improve outcomes. More recently, various technologies including pressure sensors, thoracic impedance alerts, telephone monitoring, and others have failed to significantly reduce 30-day readmissions (27–29). Abraham et al. (30) have shown that the combination of pulmonary artery pressure monitoring applied to a standardized, goal-directed medical therapy algorithm will significantly reduce HF readmissions at 60 days. By reducing RV pacing and adjusting pacing intervals frequently, the aCRT algorithm may promote structural changes in cardiac anatomy, affecting the natural history of HF, as does CRT and other primary therapies that have an impact on cardiac structure and promote reverse remodeling. This hypothesis is supported by evidence showing a reduction in readmissions.

In summary, the seminal observation of lower 30-day readmissions with aCRT suggests a physiological benefit incremental to CRT related to reduced RV pacing and frequent optimization. Preliminary evidence supports this hypothesis, and the post-market trial comparing aCRT with standard CRT will provide definitive evidence. Today aCRT can provide a safe and effective therapy that will also reduce readmissions and hence overall health care costs. Importantly, with aCRT being automated, it can be expected to have an impact largely independent of human factors.

STUDY LIMITATIONS. The sample size and the numbers of events (readmissions) were relatively small. This trial was a global trial, and significant differences in readmission rates and length of stay based on region and country have been demonstrated in an acute HF trial (31). Indications for readmission were not standardized and were at the discretion of the site investigator; in a way, this situation may actually represent a better portrayal of real-world effects because investigators could act as they wished. CMS readmission rules were not enacted during the study period. The effect observed may be limited to CRT NYHA functional class III/IV indicated patients because NYHA functional class II and recently expanded AV block indicated patients were not included in the trial. Lastly, CMS readmission rules have been slightly modified from year to year, and it is possible that unpredictable future modifications to the rules may have a material impact on these results.

CONCLUSIONS

CRT, a proven therapy for patients with systolic HF, improves survival and reduces HF-related morbidity. The aCRT algorithm has been shown to improve the therapy response rate in select patients, and this novel delivery of therapy is associated with reduced 30-day readmissions in patients with advanced HF. The observation of reduced readmissions with aCRT suggests a physiological benefit related to reduced RV pacing and frequent optimization. Whether the aCRT algorithm provides a meaningful impact to sustain improved patient outcomes warrants further investigation.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Compared with conventional CRT optimized by echocardiography, aCRT was associated with a significant reduction in 30-day readmissions after both HF and all-cause hospitalizations. In select patients with advanced HF and wide QRS, aCRT may be a favorable treatment option compared with conventional CRT because of the observed reduced risk of hospital readmission.

TRANSLATIONAL OUTLOOK: More studies are needed to assess whether the observed reduced readmissions with aCRT provides a meaningful impact to sustain improved patient outcomes.

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KEY WORDS 30-day readmission, cardiac resynchronization therapy, heart failure

APPENDIX For supplemental tables, please see the online version of this article.