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REVIEW

The Dilemma of Providing Cardioverter/ Defibrillator Back-Up for all Patients with Heart Failure Eligible for Cardiac Resynchronization Therapy

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List of Abbreviations:
CRT= cardiac resynchronization therapy
CRT-D= CRT with defibrillator back-up
CRT-P= biventricular pacing alone
ECG= electrocardiogram
ICD= implantable cardioverter defibrillator
LBBB= left bundle branch block
NYHA= New York Heart Association

KEY WORDS: *heart failure; cardiac resynchronization; biventricular pacing; left bundle branch block; implantable cardioverter defibrillators; sudden cardiac death*

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ABSTRACT

Cardiac resynchronization therapy (CRT) achieved by biventricular pacing (CRT-P) has been proved to improve symptoms and prognosis of patients with refractory heart failure. Sudden cardiac death is quite common among patients with symptomatic heart failure and implantable cardioverter-defibrillator (ICD) therapy has been proved to effectively reduce sudden deaths in heart failure patients. Given the results of the recently published primary prevention trials and the high incidence of sudden cardiac death among CRT-P recipients, CRT combined with backup defibrillator therapy (CRT-D) seems a logical therapeutic option in patients eligible for CRT. However, the apparent beneficial effects of such an appealing combination do not alleviate the skepticism about the unselected use of CRT-D therapy. This skepticism is largely related to the high cost of this method, to the limited availability of human and financial resources and to our inability to appropriately define the selection criteria for CRT candidates, which are expected to influence the clinicians' decisions when confronted with the dilemma of providing CRT-D therapy for all patients eligible for CRT.

CARDIAC RESYNCHRONIZATION THERAPY

Heart failure has emerged as a cardinal public health problem that has been plaguing our society over several decades and poses a significant financial burden on our health care system. It is estimated that acute decompensated heart failure accounts for 2.9% of all emergency room visits, and that its prevalence is steadily increasing in epidemic proportions as well as in an age-dependent manner, reaching an incidence of almost 10% in patients aged >65 years [1]. There has been considerable improvement in our therapeutic armamentarium over the years with significant benefit obtained from the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers and β-blocking agents. However, there is still a large population of heart failure patients who remain refractory to current therapeutic approaches and this therapeutic gap has recently been bridged by the newer mode of electrical therapy known as cardiac resynchronization therapy (CRT), effected by biventricular pacing [2-3].

Asynchronous contraction due to cardiac conduction abnormalities, often described as cardiac dyssynchrony, reflected by the presence of left bundle branch block (LBBB) on

the electrocardiogram (ECG), occurring in 20-30% of patients afflicted by heart failure, has been documented to adversely affect the function of the failing heart [4]. Furthermore, it has been shown that cardiac dyssynchrony has an unfavorable influence on prognosis in patients with heart failure [5,6].

Cardiac resynchronization therapy, aims to improve the mechanical function of the failing heart. Biventricular pacing is an effective way to achieve CRT and restore electromechanical synchrony by simultaneously pacing at different sites of the heart, classically at the right ventricular apex and the lateral wall of the left ventricle. This is accomplished through percutaneous techniques by inserting the left ventricular pacing lead via the coronary sinus and placing it into a lateral cardiac vein tributary. In a large number of studies, it is a consistent finding that biventricular pacing increases left ventricular ejection fraction and cardiac output and most importantly, improves quality of life, functional class and exercise capacity in the majority of the treated patients [7-10]. In terms of pathophysiology, CRT has a unique characteristic among other therapies for heart failure. Its favorable influence on cardiac performance has not been associated with increased oxygen consumption, an issue of profound importance, especially in patients with ischemic cardiomyopathy [11]. These striking beneficial effects of CRT, had not been accompanied by any detectable survival benefit in the large number of small randomized trials that were published during the initial period of biventricular pacing [7-10]. Of course, these studies were not designed to detect a survival benefit and thus, they were underpowered to study the effects of biventricular pacing on overall mortality (Table 1).

However, the lack of statistical significance should not be considered synonymous to the lack of clinical significance. In the case of CRT, this fact was firstly supported by a meta-analysis of four large randomized trials, which showed that CRT therapy significantly reduced all-cause mortality (relative risk=0.77) [12]. Thereafter, the results of the two randomized studies having total mortality as their primary end-point, the COMPANION [13] and the CARE-HF [14] trials, verified the aforementioned findings and provided the necessary evidence for the revised recommendations and guidelines on CRT use for patients with symptomatic heart failure, which were recently published by the American Heart Association (AHA)/American College of Cardiology (ACC) [15] and by the European Society of Cardiology (ESC) [16].

TABLE 1. Possible reasons for observed lack of survival benefit in initial CRT studies

1. These studies were not designed or powered to detect a survival benefit
2. Small number of studied patients
3. Limited follow-up period
4. Exclusive use of electrocardiographic criteria for CRT candidates
5. Lack of in-depth knowledge of CRT pathophysiology
6. Inability to detect non-responders
7. Technical issues (technology of coronary sinus pacing leads and delivery systems, selection of appropriate cardiac vein, post implantation optimization of programmed atrioventricular and interventricular delays)

The synopsis of these recommendations, shown in Table 2, is the result of accumulating data supporting the use of CRT, not only to improve symptoms and to decrease hospitalizations, but also to improve survival in patients with cardiac dyssynchrony (QRS ≥120 ms), low ejection fraction (≤35%), and dilated left ventricle (end-diastolic diameter ≥55 mm), who have persistently symptomatic heart failure despite optimal medical therapy (New York Heart Association-NYHA class III-IV).

However, the data that have provided the evidence for these recommendations should be considered in the context of their major limitation, which is the use of QRS duration (≥0.12 sec) as the main criterion of cardiac dyssynchrony, reflecting our limited insight into the pathophysiological mechanisms of cardiac dyssynchrony and heart failure and thus, our notorious inability to efficiently detect those patients who will mostly benefit from CRT (responders). The existence of a variable proportion (20-30%) of patients not responding to biventricular pacing (non-responders) in all published studies possibly undervalues the survival benefit afforded by CRT and emphasizes the need for reevaluation of the inclusion criteria for biventricular pacing. It has been suggested that the use of the recently developed echocardiographic indices of cardiac dyssynchrony may improve appropriate selection of responders to CRT by excluding those patients, who, despite the prolonged duration of the QRS complex, do not present any detectable electromechanical dyssynchrony [17-23]. However, among the large randomized CRT trials, only CARE-HF included echocardiographic criteria of electromechanical dyssynchrony. Although the role of echocardiography for the selection of appropriate candidates for CRT is rapidly evolving, and the criteria adopted from the CARE-HF investigators (interventricular mechanical delay and preejection aortic time) have lost their appeal in recent years, it is of interest that this was the first large-scale multicenter randomized study that resulted in significantly improved cardiac and all-cause mortality in the CRT treated arm.

Despite a plethora of data published during recent years, the use of CRT in a variety of patients and clinical conditions is still under investigation (Table 3). The main reason for this is not the inconsistent results from published studies, but the fact that the vast majority of studies that addressed specific indications for biventricular pacing were underpowered to provide mortality data, mainly due to the small number of study participants. Moreover, conclusions extrapolated by secondary analysis of data derived from the few larger studies, have

TABLE 2. Synopsis of the recently published reccomendations from AHA/ACC and ESC, concerning CRT in chronic heart failure patients.

	Patients' characteristics	Clinical end-point	Class and level of evidence	Ref.
ACC/AHA Guideline Update for Chronic Heart Failure (2005 update)	• NYHA class III-IV • LVEF ≤35% • Sinus rhythm • Symptoms despite optimal medical therapy • Cardiac dyssynchrony (currently defined as QRS >0.12 ms)	Symptoms, Hospitalizations, Mortality	I (A)	15
ESC guidelines for Chronic Heart Failure (2005 update)	• NYHA class III-IV • Reduced LVEF • Symptoms despite optimal medical therapy • Cardiac dyssynchrony (QRS>0.12 ms)	Symptoms, Hospitalizations Mortality	I (A) I (B)	16 16

LVEF= left ventricular ejection fraction; NYHA= New York Heart Association

TABLE 3. Clinical conditions where a recommendation for CRT is still precluded according to the AHA/ACC guidelines update 2005

1. Atrial fibrillation
2. Right bundle branch block (RBBB)
3. Pacemaker-induced dyssynchrony in case of pace-dependency
4. Existence of mechanical dyssynchrony in the absence of prolonged QRS duration
5. Co-existing right heart failure
6. NYHA II stage

rightfully been considered preliminary and need to be verified by specifically designed studies. However, the recommendations that have been precluded by the authors of the recently published guidelines due to the lack of solid evidence may be reasonable therapeutic choices for the individual patient in everyday practice. For instance, the decision to implant a biventricular pacemaker in a patient eligible for pacemaker therapy due to atrioventricular conduction abnormalities, and who has a prolonged PQ interval, a relatively narrow QRS complex, and suffers from severe, refractory to medical treatment heart failure, could be considered of profound benefit in selected cases, especially taking into consideration the unfavorable effects of pacemaker-induced dyssynchrony in patients with advanced heart failure and pace-dependency. However, such a policy has not been included in the recently published recommendations because it is not supported by a specifically designed large-scale randomized trial.

IMPLANTABLE CARDIOVERTER/ DEFIBRILLATOR THERAPY

Sudden cardiac death is quite common among patients with symptomatic heart failure [24]. A number of studies conducted in post myocardial infarction patients at high risk predominantly due to impaired systolic function of the left ventricle (EMIAT, CAMIAT, TRACE, SWORD and DIAMOND-MI), have reported that the cumulative incidence of arrhythmic mortality reached about 5% at 1 year and about 9% at 2 years, whereas the incidence of non-arrhythmic cardiac death was about 4% and 7%, respectively [25-29]. The MERIT-HF trial including 50% of patients with ischemic cardiomyopathy, reported an annual mortality rate of 11%, which was reduced to 7% in the metoprolol arm [30]. In symphon with a secondary analysis of the MERIT-HF data, the meta-analysis by Kjekshus et al., showed that patients with less severe heart failure are more likely to die suddenly compared to those at advanced NYHA stage [31].

It is of little doubt that patients with heart failure, previous cardiac arrest and/or documented sustained ventricular tachyarrhythmias, are at especially high risk and should be treated with an implantable cardioverter/defibrillator (ICD). In contrast, implantation of ICDs for primary prevention of sudden arrhythmic death in patients with heart failure symptoms has been considered an issue of additional complexity. Clinicians are aware of the fact that almost half of these patients present episodes of non-sustained ventricular tachycardia in routine ambulatory electrocardiographic (Holter) monitoring [32]. However, the positive predictive value of similar insensitive findings has been proved to be very low, seriously affecting our ability to accurately select those patients who are most likely to benefit from ICD therapy on an individualized basis. Until reliable genetic risk stratification and manipulation of arrhythmic background is widely available, risk stratification for arrhythmic death based solely on clinical and demographic criteria seems inevitable. In this context, the trials that investigated the protective role of ICDs in large groups of patients with structural heart disease who have not presented documented life-threatening arrhythmias (primary prevention trials) have focused specifically on patients with heart failure symptoms and reduced left ventricular ejection fraction because of their

TABLE 4. Synopsis of the recently published reccomendations from AHA/ACC and ESC, concerning implantable cardioverter-defibrillator therapy in chronic heart failure patients.

	Patients' characteristics	Clinical endpoint	Class and level of evidence	Ref.
ACC/AHA Guideline Update for Chronic Heart Failure (2005 update)	• Secondary prevention • Reduced LVEF • Heart failure symptoms	Mortality	I (A)	15
	• Primary prevention • Ischemic heart disease • LVEF ≤30% • NYHA stage II-III • >40 days post MI	Mortality	I (A)	
	• Primary prevention • Nonischemic cardiomyopathy • LVEF ≤30% • NYHA stage II-III	Mortality	I (B)	
	• Primary prevention • Any cardiomyopathy • LVEF 30-35% • NYHA stage II-III	Mortality	IIa (B)	
ESC guidelines for Chronic Heart Failure (2005 update)	• Combined with CRT • NYHA class III-IV • LVEF ≤35% • QRS duration >120 ms • Symptoms despite optimal medical therapy	Morbidity and Mortality	IIa (B)	16
	• Secondary prevention • Reduced LVEF • Heart failure symptoms	Mortality	I (A)	
	• Primary prevention • Selected symptomatic patients • LVEF <30-35% • >40 days post MI	Mortality	I (A)	

CRT= cardiac resynchronization therapy; LVEF= left ventricular ejection fraction; MI= myocardial infarction; NYHA= New York Heart Association

propensity for life-threatening arrhythmias. Although there have been a few studies that failed to detect any measurable beneficial effect of ICD therapy on mortality, the larger recently published studies strongly support the mortality benefit afforded by ICD implantation for primary prevention of sudden cardiac death in heart failure patients.

A synopsis of published trials that have focused on the role of ICDs for the primary prevention of sudden cardiac death is presented in Table 5 [13,33-37] Based on these studies, the AHA/ACC guidelines for heart failure suggest that consideration of ICD implantation is recommended in patients with left ventricular ejection fraction less than 30% and mild to moderate symptoms of heart failure, and in whom survival with good functional capacity is otherwise anticipated to extend beyond one year [15]. In accordance with the AHA/ACC recommendations, the respective ESC guidelines suggest that ICD implantation is reasonable in selected symptomatic patients with left ventricular ejection fraction <30-35%, not within 40 days of a myocardial infarction [16]. The lateral cause refers to a recent study indicating that prophylactic implantation of an ICD within the first 40 days after an acute myocardial infarction does not confer any protection against sudden cardiac death [35]. Patients should also have had a revascularization procedure at least 3 months before they are considered for ICD implantation for primary prevention.

IMPLANTABLE CARDIOVERTER/ DEFIBRILLATORS IN PATIENTS WITH ADVANCED HEART FAILURE ELIGIBLE FOR CARDIAC RESYNCHRONIZATION THERAPY

One could hypothesize that, based on the recently pub-

TABLE 5. Selected primary prevention trials of implantable cardioverter-defibrillator therapy in patients with heart failure.

Study	Patients (n)	Etiology of structural heart disease	LVEF (%)	Relative risk for mortality (ICD vs control)	P value	Ref.
MADIT II	1232	IHD	≤30	0.69 (0.51-0.93)	0.007	33
CABG-PATCH	900	IHD (Plus late potentials)	≤35	1.07(0.81-1.42)	0.640	34
DINAMIT	674	IHD (<40 days post MI)	≤35	1.08 (0.76-1.55)	0.660	35
SCD-HeFT	2521	IHD/nonIHD	≤35	0.77 (0.62-0.96)	0.007	36
DEFINITE	458	nonIHD	≤35	0.65 (0.40-1.06)	0.080	37
COMPANION (CRT-D study)	1520	IHD/nonIHD	≤35	0.50 (0.29-0.88)	0.010	13

CRT denotes cardiac resynchronization therapy, ICD implantable cardioverter defibrillator, IHD ischemic heart disease, MI myocardial infarction, LVEF left ventricular ejection fraction

lished studies and guidelines, the addition of ICD capability is crucial for the vast majority of patients eligible for CRT. Indeed, the majority of patients eligible for CRT could be included in the groups of patients eligible for ICD therapy, mainly because of the expanded indications of ICD therapy for primary prevention of sudden cardiac death in patients with heart failure of ischemic and of non-ischemic cardiomyopathy (Table 5). Furthermore, despite their differences regarding baseline characteristics of the studied patients, the selection criteria for the treated arms, and mortality at 12 months (19 vs 12.6%, respectively), in both COMPANION and CARE-HF studies it was reported that one-third of deaths that occurred during the follow-up period in the CRT-treated patients were sudden [13-14]. Availability of back-up defibrillator therapy would have avoided the majority of these deaths. This plausible assumption was supported by the 55% reduction of risk for sudden cardiac death in the CRT-D compared to the CRT arm in the COMPANION study and was further validated by the fact that only 2.9% of the CRT-D treated patients in the COMPANION trial died suddenly, compared to 7% of the CRT treated patients in the CARE-HF study.

Despite the appeal of the accumulating evidence on the beneficial effects of back-up defibrillator therapy in CRT patients there is still plenty of room for skepticism when the clinicians consider CRT-D treatment for their patients, especially in the absence of documented life-threatening ventricular tachyarrhythmia and/or syncope of unknown etiology. Evidence-based reduction of the mortality relative-risk afforded by ICD therapy is an important issue, but not the only one that should be taken into consideration.

REASONS OF SKEPTICISM FOR THE WIDER USE OF CRT-D THERAPY

Due to the inordinately increased cost incurred by the ICD therapy, but also because of the lack of firm and conclusive data from large randomized and controlled studies decisively supporting the use of ICD back-up in all patients eligible for CRT, there has been plenty of skepticism in recommending the general use of combined CRT-D therapy in all patients receiving CRT. Several of these reasons for skepticism and relative issues are detailed below:

- Recently published data from primary prevention trials have shown that the survival benefit of ICD therapy is enhanced in patients with low ejection fraction who are at NYHA functional class II-III [36]. In contrast, CRT therapy has been convincingly tested in patients at advanced NYHA stage (class III and IV).
- The AHA/ACC guidelines suggest that ICD should be considered in patients whose survival with good functional capacity is anticipated to extend beyond 1 year. However, there is no specific marker or prognostic tool for the clinicians, which could enable them to accurately define this subgroup of patients. Given that 12-month mortality in CRT candidates ranged from 12 to 19%, providing ICD therapy to all CRT candidates may imprudently extend this expensive therapy to patients with inevitably unfavorable prognosis [10-11]. In this subgroup of patients, relative-risk reduction attributed to defibrillator therapy, although possible, may not accurately reflect absolute survival benefit.
- Dr Feldman and colleagues [38] have published a cost-effectiveness analysis of the therapeutic choices in the COMPANION trial. The authors concluded that for the COMPANION trial patients, the use of CRT-P (biventricular pacing alone) and CRT-D (with ICD back-up) was associated with a cost-effectiveness ratio below the generally accepted landmarks for therapeutic interventions of $50,000 per quality life-year (QALY) to $100,000 per QALY. Based on Medicare data to calculate the aforementioned costs, the authors suggested that the clinical benefits of CRT-P and CRT-D can be achieved at a reasonable cost. However,

these results, although well-defended, do not necessarily apply to the majority of the European countries, where the cost of the devices is generally higher and the cost of hospitalizations and drug therapy considerably lower. The excessive cost of defibrillator therapy in patients with poor prognosis should be considered in the context of local individualized socioeconomic capabilities, which vary significantly among countries. Should medical practice vary accordingly? This is a difficult question exceeding the scope of this analysis. However, physicians should be aware that cost-effectiveness of medical practice is an issue of increasing importance in the industrialized world and that appropriate selection of candidates for CRT would actually increase the cost-effectiveness by eliminating the proportion of non-responders. Given this, in terms of cost-effectiveness, backup defibrillator therapy may be accessible to a wider proportion of patients eligible for CRT.

- Although the COMPANION trial favored the CRT-D therapy versus the CRT-P therapy, this study was underpowered to directly compare these two therapies. The follow up was limited to 14 months by study design and after the ninth month the survival curves were absolutely parallel. Dr Daubert et al. [39] rightfully claimed that only a specifically designed study with 1,300 patients per group and a follow-up period equivalent to that of the CARE-HF trial would have a statistical power of 90% to detect a 5% absolute relative risk reduction of death from any cause with the use of CRT-D compared with CRT alone. But, who would undertake such a study? Having said that, we have to admit that the core issue of this dilemma has not been definitively answered yet. On the other hand, medical practice should not be based exclusively on solid irrefutable evidence. In a variety of situations this would be a terrible waste of valuable human and financial resources.
- The implantation of CRT-P devices is a demanding and potentially hazardous procedure. The learning curve of operators is heavily dependent on the number of implantations and thus, high-volume centers are expected to be better qualified for CRT therapy, limiting the availability of the therapy. Implantation of CRT-D is an issue of additive complexity. Peri-procedural complications are expected to be more frequent in CRT-D versus CRT-P patients. This is one more argument in favour of those who defend the use of backup defibrillator therapy exclusively for those who are most likely to benefit from it.

CONCLUSIONS

According to the published data from large-scale trials and in agreement with the recently published recommendations from both the AHA/ACC and the ESC, availability of backup defibrillator therapy in all patients eligible for CRT seems a logical therapeutic option (Figure 1). However, once again, reality tempers the optimism of the experts. Cost-effectiveness, limited availability of human and financial recourses and our inability to appropriately define the selection criteria for CRT candidates are the main unresolved issues that are expected to restrain the unselected use of CRT-D therapy in CRT candidates. The technological and medical steps towards CRT-D therapy for all patients eligible for CRT have not been completed yet. Less expensive, smaller CRT devices and improved selection criteria for CRT candidates will definitely make the answer to our dilemma obvious. Being realistic rather than optimistic, these prerequisites are all expected in the near future. Indeed, we are in dire need of randomized controlled studies between CRT-P and CRT-D having all-cause mortality as their primary end-point so as to settle a poignant issue in cardiac resynchronization therapy in heart failure patients [40].

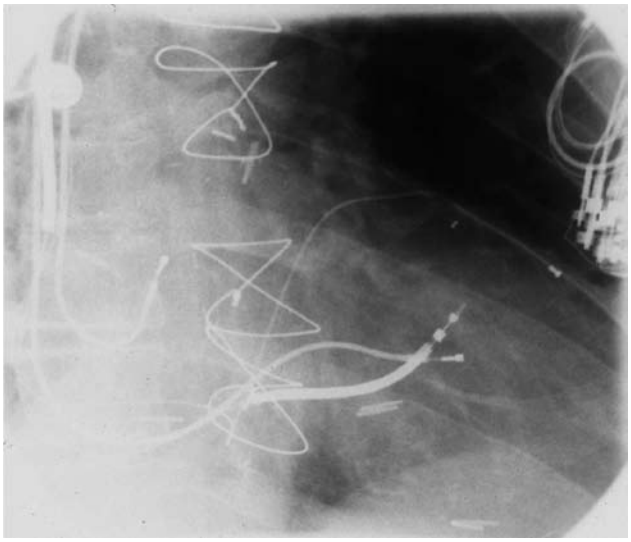

FIGURE 1. This is a patient with a history of coronary bypass graft surgery in the remote past, who has now developed severe left ventricular dysfunction and refractory heart failure. He has received a triple atrioventricular biventricular pacing system with defibrillator back-up, which provides not only cardiac resynchronization therapy (CRT) but also protects the patient against sudden cardiac death. The second right ventricular pacing lead was left in place when the pacemaker was upgraded to a CRT-D system. This complete set of electrical therapy, combining the best of two worlds (enhancing pump function and effectively protecting against malignant ventricular tachyarrhythmias), would be desirable for every heart failure patient, if it were not for the very high cost and if all the data from properly designed studies were conclusive.

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