Importance of Adjunctive Heart Failure Optimization Immediately After Implantation to Improve Long-Term Outcomes With Cardiac Resynchronization Therapy

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Despite improvement in morbidity and mortality with cardiac resynchronization therapy (CRT), disease progression continues to affect a subset of patients and there is limited effort to identify contributing factors. Our objective was to investigate if a protocol-driven approach incorporated in a management strategy of heart failure immediately after implantation would provide incremental benefits beyond usual care after implantation. We reviewed 114 consecutive patients with CRT implanted from 2005 through 2009 who received usual care after implantation or underwent protocol-driven CRT care after implantation. Preimplantation characteristics in patients receiving usual versus protocol-driven care were similar in left ventricular (LV) dimension (LV internal diastolic diameter 6.2 ± 0.8 vs 6.4 ± 1.0 cm), LV ejection fraction (26 ± 8% vs 25% ± 8%), QRS width, and medication usage. Major adjustments during the protocol-driven approach were uptitration of neurohormonal blockers (64%), echocardiographically guided atrioventricular optimization (50%), heart failure education (42%), arrhythmia management (19%), and LV lead repositioning (7%). Although positive LV remodeling was noted in the 2 groups at 6 months, extent was significantly greater in the protocol-driven approach compared to usual care (change in LV internal diastolic diameter 0.7 ± 0.6 cm vs 0.2 ± 1.2 cm, p = 0.01; change in LV ejection fraction 11 ± 7% vs 7 ± 9%, p = 0.01), which was associated with fewer major adverse events (14% vs 53%, p <0.001). In conclusion, a protocol-driven approach for patients with CRT started immediately after implantation is associated with incremental favorable effects on reverse remodeling and fewer adverse events compared to usual care after implantation. These effects appeared to be driven not only by changes in device settings and arrhythmia management but also by concomitant medication optimization and heart failure education. **(Am J Cardiol 2011;108:409–415)**

Most therapeutic effects of cardiac resynchronization therapy (CRT) have been attributed to device-induced decrease in dyssynchrony. For those who do not demonstrate noticeable improvements immediately after implantation, further optimization of specific device programming, arrhythmia management, and considerations for lead repositioning, if suboptimal, can be beneficial.[1] However, it is often assumed that only those who did not respond over time would benefit from such optimization strategies because the maximal therapeutic effect of CRT should be derived if implantation and device programming are optimal. Factors favorably or adversely affecting CRT efficacy, particularly those in the immediate postimplantation setting, have not been extensively studied. Therefore, the objective of this study was to investigate if a protocol-driven approach incorporated in a management strategy of heart failure immediately after implantation would provide incremental benefits beyond usual care after implantation including changes in exercise and echocardiographic parameters and long-term adverse cardiac events.

Methods

This study included consecutive patients with CRT using an implanted pacemaker or defibrillator under standard clinical indications in a single tertiary cardiac care institution from November 2005 through February 2010. All patients demonstrated stable but advanced heart failure symptoms (New York Heart Association functional class III or IV symptoms) despite receiving optimal medical therapy as tolerated by the patient, decreased left ventricular (LV) ejection fraction (≤35%), and prolonged QRS duration (≥120 ms) at time of implantation. Because of stringent reimbursement criteria in Belgium, CRT using implanted defibrillators was performed only cases of previous episodes of sustained ventricular tachycardia or inducible ventricular

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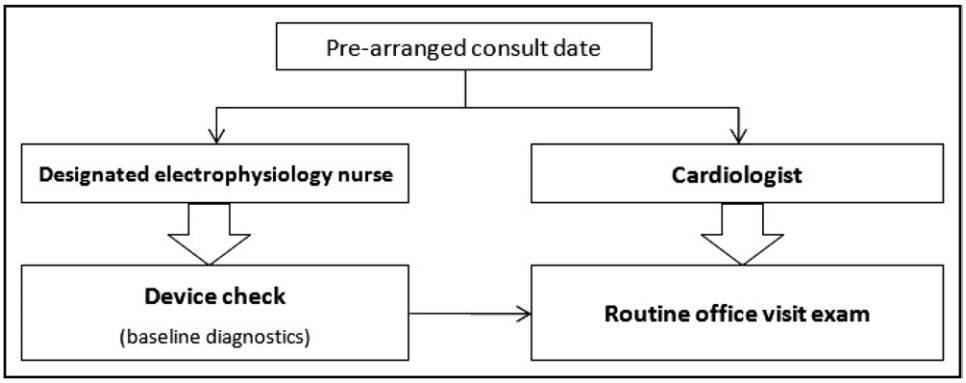

Figure 1. Flow chart presenting usual care after implantation.

arrhythmia. The study complied with the Declaration of Helsinki, the locally appointed ethics committee approved the research protocol, and informed consent was obtained from the subjects.

A protocol-driven CRT optimization protocol was established in August 2008; thus patients were stratified in 2 groups according to CRT implantation before August 2008 ("usual care") versus after August 2008 ("CRT optimization protocol"). Before August 2008 patients received usual care after implantation performed generally by different hospital staffs. In this model, an electrophysiology nurse performed a standard device check. Afterward a patient was seen by a treating cardiologist to assess the patient's current health status and symptoms, often also performing echocardiography (Figure 1). Changes in device settings and heart failure therapy were at the discretion of the treating cardiologist.

A postimplantation stepwise CRT optimization protocol was established as part of a multidisciplinary approach toward postimplantation CRT care incorporated in management program of heart failure in August 2008. In the CRT optimization protocol, number of scheduled clinic visits was similar to that of the usual-care group (6 weeks, 3 and 6 months after implantation). Beyond the standard device check, a more thorough CRT optimization clinic protocol was conducted, which included a wider variety of measurements and prespecified optimization guidelines performed in a designated clinic staffed with physicians and nurses with a broad interest in heart failure and cardiac devices as previously described (Figure 2).[1] In summary, a heart failure nurse recorded an electrocardiogram to assess heart rate, QRS width, and AV/PR intervals. This was performed 2 times with the implanted pacemaker turned on and off to ensure adequate biventricular pacing. Next, an anterior–posterior and lateral chest x-ray was carried out to determine optimal positioning of the right atrial, right ventricular, and LV leads (in basal or midlateral and posterior position). In the meantime, routine laboratory tests were done to detect occult hematologic and metabolic derangements. After these measurements, the designated cardiologist recorded a detailed history on heart failure symptoms, occurrence of arrhythmias, and potential device-related issues, checked for compliance to medication usage and salt/fluid restriction, and completed a full physical cardiovascular examination.

Afterward a comprehensive 2-dimensional echocardiographic examination was performed (Philips Medical Systems, Andover, Massachusetts) with nominal settings of the CRT device. All reported echocardiographic measurements including LV size/function and mitral regurgitation were averaged from ≥3 consecutive cycles as recommended by the American Society of Echocardiography.[2] Then an effort was made to optimize LV diastolic filling when it differed from stage I by altering AV timing using conventional Doppler echocardiography. Optimal AV interval was determined by sampling mitral inflow with pulse-wave Doppler to correspond with the shortest AV interval that dissociated the E and A waves but did not interrupt the end of the A wave.[3–5]

To evaluate a patient's physical fitness and ensure biventricular pacing was persistent even during exercise, a cycloergometric bicycle test with maximum oxygen uptake recording was performed. Based on the findings, a recommendation was proposed to the patient to maximize the potential of CRT. These recommendations were not mutually exclusive because actions could be categorized by repositioning of the LV lead to correct inappropriate lead positioning, changes in device programming for suboptimal device programming (mostly AV timing), or treatment of arrhythmias medically or invasively.

Thorough efforts were taken toward optimization of medical therapy, i.e., uptitration of neurohormonal blockers to guideline-recommended doses, which were often not tolerated before implantation. In addition, adequate heart failure education was provided to familiarize a patient with heart failure risk factors and modifications in lifestyle. Patients were informed through dietary consults about salt-free diets (2 to 3 g/day) and fluid restriction (1 to 1.5 L/day), which often coincided with a progressive decrease in loop diuretic doses. Importantly, all these adjustments were implemented in close collaboration with general practitioners who were informed through telephone contact the day of the patient's clinic visit and provided with the findings and recommendations of the clinic through an on-line letter sent immediately after the CRT clinic visit to ensure optimization of medical therapy was accomplished at home under close supervision.

We prespecified the primary end points for analysis as time to first occurrence of any of the following: all-cause mortality, cardiac transplantation, and/or first readmission

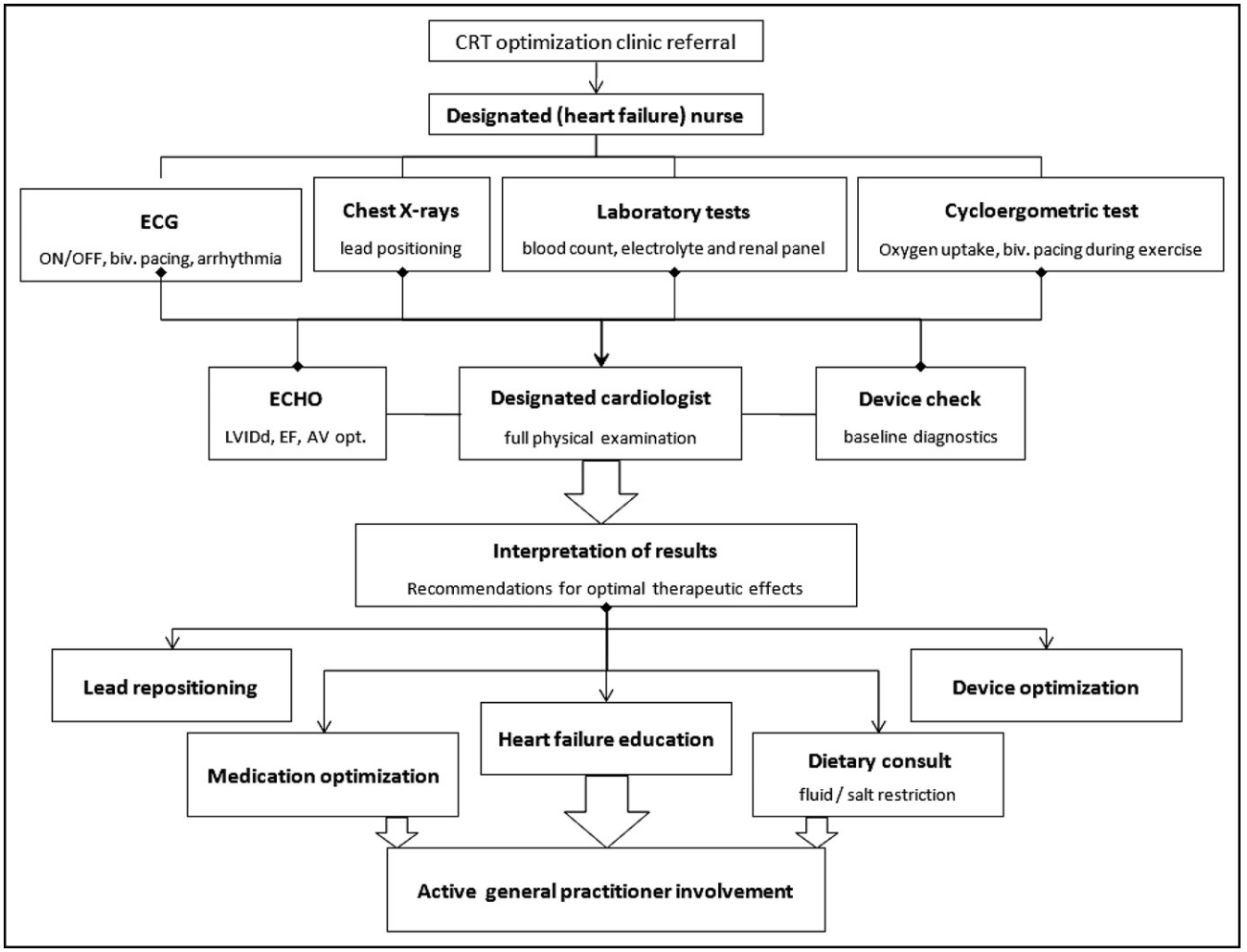

Figure 2. Flow chart presenting protocol-driven postimplantation management in cardiac resynchronization therapy clinic. AV opt. = atrioventricular optimization; biv. = biventricular; ECG = electrocardiography; ECHO = echocardiography; EF = ejection fraction; LVIDd = left ventricular internal diastolic diameter.

for heart failure after implantation. Patients in the usual-care group were followed from implantation to the date of the first visit to the protocol-driven care clinic, whereas patients in the protocol-driven group were followed until April 30, 2010.

Collected data are expressed as mean ± SD for continuous data and as ratio for categorical data. Paired-sample *t* tests were performed for variables between related patient data groups and independent-sample *t* tests were performed for variables between unrelated patient data groups. Statistical significance was set at a 2-tailed probability level with alpha equal to 0.05. Kaplan–Meier survival curves were calculated with combined end points for all patients stratified in 2 groups. Cox proportional hazards regression model was used to determine which variables were related significantly to the different end point during the follow-up period. The authors had full access to the data and take responsibility for the integrity of the data. All authors have read and agreed to the report as written. All statistical analyses were performed using SPSS 17.0 for Windows (SPSS, Inc., Chicago, Illinois).

Results

Preimplantation patient characteristics are presented in Table 1 and were similar in the 2 groups (n = 53 in usual-care group and 61 in protocol-driven group) including degree of LV remodeling and maximum exercise capacity. There was a large and similar proportion of use of neurohormonal blockers. For the CRT optimization group, mean clinic visit duration was 40 minutes with involvement of a designated nurse (±20 minutes) and a cardiologist (±20 minutes).

All patients had a lead implanted in the right atrium, right ventricle, and left ventricle through the coronary sinus (72%) or epicardially (28%). X-rays demonstrated no lead dislodgement but indicated a suboptimal positioning of the LV lead for 8 patients. One patient was scheduled for LV lead repositioning.

Device interrogation was successful in all patients, which was paced mostly in an atrial sensing–ventricular pacing mode. No battery depletion or lead integrity was noted.

Table 1
Baseline demographics

	Total (n = 114)	Usual Care (n = 51)	Protocol-Driven (n = 63)	p Value
Demographics				
Age (years)	71 ± 10	72 ± 10	71 ± 11	NS
Men	64%	55%	73%	0.04
Cardiac resynchronization therapy with defibrillator	51%	52%	48%	NS
Weight (kg)	77 ± 17	76 ± 16	79 ± 17	NS
Body mass index (kg/m^2)	28 ± 5	27 ± 5	28 ± 5	NS
>25	73%	70%	76%	NS
>30	33%	30%	36%	NS
Hypertension (>140/90 mm Hg)	42%	40%	43%	NS
Hyperlipidemia (low-density lipoprotein >110 mg/dl)	33%	28%	37%	NS
Quit smoking	20%	21%	18%	NS
Active smoking	10%	12%	9%	NS
Diabetes mellitus	30%	30%	30%	NS
Atrial fibrillation	42%	38%	44%	NS
Medications				
Aspirin	76%	76%	75%	NS
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers	88%	84%	90%	NS
β Blockers	89%	82%	94%	NS
Spironolactone	58%	39%	73%	0.001
Loop diuretic	75%	84%	67%	0.02
Statin	59%	55%	62%	NS
Hydralazine	9%	2%	14%	0.02
Isosorbide dinitrate	6%	2%	10%	NS
Digoxin	24%	24%	24%	NS
Electrocardiographic data				
Heart rate (beat/min)	72 ± 21	75 ± 19	70 ± 22	NS
PR width (ms)	192 ± 47	192 ± 48	191 ± 44	NS
QRS width (ms)	159 ± 31	155 ± 31	160 ± 31	NS
Cycloergometric data				
Maximum exercise capacity (watts)	89 ± 32	84 ± 22	90 ± 34	NS
Systolic/diastolic blood pressure at rest (mm Hg)	126/74	115/71	127/74	NS
Systolic/diastolic blood pressure during exercise (mm Hg)	151/74	145/67	153/75	NS
Maximum heart rate (beats/min)	112 ± 23	113 ± 18	112 ± 25	NS
Maximum volume (ml/kg/min)	13.9 ± 4.6	12.4 ± 3.2	13.9 ± 4.7	NS
Echocardiographic data				
Left ventricular internal diastolic diameter (cm)	6.3 ± 1	6.2 ± 0.8	6.4 ± 1	NS
Left ventricular ejection fraction (%)	25 ± 8	26 ± 8	25 ± 8	NS
Mitral valve regurgitation (grade >II)	10%	11%	10%	NS
Tricuspid valve regurgitation (grade >II)	3%	2%	3%	NS

Arrhythmias were present in 19% of patients, mostly atrial fibrillation, but in 7% frequent ventricular ectopy was present, leading to <100% biventricular pacing in 19% and <90% in 17% of patients. All arrhythmias were treated accordingly at least to ensure >90% biventricular pacing in 95% instead of 83% of patients.

An additional 50% of patients were found to be programmed with suboptimal AV timing settings. AV timings were always optimized in these patients after an improvement in LV filling. These improvements were confirmed during the next clinic visit, with only 2 patients needing an additional change in their AV timings.

Uptitration in neurohormonal blockers was possible for 64% of patients, although >90% were already receiving angiotensin-converting enzyme inhibitor and β-blocker medication at time of implantation. Interestingly, all these patients were already taking a similar dosage of neurohormonal blockers for >3 months before device implantation and only noted an improved tolerance toward uptitration of these drugs after implantation (Figure 3).

Failure in patient compliance with regard to salt/water restriction and stringent intake of medication was high because 42% patients testified to having poorly followed their daily medication intake and dietary advice. After implementation of heart failure education and dietary consult, in collaboration with general practitioners 22% of patients had a decrease in dosage of loop diuretic (Figure 4).

In addition, 63% patients were obese, 13% of patients had anemia, but only 1 patient had hemoglobin <10 g/dl, which was treated with transfusion or erythropoietin agents.

Starting from August 2008 all patients receiving usual care were also referred to the protocol-driven CRT clinic. Interestingly, clinical, electrophysiologic, and device-related interventions were similar overall compared to patients followed in the protocol-driven clinic immediately after implantation. Indeed, uptitration of neurohormonal

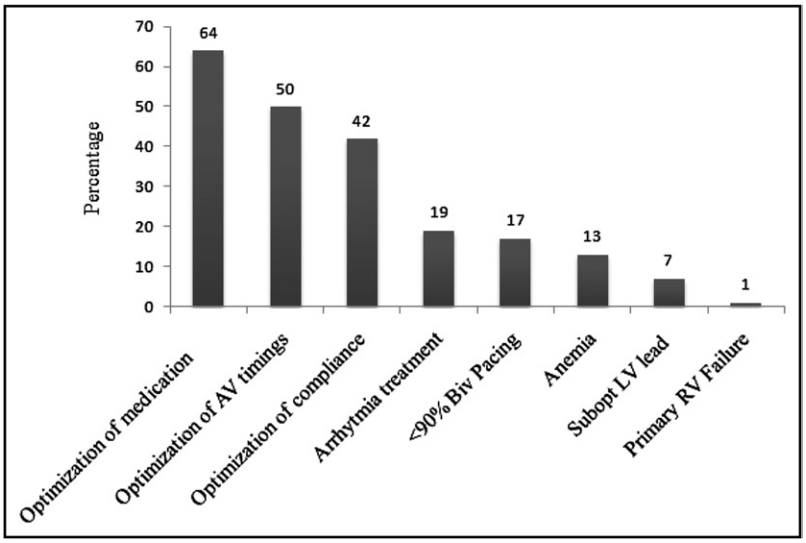

Figure 3. Interventions performed during visit to protocol-driven optimization cardiac resynchronization therapy clinic. RV = right ventricular; Subopt = suboptimal. Other abbreviations as in Figure 2.

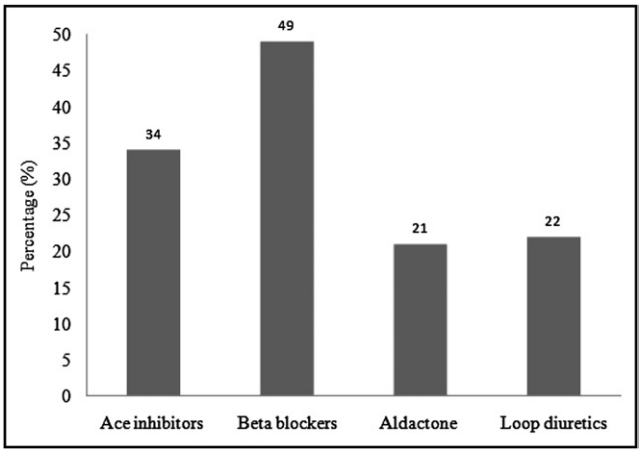

Figure 4. Bar graph presenting percentage of patients whose medication was optimized in the protocol-drive optimization cardiac resynchronization therapy clinic. Ace = angiotensin-converting enzyme.

drugs was possible for 1/2 the patient population, decrease in dosage of loop diuretics for 20% of patients, and 43% of patients confirmed to having poorly maintained their medication and dietary guidelines. In addition, 51% of patients were shown to be paced with suboptimal AV timings and 20% of patients presented with arrhythmias.

Positive remodeling was noted in the 2 groups with regard to LV dimension and LV function. However, extent of positive LV remodeling and improvement in LV ejection fraction were significantly greater in the group receiving a protocol-driven approach from the start (Figure 5). Moreover, as presented in Table 2, improvement in maximum exercise capacity as measured through maximum oxygen consumption was more pronounced for the protocol-driven group. Interestingly, these positive effects did not seem to relate to a greater decrease in dyssynchrony because the decrease in QRS and PR times did not differ between groups.

At the end of the follow-up period (mean follow-up duration 19 ± 11 months for the 2 groups), 36% of patients had

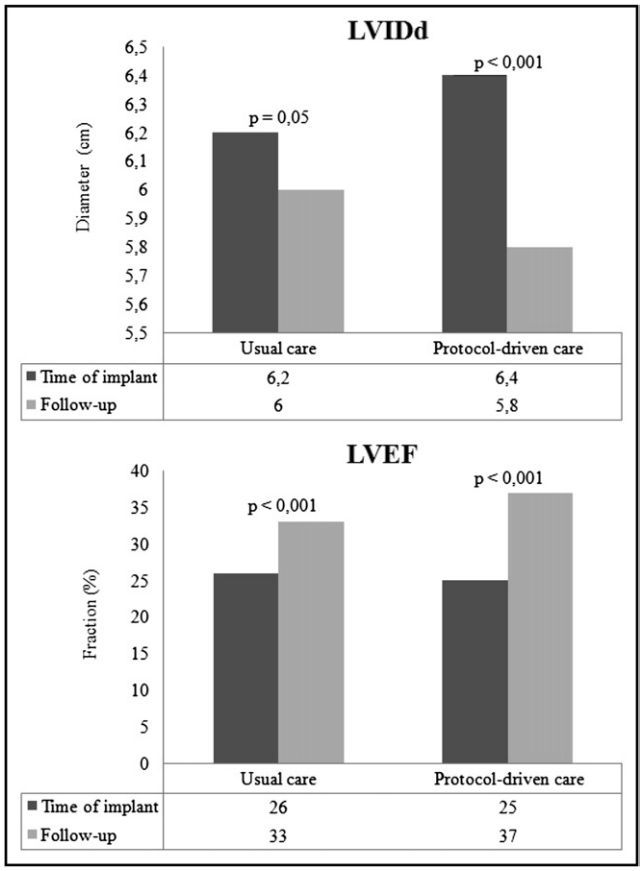

Figure 5. Bar graph for left ventricular internal diameter in diastole (centimeters) and left ventricular ejection fraction (percentage) at time of implantation versus follow-up for the 2 study groups. Abbreviations as in Figure 2.

died, undergone cardiac transplantation, and/or were hospitalized for decompensated heart failure. Although overall mortality/cardiac transplantation was similar for the 2 groups (3 vs 4 events, p = 1), patients receiving protocol-driven care had

Table 2
Clinical data

	Time of Implantation	Follow-Up	p Value
Echocardiographic data			
Left ventricular internal diastolic diameter (cm)			
Usual care	6.2 ± 0.8	6.0 ± 1.0	0.05
Protocol-driven care	6.4 ± 1.0	5.8 ± 0.9	<0.001
Left ventricular ejection fraction (%)*			
Usual care	26 ± 8	33 ± 9	<0.001
Protocol-driven care	25 ± 8	37 ± 9	<0.001
Cycloergometric data			
Maximum volume (ml/kg/min)*			
Usual care	14.1 ± 3.2	14.5 ± 2.5	NS
Protocol-driven care	14.0 ± 4.8	15.5 ± 4.2	0.03
Maximum heart rate (beats/min)			
Usual care	117 ± 18	104 ± 22	NS
Protocol-driven care	115 ± 24	105 ± 26	0.02
Electrocardiographic data			
PR width (ms)			
Usual care	187 ± 45	142 ± 26	<0.001
Protocol-driven care	188 ± 46	128 ± 30	<0.001
QRS width (ms)			
Usual care	155 ± 32	149 ± 30	NS
Protocol-driven care	157 ± 29	150 ± 21	NS

* There was a significant difference between the 2 study groups at follow-up.

fewer adverse events during follow-up (28 vs 9 events, p <0.001; Figure 6). The protocol-driven follow-up was not associated with lower all-cause mortality (odds ratio 1.085, 95% confidence interval 0.231 to 5.084, p = NS) but did lead to a decrease in heart failure hospitalization (odds ratio 0.137, 95% confidence interval 0.056 to 0.335, p <0.001) compared to routine care after implantation.

Discussion

The potential benefit of heart failure management in addition to a comprehensive protocol-driven CRT optimization strategy has been demonstrated in patients without robust clinical or echocardiographic responses to CRT.[1] We report for the first time a potential incremental benefit of such a CRT optimization strategy immediately after implantation of CRT, which is in part driven not only by device optimization but also by judicious uptitration of neurohormonal blockers and decreases in loop diuretics and heart failure education in close coordination of care with primary caregivers.

As in other interventions, extent of response to CRT can be heterogenous, and there is ongoing debate regarding the best strategies to optimize device performance. Much attention has focused primarily on refining preimplantation patient selection to predict a favorable response or on improving techniques and determination of optimal lead positioning to achieve maximal synchronization. However, maximizing benefits of CRT for those with implants is particularly important because CRT is an invasive intervention with known complications. Our group previously demonstrated in a systematic evaluation of implementation that nonresponding patients in a large subset of patients achieved substantial benefit by a combination of device adjustments and standard components of heart failure management interventions.[1] We extend our findings to all patients immediately after CRT implantation in which immediate assessment of device parameters guided by clinical and echocardiographic evaluation may be associated with incremental clinical and echocardiographic responses that are directly associated with better long-term outcomes. Similar to our previous findings in the nonresponder population, a large majority of issues identified included presence of rhythm abnormalities (19%) with concomitant inadequate delivery of biventricular pacing, improving compliance in decreasing salt and fluid intakes (42%), optimization of medical management as an adjunct to device adjustments (64%), and echocardiographically guided AV-optimization (50%). These observations were unlikely biased by selection because the indication, implantation, and postprocedure care were provided by the same personnel with the exception of the additional upfront protocol-driven evaluation. Hence, our observations highlight the notion that current postimplantation approaches to longitudinal monitoring may overlook important issues such as optimization of medical therapy and heart failure education.

One of the most intriguing findings in our report is that for the first time we observed that up to 2/3 of patients tolerated uptitration of neurohormonal blockers after CRT implantation to dosages previously not tolerated before CRT implantation. There may be several reasons that may explain this observation. First, the ability for CRT to provide hemodynamic augmentation in the setting of dyssynchrony has been well described in the literature and has been the basis for its indication.[1,6,7] Second, the dependency of diuretic therapy to relieve congestion may be decreased; hence, adjustments of diuretic therapy may be necessary to better optimize the filling pressures needed to promote recovery. The 2 effects can commence immediately after CRT and perhaps more promptly after better adjustments of atrioventricular delay to establish the most optimal mitral inflow pattern. The ability to increase transition of care from time of discharge after device implantation to long-term management of heart failure likely further facilitates long-term improvement.

The design of our protocol-driven follow-up of ambulatory patients implanted with a CRT is unique yet scalable to broad adoption. First, it commenced immediately after implantation in all patients with implanted CRT, thus providing an upfront assessment and intervention that may benefit a larger proportion of patients especially when applied even at the time of discharge from hospitalization for implantation. Second, it used a combination of readily applicable (rather than research-based) testing and interventions that is familiar to patients and health care providers in a manner similar to our approach in the nonresponder population.[1]

Although positive effects toward improvement in exercise capacity and remodeling were noticeable in the 2 groups, the extent of these positive effects was significantly greater with the protocol-driven approach, ultimately leading to a decreased incidence of adverse events at follow-up. Interestingly, this was not attributable to a more pronounced decrease in electrical dyssynchrony in the protocol-driven

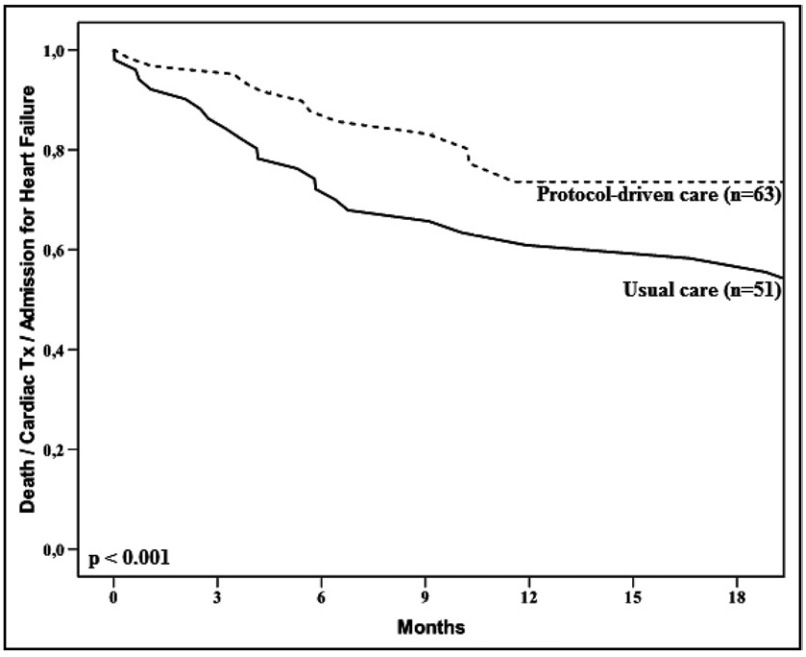

Figure 6. Kaplan–Meier survival curve for clinical outcomes of usual cardiac care versus protocol-driven care with combined end point of death, cardiac transplantation (Tx), and admission for heart failure.

approach. It is therefore conceivable that nondevice-related contributors of CRT response that can act independently of (but synergistically to) cardiac resynchronization will directly influence clinical and echocardiographic responses to CRT. Because contemporary postimplantation patient management is evolving more and more toward remote evaluation and monitoring, our data may argue conversely that an improvement in clinical or echocardiographic response after successful resynchronization should not imply that a routine follow-up visit or just a remote device follow-up is sufficient. Instead, it is conceivable that an upfront comprehensive heart failure management approach is warranted in patients receiving CRT to ensure a more persistent and meaningful alteration in the natural history of heart failure, thus maximizing chances to delay disease progression.

It is important to recognize that this is a single-center experience and not a randomized but a historical control comparison of 2 treatment strategies. Nevertheless, the period was selected because implantation indications and techniques were relatively mature and care patterns delivered by health care providers (including indications for medical and device therapies) were largely unchanged during this period.

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