Insights from implementing a routine Cardiac Resynchronization optimization clinic in a tertiary Belgian Hospital

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Masterproef voorgedragen tot het bekomen van de graad van
master in de biomedische wetenschappen

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FOREWORD

I am happy to introduce this Master's thesis, intended for all those who are involved in preparing a research paper or thesis relating to cardiac care. I hope this might contribute substantially to the research accomplishments of the conjoined, and promising, partnership between the Sint Jan's hospital Oost-Limburg in Genk and the Hasselt University in Diepenbeek. There were no financial conflicts of interest and this project did not receive funding support.

Preparing a thesis is something of an adventure, usually involving a few unforeseen challenges and technical difficulties. During this adventure I was assisted by many people, for whom I would like to reserve this short section to properly thank them for making this long adventure manageable.

First and utmost I would like to thank my promoters, Wilfried Mullens, for all the kind yet very dedicated guidance he provided during my senior practical training at the hospital; and Patrick Wagner, for all his helpful, and often playful, advice which I so often needed.

Next, I would like to thank all the staffs that made finishing this degree possible. Starting with the hospital's staff of nurses, secretaries and cardiologists, which were always prepared to help me with a smile whenever a problem arose that I couldn't handle myself. Of course, perhaps even more important, I thank the entire "life sciences" university staff of secretaries, all the assistants and PhD students, not forgetting about the numerous professors which taught me all I needed to know to pass this important period in my life.

Last, but definitely not least, to all the friends I acquired during my years in college along with all the joyful moments we shared, both in- and outside of class, which somehow made all the time pass in the blink of an eye.

> *"The scientist does not study nature because it is useful; he studies it because he delights in it, and he delights in it because it is beautiful. If nature were not beautiful, it would not be worth knowing, and if nature were not worth knowing, life would not be worth living".*
>
> *Jules Henri Poincaré (1854-1912) ~ French mathematician.*

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LIST OF ABBREVIATIONS

AV: AtrioVentricular

BP: Blood Pressure

CRT: Cardiac Resynchronization Therapy

ECG: Electrocardiograph

ECHO: Echocardiograph

EF: Ejection Fraction

FU: Follow-Up

HF: Heart Failure

ICD: Implantable Cardioverter-Defibrillator

IVCD: Intra- or Interventricular Conduction Delay

LV: Left Ventricle

LVEF: Left Ventricular Ejection Fraction

LVIDd: Left Ventricular Internal Diameter in diastole

NYHA: New York Heart Association

RV: Right Ventricle

VV: VentroVentricular

SUMMARY

The western society is confronted by an aging population correlated to a higher incidence of cardiac problems, such as heart failure. Selected heart failure patients show conduction disturbances leading to so-called ventricular dyssynchrony, i.e. instead of beating simultaneously the two ventricles beat slightly out of phase. Cardiac resynchronization therapy (CRT) is a device-based intervention inspired by the technology utilized in pacemakers. Its main feature is that it's capable of pacing both heart chambers simultaneously, which improves heart function as well as relieves symptoms.

However, up to one-third of patients seem non-responsive to CRT, despite correct implementation and programming of the device. To assess this issue, strenuous effort was taken to define a multidisciplinary protocol-driven approach for post-implant care, which served to evaluate ambulatory CRT patients who did not exhibit a positive response. Even though the achieved results in the non-responder's group were promising, this protocol was yet to be tested systematically for all CRT patient groups following device implant. To rate its impact, a total of 114 consecutive CRT patients implanted between 2005-2009 were analyzed and stratified in two groups; those that received routine post-implant care (11/2005-07/2008) versus those that underwent the protocol-driven post-implant care (09/2008-02/2010) in a dedicated heart disease management clinic.

Therefore, the objective of this study is to investigate if a protocol-driven approach, incorporated in a heart failure disease management clinic for all CRT patients started immediately after device implant, is associated with more favorable effects on reverse remodeling conjoined with fewer adverse events, when compared to routine post-implant care. Secondly, to report whether these effects are driven not only by changes in device settings and arrhythmia management, but also by concomitant patient education in terms of heart failure of and/or medication optimization. Its results may have clinical implications on routine cardiac care and serve to prove that CRT is not just a localized intervention but a full body therapy.

I. INTRODUCTION

HEART FAILURE

Heart failure [HF] is a clinical syndrome that impairs the ability of the heart to eject blood commensurate to the needs of the body (1). It is considered the end stage of all diseases of the heart and is the number one cause of hospitalization and mortality in developed countries, affecting predominantly the elderly. People whose heart cannot sustain an adequate cardiac output become breathless and develop swollen feet and ankles. In Belgium, an average of 43 cases of HF is reported each day, resulting in an estimated 15.643 novel patients per year, as of 2009 (2). Furthermore, the resulting emergency admission leads to an average length of stay of 14 days in a properly equipped Belgian hospital, representing 1.8% of a total hospital's expenditure (3). Needless to say, HF represents a considerable socio-economic burden for the western society.

There are a lot of functional and structural cardiac disorders leading to HF. For practical purposes, patients with HF symptoms are classified primarily in terms of myocardial dysfunction: those with systolic dysfunction and those with diastolic dysfunction (1,4). This division is based on the left ventricular ejection fraction [LVEF], which by definition is the percentage of blood pumped out of the left ventricle [LV] with each heart beat. Patients with a low LVEF, below 45%, are considered to have systolic dysfunction and typically present with an enlarged LV and decreased cardiac output. In contrast, patients with signs and symptoms of HF but with a preserved LVEF are said to have diastolic dysfunction, which is a disease of impaired ventricular filling.

All causes for HF, resulting from either damage or dysfunction of tissue, are classified as non-ischemic and ischemic, meaning due to a restriction in blood supply. In western countries the most common causes of ischemic HF are identified as smoking, hyperlipidemia and hypertension – either alone or in combination. Diabetes mellitus is also an important risk factor, as well as some degree of familial, thereby genetic, factors.

VENTRICULAR DYSSYNCHRONY

Disorders of the conduction system might be associated with myocardial dysfunction. Indeed, many patients with advanced systolic heart failure exhibit significant intra- or interventricular conduction delays [IVCD's], which disturb the synchronous beating of the two ventricles. This delay in ventricular activation and contraction between the right ventricle [RV] and the LV is referred to as ventricular dyssynchrony; generally diagnosed through a wide QRS complex on Electrocardiographs [ECG's - Figure 1], it reflects the increased time needed for depolarization of both ventricles. Prolongation of QRS, defined as surpassing 120ms, occurs in approximately 14 to 40% of patients experiencing HF symptoms, depending on the underlying causes (5,6).

FIGURE 1. ECG - DEPICTING INTRAVENTRICULAR CONDUCTION DELAY.

Ventricular dyssynchrony has been shown to produce a number of deleterious effects on cardiac function, such as reduced diastolic filling time, weakened muscle contractility, mitral as well as tricuspid regurgitation, which altogether result in a diminished stroke volume. In patients with HF, mortality rates progressively increase as the IVCD increases (7,8).

Treating dyssynchrony as a symptom is often easier than treating the cause, which may as well be irreversible. The underlying problems could arise from an electrical conduction delay and/or structural and mechanical impairments. The latter can be identified as resulting malformations in the myocardial matrix due to the increased workload and stress of the heart's compensatory mechanism. Theoretically, the best place for electrical stimulation would be right behind the impairments causing the conduction delays, up against the Purkinje fibers [Figure 2].

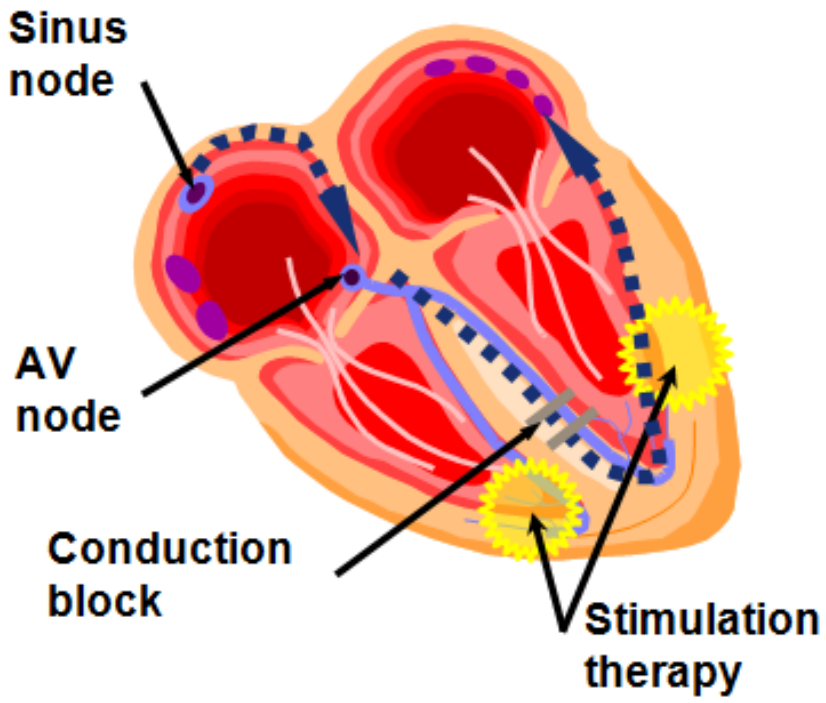

FIGURE 2. GRAPHIC REPRESENTATION OF THE CONDUCTION PATHWAYS IN THE HEART. In case of a left bundle branch block, ventricular dyssynchrony can arise between the left and right ventricle. Theoretically, the best place for electric stimulation would be against the Purkinje fibers in both ventricles.

CARDIAC RESYNCHRONIZATION THERAPY

Cardiac resynchronization therapy [CRT] is a device-based intervention for selected patients showing advanced HF symptoms and evidence of ventricular conduction delay. Importantly, it relieves symptoms as well as improves heart function through restoration of the synchronous coordination of the ventricles' contraction and relaxation, leading to improved exercise tolerance, cardiac remodeling (i.e. reduction in LV volumes along with improvement in LVEF) as well as better survival rates (9-11).

Based on the technology used in pacemakers and implantable cardioverter-defibrillators [ICD's], CRT introduces the use of an additional tertiary lead. Indeed, a biventricular pacemaker is connected to three cardiac electrodes placed up against the RV, the LV as well as the right atrium [Figure 3]. Its main feature is to pace both heart chambers simultaneously, whereas traditional pacemakers only stimulate the right side directly.

Selected patients with gravely decreased cardiac function often develop malignant ventricular rhythm disorders. These are controlled with a defibrillator function capable of reestablishing the heart's rhythm through a controlled therapeutic pulse of electrical energy triggered by an

arrhythmia. CRT devices with an additional defibrillator function are called CRT-D devices, wherein the classic RV electrode is replaced by a larger RV shock electrode.

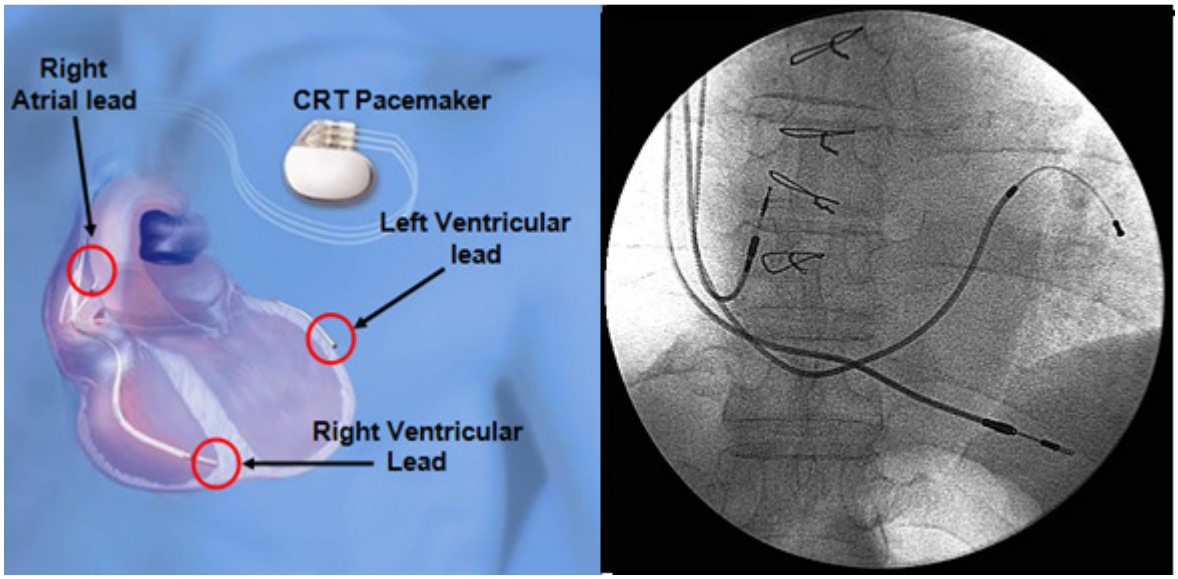

FIGURE 3. GRAPHIC REPRESENTATION (LEFT) AND A FLUOROSCOPIC VIEW (RIGHT) OF THE THREE LEADS USED FOR CRT; Transvenous approach for the left ventricular lead through the coronary sinus.

The objectives of CRT in HF patients are both short- (1-3 months) and long-term (6 months up to years). Short-term goals include optimizing AV timing, prolonging LV filling and coordinating RV and LV contraction by minimizing the inter- and intraventricular mechanical delay. The long-term goals are for the acute changes to translate into structural and functional reverse remodeling, alleviation of symptoms and improved survival rates. However, up to one-third of patients may not experience any improvement in clinical status and/or reversal of cardiac remodeling after CRT, based on current selection criteria (10,12-15).

PROTOCOL-DRIVEN POST-IMPLANT OPTIMIZATION CLINIC

Most of the beneficial effects of CRT have been attributed to device-induced reduction in dyssynchrony, which can be improved further through optimization of specific device programming, arrhythmia management and lead repositioning. Therefore, if implantation and device programming is optimal, a patient should demonstrate maximal therapeutic effects. As a result, the classical follow-up [FU] of CRT patients is often limited to optimization of device parameters by an electrophysiology nurse, while the heart failure FU is most commonly performed by a different physician, who takes note of the patient's HF symptoms and complaints.

Additionally, the literature regarding post-implantation management of CRT, besides device-programming optimization, is rather sparse; particularly with regards to non-device-based post-implant therapy management. The literature that does exist however, lacks scientific significance due to statistically too small patient trials and few secondary confirmations.

To clarify this issue, a protocol-driven CRT optimization clinic was established as part of a heart failure disease management program in a tertiary Belgian hospital. Therein clinical care was given to ambulatory patients with persistent heart failure symptoms and/or disease progression long after their device implantation, based on a protocol designed to achieve optimal response in a non-CRT-responder's group (16), assessing both device-based criteria as well as medication- and heart failure therapy. Even though the achieved results in the non-responder's group were promising, this protocol was yet to be tested systematically on all CRT patients following device implant.

STUDY OBJECTIVES AND GOALS

Since most clinical research focuses on pre-implant management of patient population to define CRT responders and non-responders, it is yet unknown whether additional effort to optimize potential CRT contributors would have an advantageous effect. However, this post-implant optimization through revision of medical therapy, accompanied by proper patient education in terms of heart failure, on top of protocol-driven device management in one centralized clinical visit, might contribute to improved clinical and/or remodeling outcomes.

Therefore, the objective of this study is to investigate if a protocol-driven approach, incorporated in a heart failure disease management clinic for all CRT patients started immediately after device implant, would improve outcomes from a clinical or remodeling endpoint, when compared to routine post-implant care. A secondary objective will be to identify potential clinically-related factors that might contribute to a better response (17).

II. METHODS

STUDY POPULATION

Consecutive CRT patients, implanted with either a CRT pacemaker or a CRT-D defibrillator between November 2005 and December 2009, were analyzed and stratified in two groups. The first group included patients receiving routine post-implant care, since they were implanted prior to the initiation of a protocol-driven CRT optimization clinic, which was implemented in August 2008. The remaining patients implanted from September 2008 onwards were included in the second group. Starting from August 2008, all patients receiving routine care were also systematically referred to the protocol-driven CRT optimization clinic. From that date onwards, all data from the routine care patient group was respecified into a group having received routine care and a new group being treated by protocol-driven care.

The CRT-device was always implanted because of stable but advanced heart failure symptoms, despite receiving optimal medical therapy as tolerated by the patient, a depressed left ventricular ejection fraction (≤ 35%) and a prolonged QRS duration (≥120 ms). Due to stringent reimbursement criteria in Belgium, patients were only implanted with a CRT-D defibrillator in case of episodes of sustained ventricular tachycardia or inducible ventricular arrhythmias, during diagnostic electrophysiological examination. The "Ziekenhuis Oost-Limburg Genk" Review Board approved this research project.

READILY AVAILABLE TECHNICAL EXAMS TO ASSESS VENTRICULAR DIMENSIONS AND EXERCISE CAPACITY

A properly equipped health care clinic should have several non-invasive tools available for diagnosis of HF disease. Among these is the ECG test, which is basically a recording of the heart's electrical activity. Delays in specific segments of the ECG, which correspond with the heart's mechanical relaxation and contraction, can be used to determine IVCD's.

To assess remodeling of the heart due to increased workload an echocardiograph [ECHO] can be recorded. This test allows for real-time visual measurements of cardiac tissue width and the direction and velocity of blood flow. Afterwards, a number of important parameters, such as the left ventricular diameter in diastole [LVIDd] and LVEF, can be calculated, as seen in Figure 4. Using Doppler sound waves the leakage through the mitral valve, located between the left atrium and the LV, and tricuspid valve, located between the right atrium and RV, can be

visualised. Depending of the degree, a classification is made ranging from 0 (almost no leakage) to IV (very serious leakage), also known as mitral and tricuspid regurgitation.

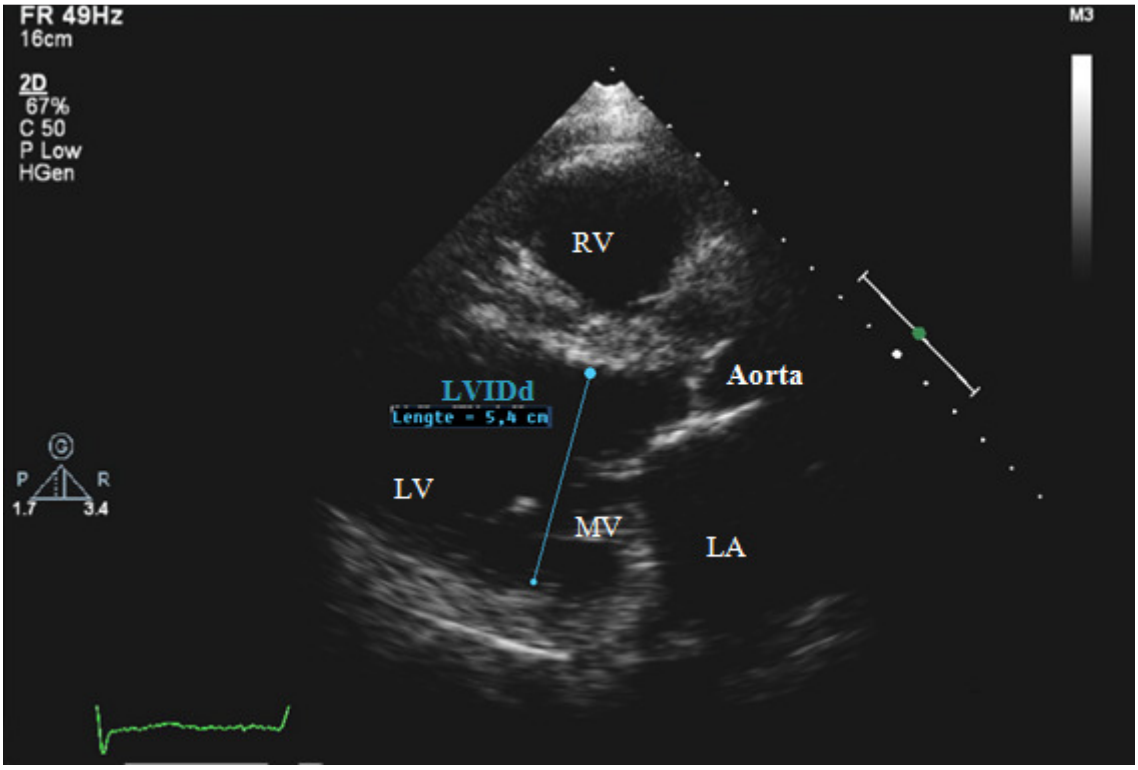

FIGURE 4. ECHOCARDIOGRAPH LAX IMAGE, along with the measurement of the left ventricular diameter in diastole (blue line), measured against the tip of the mitral valve in the left ventricle. **MV: Mitral Valve ; LV: Left Ventricle ; RV: Right Ventricle ; LA: Left Atrium**

During a cycloergometric test the patient is asked to drive a bicycle for as long as they can manage against a predetermined increasing resistance value. During this trial the BP and HF is constantly monitored, while the oxygen uptake is measured through a mask. Sequentially, the maximal oxygen uptake (VO_2^{max}) represents the physical fitness capacity of the patient.

CRT OPTIMIZATION PROTOCOL

The two patient groups differed only with regards to post-implant management strategy; a stepwise protocol was established as part of a multidisciplinary approach towards post-implant CRT optimization, incorporated in a heart failure disease management program, to be implemented starting from September 2008. Pre-implant care was similar among both groups; this included general cardiology FU with implementation of guideline recommended heart failure care, including uptitration of neurohormonal blockade to maximal tolerated doses.

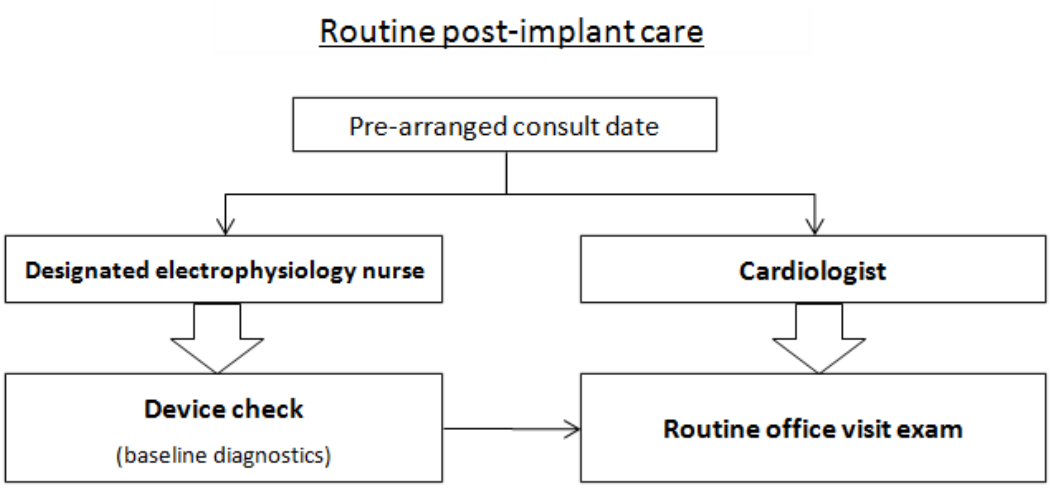

FIGURE 5. FLOW CHART representing routine post-implant care.

Accession of the aforementioned protocol is the main difference between the two study groups. However, the number of scheduled clinic visits were similar among groups; in general at 6 weeks, 3 and 6 months after implant. The first group was subject to routine post-implant care, performed in general by different hospital staffs. In this model, an electrophysiology nurse performed a standard device check: rating the battery status and lead impedances, looking for presence of atrial and ventricular tachyarrhythmia, as well as re-checking critical device settings such as thresholds, heart rate and percentage of atrial and ventricular pacing (Table 1). Afterwards, the patient was seen by its treating cardiologist to assess the patient's current health status and symptoms, often also performing an echocardiogram (Figure 5). Changes in device settings and heart failure therapy were at the discretion of the treating cardiologist.

TABLE 1. COMPREHENSIVE DEVICE CHECK PROTOCOL.

- Battery voltage and battery impedance
- Charge time (in case of ICD)
- Pacing and sensing thresholds for atrium and ventricles
- Pacing lead impedances for all leads
- Shocking impedances for defibrillation leads
- Arrhythmias detected by device
- % Of pacing/sensing in each chamber
- Therapies required for termination of SVT/VT/VF
- Review of main programmed parameters
- Review of any device triggered alerts
- Review of hemodynamic measurements when available

In comparison, patients receiving the multidisciplinary protocol-driven care were subjected to a more thorough CRT optimization clinic protocol, which included a wider variety of measurements and optimization pre-specified guidelines performed in a designated clinic, staffed with physicians and nurses with a broad interest in heart failure and cardiac devices (Figure 6). In summary, a heart failure nurse recorded an ECG to assess heart rate, QRS width and AV/PR intervals. This was performed twice, with the implanted pacemaker turned both ON and OFF, in order 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 mid-lateral and posterior position). In the meantime routine laboratory tests, including a complete blood count along with an electrolyte and renal panel, were drawn to detect occult anemia and metabolic derangements. Of course, a comprehensive device check parallel to the one performed in the routine care was also performed. Following these measurements, the designated cardiologist recorded a detailed history in relation to 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. Afterwards, a comprehensive 2-dimensional ECHO examination was performed (Philips) with nominal settings of the CRT device. All reported echocardiographic measurements, including LV size/function and mitral regurgitation were averaged from at least 3 consecutive cycles, as recommended by the American Society of Echocardiography (18). Then an effort was made to optimize the LV diastolic filling, when it differed from stage I, by altering AV timing using conventional Doppler echocardiography. The optimal AV interval was determined by sampling mitral inflow with pulsed-wave Doppler to correspond with the shortest AV interval that dissociated the E- and A-wave, but did not interrupt the end of the A-wave (19-22). Finally, in order 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.

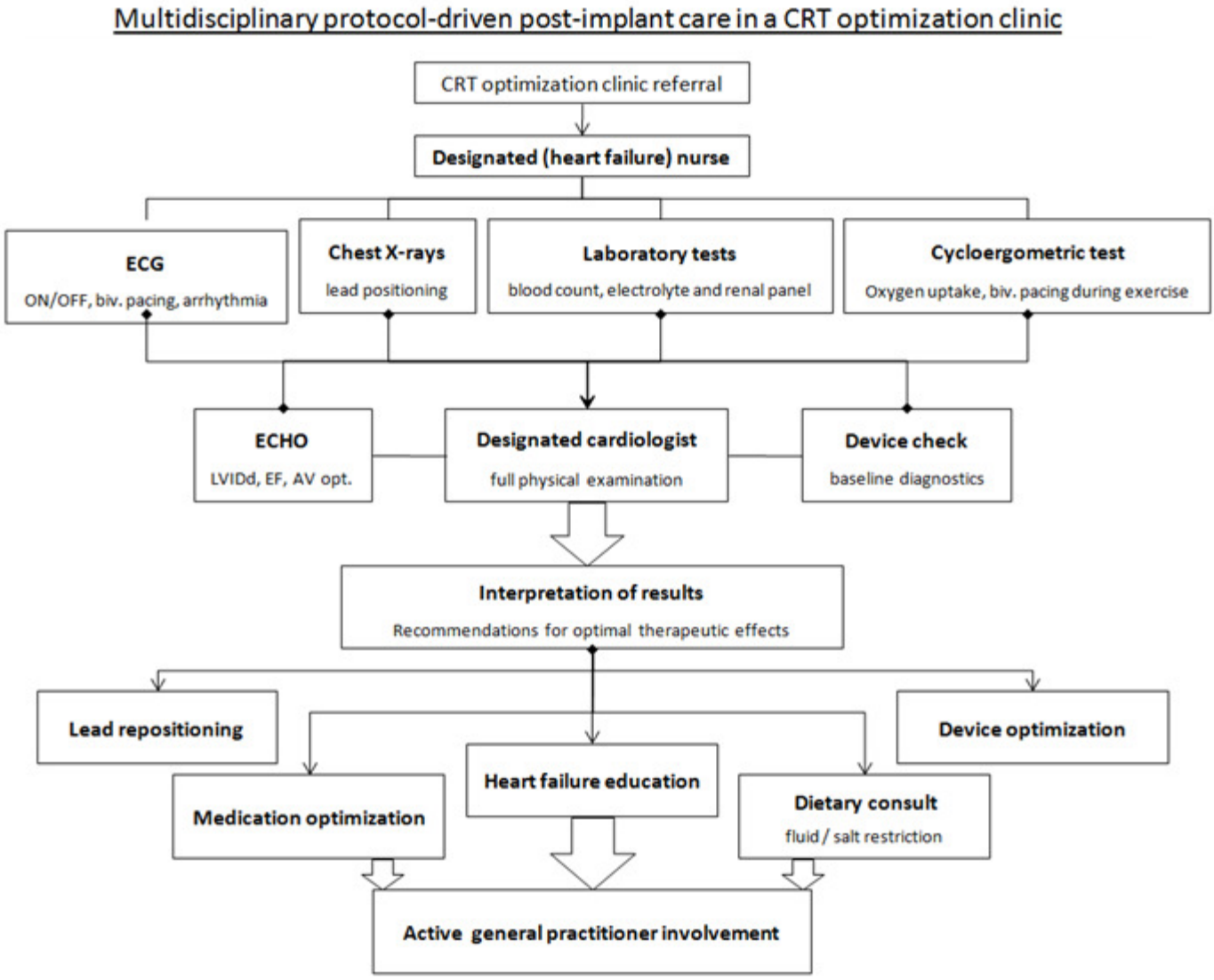

FIGURE 6. FLOW CHART representing the protocol-driven post-implant care in a dedicated heart failure disease management clinic.

CRT = cardiac resynchronization therapy ; ECG = Electrocardiograph ; ECHO = Echocardiograph

MULTIDISCIPLINARY HYPOTHESIS AND RECOMMENDATIONS

Based upon the findings of the protocol-driven measurements, a recommendation was proposed to the patient in order to maximize the potential of CRT. These recommendations were not mutually exclusive, as actions could be categorized by repositioning of the LV lead to prevent inappropriate lead positioning, changes in device programming in case of suboptimal device programming (mostly AV timing), or treatment of arrhythmias either medically or invasively. Thorough efforts were taken towards optimization of medical therapy (Table 2), i.e. uptitration of neurohormonal blockers to guideline-recommended doses, which were often not tolerated pre-implant. Importantly, these changes were done stepwise along with sufficient explanation to the patient, who was always provided with detailed written instructions how and

when to adjust their medication. In addition, adequate heart failure education was provided to familiarize the patient with heart failure risk factors and modifications in lifestyle. Patients were informed through dietary consults about salt free diets (2-3 grams NaCl daily) and fluid restriction (1-1.5 liters H_2O daily), which often coincided with a progressive reduction in loop diuretic doses. This concomitant clinical evaluation and education advised patients to become more knowledgeable in terms of their disease, in order to achieve maximal therapeutic effects. Importantly, all these adjustments were implemented in close collaboration with the 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 to ensure optimization of medical therapy was accomplished at home under close supervision.

TABLE 2. COMMON CARDIAC MEDICATIONS

Class name	**Properties**	*Mechanism*
ACE inhibitor & Sartan	**Antihypertensive**	*Blocks the RAAS pathway*
Hydralazine	**Antihypertensive**	*Relaxes vascular smooth muscle*
Beta-blocker	**Antiarrhythmic**	*Inhibits receptors at the heart*
Digoxin	**Antiarrhythmic**	*Controls heart rate during atrial flutter*
Aspirin	**Anti-inflammatory**	*Suppresses production of prostaglandins*
Clopidogrel	**Antiplatelet**	*Inhibits an ADP chemoreceptor*
Phenprocoumon	**Anticoagulant**	*Vitamin K antagonist*
Calcium channel blocker	**Antihypertensive**	*Disrupt the conduction of Ca^{2+} Channels*
Statin	**Anti cholesterol**	*Decreases cholesterol synthesis*
Isosorbide dinitrate	**Vasodilator**	*Dilates arteries*
Spironolactone	**Diuretic**	*Inhibits the effect of aldosterone*
Loop diuretic	**Diuretic**	*Inhibits sodium and chloride reabsorption*

END POINTS

We pre-specified the primary end-points for analysis as time of first occurrence of any of the following: all-cause mortality, cardiac transplantation, and/or first readmission for heart failure following the implant. Patients in the routine post-implant care group were followed from implant to date of first visit to the protocol-driven care clinic; whereas patients in the protocol-driven group were followed until April 30st 2010.

STATISTICAL ANALYSIS

Collected data is expressed as mean ± standard deviation, for continuous data and as a ratio for categorical data. Paired samples t-tests were performed for variables between related patients' data groups and independent samples t-tests were performed for variables between unrelated patients' data groups. Statistical significance was set at a 2-tailed probability level with $\alpha = 0.05$, equal variances were assumed with a significant equality of variances test. Kaplan-Meier survival curves were calculated with the combined endpoints for all patients stratified in two groups. The Cox Proportional hazards regression model was used to determine which variables were related significantly to the different endpoints during the FU period. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written. All statistical analyses were performed using SPSS for Windows, release 17.0 (SPSS Inc., Chicago, Illinois) under uHasselt license.

III. RESULTS

PATIENT CHARACTERISTICS

Baseline pre-implantation characteristics are summarized in Table 3 and were similar between both study groups. The extent of negative reverse remodeling at moment of implant was similar in both groups with regards to LV dimension (LVIDd, 6.2 ± 0.8cm vs. 6.4 ± 1cm, p = 0.26) and systolic function (LVEF, 26 ± 8% vs. 25 ± 8%, p = 0.68). All patients were classified as experiencing New York Heart Association [NYHA] functional class III or IV symptoms at moment of implantation, with a higher prevalence of NYHA class III symptoms in the group receiving routine care, 86% vs. 70%, as compared to more NYHA class IV symptoms in the group undergoing protocol-driven care, 14% vs. 30%. Nevertheless, physical fitness capacity measured during a cycloergometric test was also similar (Maximum Volume, 12.4 ± 3.2 ml/kg/min vs. 13.9 ± 4.7 ml/kg/min, p = 0.58).

Table 3. BASELINE DEMOGRAPHICS, 2-tailed independent samples t-test performed to test for statistical significance with confidence interval = 95% (*p-value ns: not significant*).

	Total	Routine	Protocol-driven	p-value
Demographics				
n	114	51	63	
Age (yrs)	71 ± 10	72 ± 10	71 ± 11	*ns*
Men (%)	64	55	73	**0,04**
CRT-D (%)	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*
BMI > 25: Obesity (%)	73	70	76	*ns*
BMI > 30: Morbid Obesity (%)	33	30	36	*ns*
Hypertension (%)	42	40	43	*ns*
Hyperlipidemia (%)	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*
Medication uptake				
Aspirin (%)	76	76	75	*ns*
ACE-inhibitors & Sartans (%)	88	84	90	*ns*
Beta-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*

Laboratory data

Hemoglobin (g/dl)	13,6 ± 1,6	14 ± 1,3	13,2 ± 1,5	**0,02**
Sodium (mEq/l)	139 ± 4	138 ± 5	139 ± 4	*ns*
Potassium (mEq/l)	4,39 ± 0,65	4,37 ± 0,47	4,41 ± 0,75	*ns*
Ureum (mg/dl)	59 ± 32	58 ± 33	60 ± 31	*ns*
Creatin (mg/dl)	1,3 ± 0,53	1,32 ± 0,52	1,28 ± 0,54	*ns*
eGFR* (ml/min)	50 ± 16	51 ± 4	50 ± 18	*ns*

***: estimated Globular Filtration Rate**

ECG 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 (Watt)	89 ± 32	84 ± 22	90 ± 34	*ns*
BP S/D* at rest (mmHg)	126 – 74	115 – 71	127 – 74	*ns*
BP S/D* exercise (mmHg)	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*

***: Systole / Diastole**

ECHO data

LVIDD (cm)	6,3 ± 1	6,2 ± 0,8	6,4 ± 1	*ns*
LV Ejection Fraction (%)	25 ± 8	26 ± 8	25 ± 8	*ns*

Total population:	**Mitral regurgitation (%)**	**Tricuspid regurgitation (%)**
0	22	46
I	33	29
II	34	23
III	7	1
IV	3	1

Medication uptake at time of implant was very similar for neurohormonal drugs (ACE-Inhibitors, 84% vs. 90%, p = 0.46 ; Beta-blockers, 82% vs. 94%, p = 0.12), with a higher usage of loop diuretics (84% vs. 67%, p = 0.02) in the routine group, compared to a higher intake of spirolactone (39% vs. 73%, p = 0.001) and oral vasodilators (Hydralazine, 2% vs. 14%, p = 0.02; Isosorbide dinitrate, 2% vs. 10%, p = 0.08) for the protocol-driven group.

In addition, the estimated globular filtration rate repeatedly kept dropping below the recommended 60 ml/min (eGFR, 51 ± 4 ml/min vs. 50 ± 18 ml/min, p = 0.78) , which is a diagnostic for signs of kidney insufficiency at time of implant. Aside from that, the hemoglobin readings of the protocol-driven care group proved to be slightly lower than that of the routine care group (Hemoglobin, 14 ± 1.3 g/dl vs. 13.2 ± 1.5 g/dl p = 0.2), though still far from anemic levels.

CLINICAL INTERVENTIONS DURING PROTOCOL-DRIVEN CARE

Uptitration in neurohormonal blockers was possible for 64% of patients (Figure 7), despite the fact that over 90% already was receiving ACE-inhibiting and Beta blocking medication at moment of implantation. Interestingly, most of these patients were already taking a similar dosage of neurohormonal blockers for more than three months before device implant and noted an improved tolerance to uptitration of these drugs after device implant.

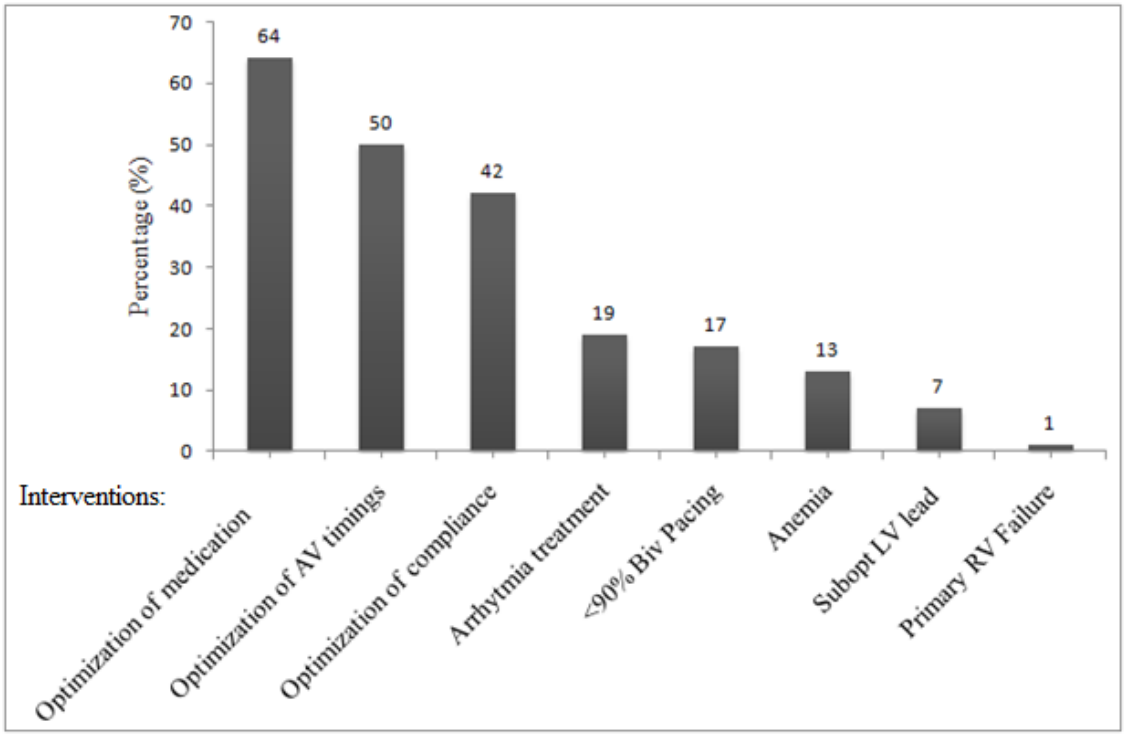

FIGURE 7. CLINICAL INTERVENTIONS performed at time of first visit to the protocol-driven CRT optimization clinic towards the whole patient population.

Failure in patient compliance with regards to salt/water restriction as well as stringent intake of medication was high, as 42% patients testified to having poorly followed their daily medication intake and dietary advice. After implementation of heart failure education together with dietary consult, in collaboration with the general practitioners, this issue seemed to be resolved almost completely afterwards. Importantly, this lead to a reduction in dosage of loop diuretics in 22% of patients (Figure 8).

In addition, 73% patients were deemed obese (Body mass index [BMI] > 25 kg/m2) of which 33% had morbid obesity (BMI > 30 kg/m2). Finally, 13% of patients had anemia, defined as hemoglobin < 11 g/dl for female and < 12 g/dl for male patients; but only 1 patient had hemoglobin < 10 g/dl, which was treated with transfusion or erythropoietin agents.

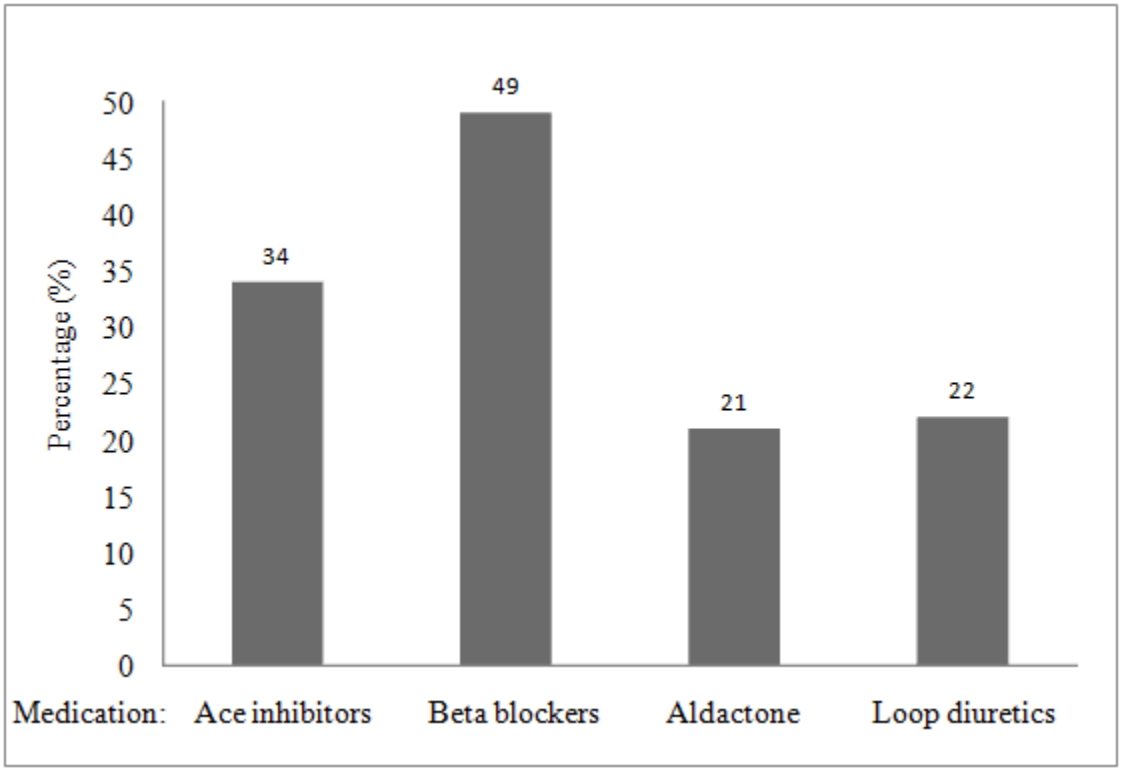

FIGURE 8. MEDICATION BAR GRAPH representing the total percentage of patients whose medication needed to be optimized at time of first visit to the protocol-driven care CRT optimization clinic.

ELECTROPHYSIOLOGICAL AND DEVICE RELATED INTERVENTIONS DURING PROTOCOL-DRIVEN CARE

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

Device interrogation was successful in all patients, which were paced in biventricular mode on an average 97% of the time, mostly in an atrial sensing – ventricular pacing mode. No battery depletion or lead integrity was noted.

Arrhythmias were present for 35% patients, mostly as atrial fibrillation, however for 11% frequent ventricular ectopy was present, leading to <100% biventricular pacing in 17% and <90% biventricular pacing in 26% of patients. All arrhythmias were treated accordingly, at least to ensure >90% biventricular pacing in 85% instead of 74% 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, following 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.

EFFECTS ON LEFT VENTRICULAR REMODELING AND EXERCISE CAPACITY

Positive remodeling was noted in both groups with regards to LV dimension and LV function. However, the extent of positive LV remodeling was significantly greater in the group receiving protocol-driven care from the very start. Indeed, while the LVIDd had decreased from 6.2 to 6.0 cm ($p = 0.05$) in the routine FU, patients undergoing the protocol-driven FU had a more extensive decrease from 6.4 to 5.8cm ($p < 0.001$) (Figure 9). In addition, while the routine care group experienced an increase in LVEF from 26 to 33% ($p < 0.001$), this was more pronounced in the protocol-driven care group, from 25 to 37% ($p < 0.001$) (Figure 10).

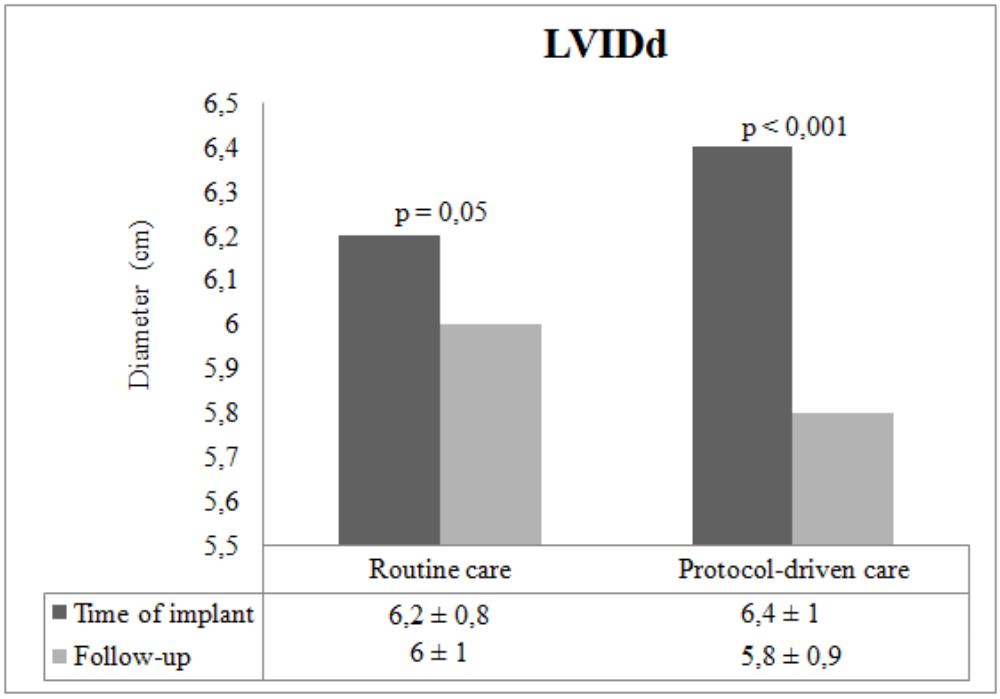

FIGURE 9. THE LEFT VENTRICULAR INTERNAL DIAMETER IN DIASTOLE GRAPH, representing the internal width in cm at time of implant vs. follow-up for both study groups.

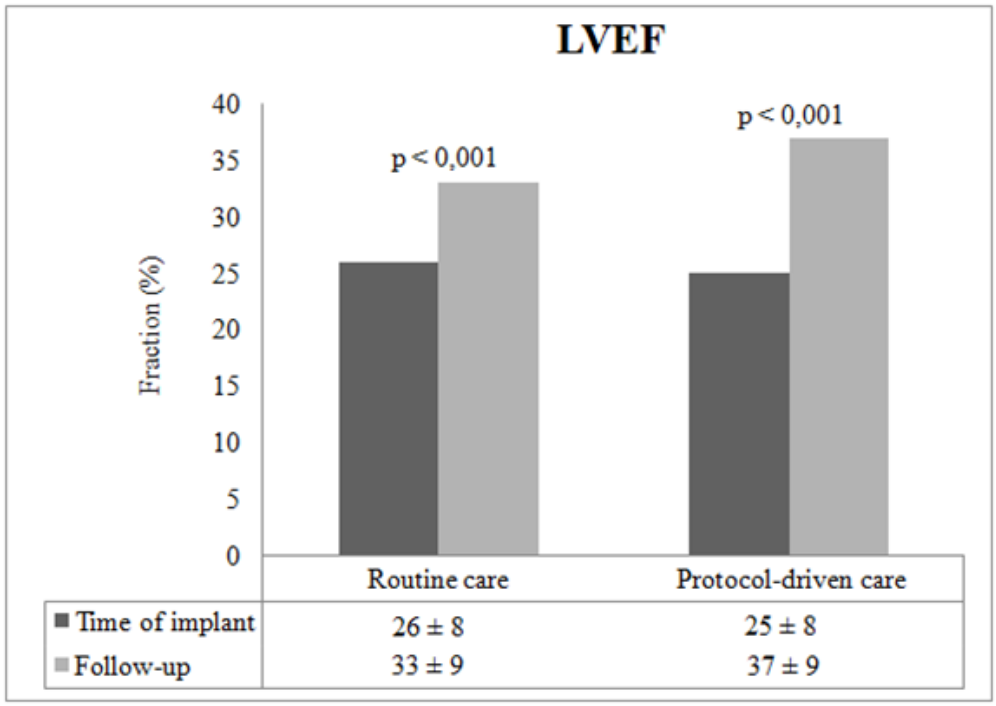

FIGURE 10. THE LEFT VENTRICULAR EJECTION FRACTION (%) GRAPH, which is the ejected fraction of blood from the left ventricle during each heart beat, at time of implant vs. follow-up for both study groups.

Moreover, as summarized in Table 4, the improvement in exercise capacity as measured through maximum oxygen uptake was more noticeable for the protocol-driven care group, increasing from 14 to 15.5 ml/kg/min (p = 0.03). Interestingly, these positive effects did not seem to be related with a reduction in ventricular dyssynchrony, as the reduction in QRS and

PR times did not differ significantly among the study groups (PR, 142 ± 26ms vs. 128 ± 30ms, p = 0.16; QRS, 150 ± 30ms vs. 158 ± 21ms, p = 0.81).

However, the time of implant results differ slightly from those in the baseline demographics because of a lower number of paired couples (Time of implant vs. Follow-up) available for statistical testing, resulting in a lower data variance for both patient groups.

TABLE 4. CLINICAL DATA, 2-tailed paired samples t-test performed to test for statistical significance with confidence interval = 95% (*p-value ns: not significant*).

	Time of implant	Follow-up	p-value
ECHO data			
LVIDD (cm)			
Routine care	6,2 ± 0,8	6,0 ± 1,0	**0,05**
Protocol-driven care	6,4 ± 1,0	5,8 ± 0,9	**< 0,001**
LVEF (%) *(p = 0,05)			
Routine care	26 ± 8	33 ± 9	**< 0,001**
Protocol-driven care	25 ± 8	37 ± 9	**< 0,001**
Cycloergometric data			
Maximum oxygen uptake (ml/kg/min) *(p = 0,05)			
Routine 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)			
Routine care	117 ± 18	104 ± 22	*ns*
Protocol-driven care	115 ± 24	105 ± 26	**0,02**
ECG data			
PR width (ms)			
Routine care	187 ± 45	142 ± 26	**< 0,001**
Protocol-driven care	188 ± 46	128 ± 30	**< 0,001**
QRS width (ms)			
Routine care	155 ± 32	150 ± 30	*ns*
Protocol-driven care	157 ± 29	158 ± 21	*ns*

***: There is a significant difference between the 2 study groups at follow-up, CI=95%**

When comparing the results from both post-implant care patient groups at FU, those in the protocol-driven care group proved to have a significantly higher ejection fraction (LVEF, 33 ± 9% vs. 37 ± 9%, p = 0.05) and a physical fitness capacity (Maximum oxygen uptake, 14.5± 2.5 ml/kg/min vs. 15.5 ± 4.2 ml/kg/min, p = 0.05) when compared to the routine care group.

FINDINGS OF ROUTINE CARE PATIENTS AT MOMENT OF FIRST VISIT TO THE CRT CLINIC

As of August 2008, all patients receiving routine care were also referred to the protocol-driven CRT clinic. Interestingly, clinical, electrophysiological and device-related interventions were in overall similar compared to the group which was followed in the protocol-driven CRT clinic straight after implantation. Indeed, uptitration of neurohormonal drugs was necessary for nearly half the patient population (Figure 11), which coincided with a reduction in dosage of loop diuretics for 20% patients. Also, up to 43% patients confirmed to having poorly maintained their medication and dietary guidelines set by the treating cardiologist. In addition, 51% of patients were shown to be paced with suboptimal AV timings and 20% of patients presented with arrhythmias.

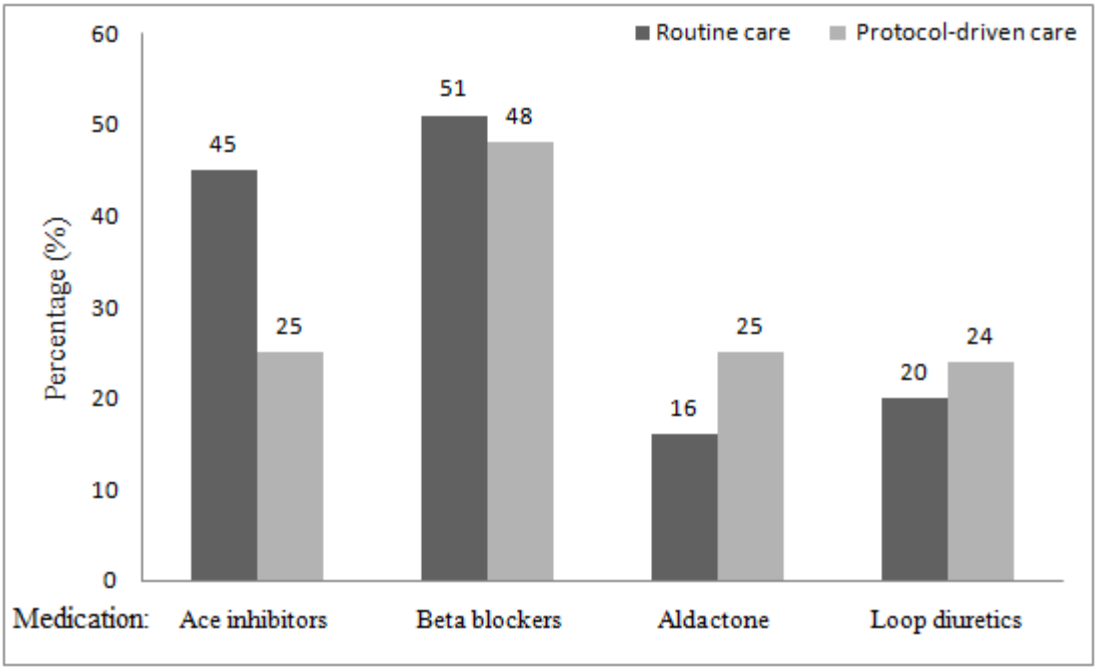

FIGURE 11. MEDICATION BAR GRAPH representing the percentage of patients whose medication needed to be optimized at time of first visit to the protocol-driven driven CRT optimization clinic for routine care vs. protocol-driven care groups.

ROUTINE CARE PATIENTS INCLUDED TO PROTOCOL-DRIVEN CARE

Even though positive remodeling was already noted in the routine care group at FU, its extent was limited when compared to the group receiving protocol-driven care. Therefore, there was still room for further remodeling at a the FU's succeeding the clinical interventions performed at the protocol-driven care CRT optimization clinic. Indeed, following the first clinic's visit, the LVIDd had decreased even further from 6.0 to 5.8 cm ($p = 0.02$). Likewise,

the LVEF also showed a significant increase from 33% to 36% (p = 0.02) (Table 5). Take note that these are the same patients being investigated pre and post protocol-driven care, the only difference lies in the extent of multidisciplinary care received during their therapy.

TABLE 5. ECHO DATA, 2-tailed paired samples t-test performed to test for statistical significance with confidence interval = 95%.

Routine care group		p-value
ECHO data		
LVIDD (cm)		
Time of implant	6,2 ± 0,8	
Routine care FU	6,0 ± 1,0	**0,05**
Protocol-driven care FU	5,8 ± 1,1	**0,02**
LVEF (%)		
Time of implant	26 ± 8	
Routine care FU	33 ± 9	**< 0,001**
Protocol-driven care FU	36 ± 13	**0,02**

OUTCOMES

Mean clinic visit duration was 45 minutes with involvement of a designated nurse (± 25 minutes) and cardiologist (± 20 minutes). At the end of the FU period (mean follow-up duration was 19 ± 11 months), 36% of the patients had either died, undergone cardiac transplantation and/or were hospitalized for decompensated heart failure. While overall mortality / cardiac transplantation was similar for both groups (3 vs. 4 events, p = 1) (Figure 12 - left), patients receiving the protocol-driven care had fewer adverse events during FU (28 vs. 9 events, p < 0.001) (Figure 12 - right). The protocol-driven FU was not associated with lower all-cause mortality (OR: 1.085; p = ns ; 95% CI: 0.231 – 5.084), but did lead to reduction in heart failure hospitalization (OR: 0.137; p < 0.001 ; 95% CI: 0.056 – 0.335) when compared to routine post-implant care. A Kaplan-Meier survival curve was calculated for the combined endpoints (29 vs. 12 events; OR: 0.178; p < 0.001 ; 95% CI: 0.077 – 0.413) (Figure 13).

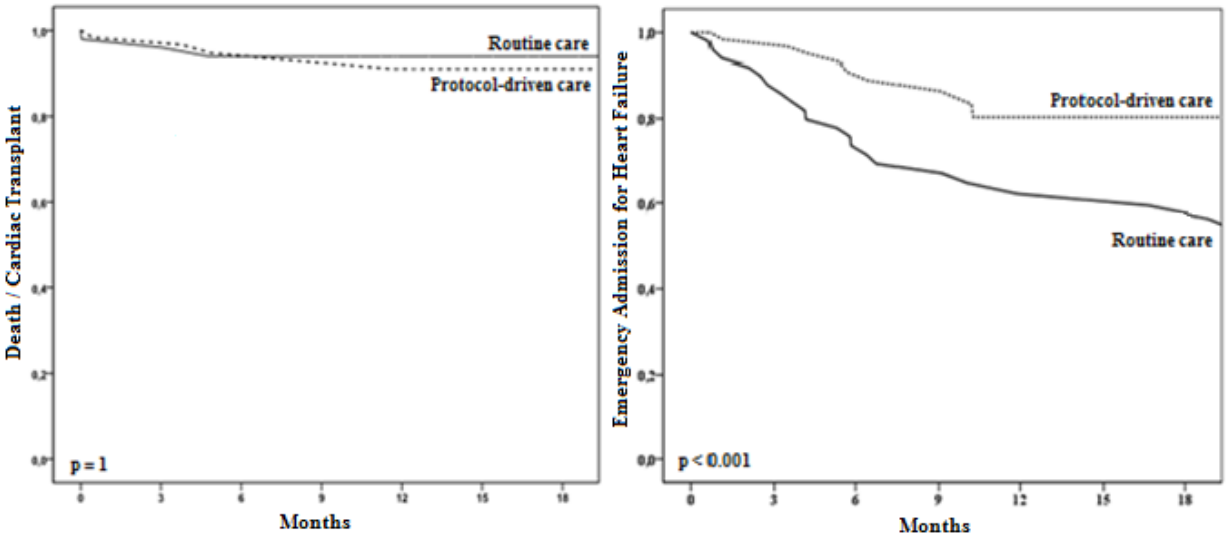

FIGURE 12. KAPLAN-MEIER SURVIVAL CURVE FOR CLINICAL OUTCOMES of "Routine care" versus "protocol-driven care" with following endpoints: death and cardiac transplant (left) and emergency admission for heart failure (right).

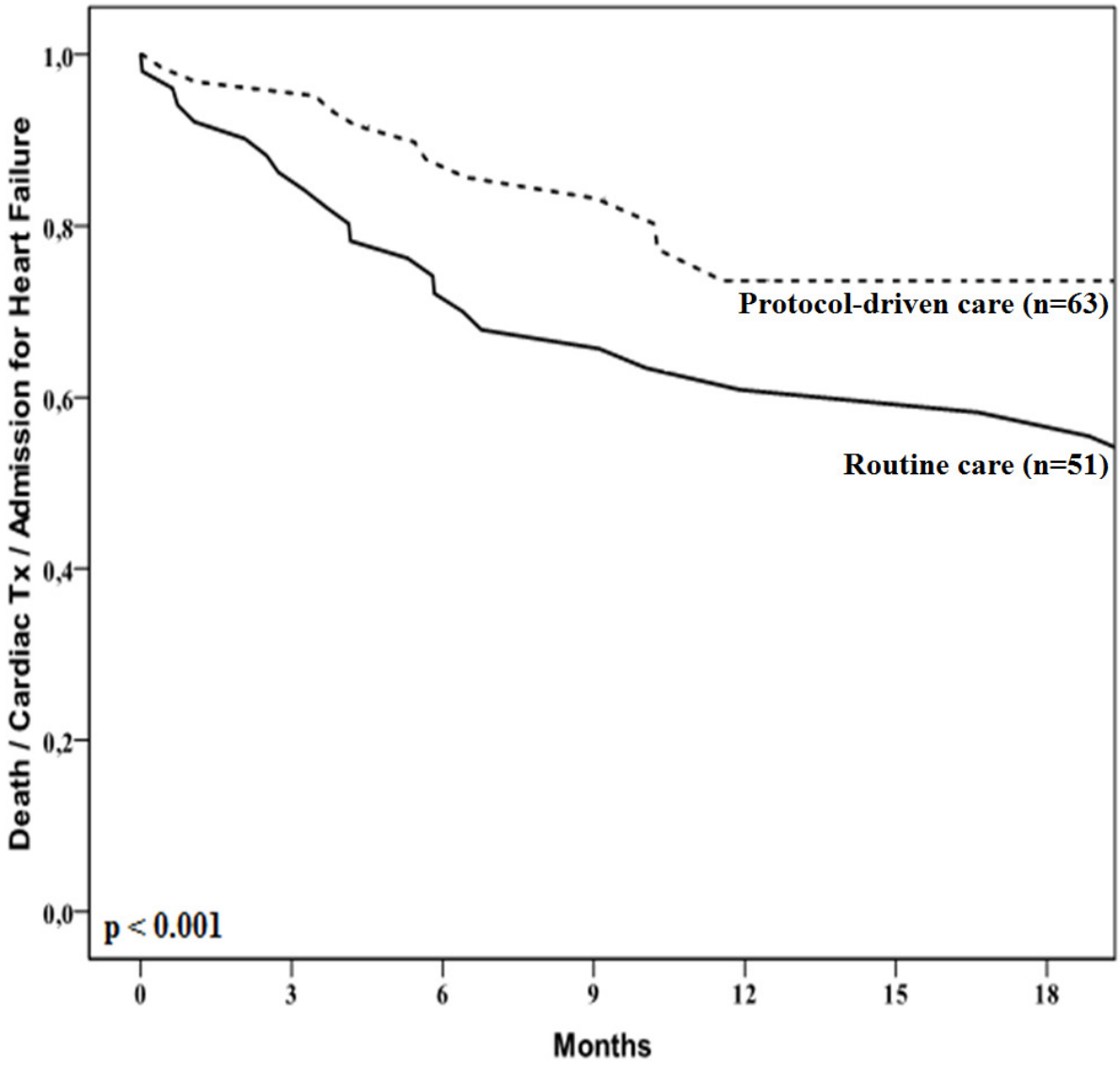

FIGURE 13. KAPLAN-MEIER SURVIVAL CURVE FOR COMBINED CLINICAL OUTCOMES of "Routine care" versus "protocol-driven care" with following endpoints: death, cardiac transplant and emergency admission for heart failure.

IV. DISCUSSION

There have been very few contemporary reports describing post-implantation management of CRT, particularly with regards to optimization of medical therapy and heart failure education. Based on earlier work which described the feasibility and value of a multidisciplinary protocol-driven CRT optimization clinic, as part of a heart failure disease management program for ambulatory patients with persistent symptoms and/or disease progression long after their implantation (16), we now report on the feasibility and results of a protocol-driven approach during FU of all CRT patients straight after their implant.

A consistent finding in this study has been the improvement in exercise capacity and clinically improved LV dimensions in the majority of patients with systolic heart failure. The changes in LV size as a result of CRT were associated with an increase in ejection fraction at 3 months, with further incremental improvement at 6 months.These beneficial effects of CRT were achieved in patients already receiving optimal medical therapy along with the necessary surgical procedures.

Using an algorithm with standard equipment and readily available clinical exams that can be reproduced in any outpatient cardiology clinic; for the majority of patients further uptitration of neurohormonal blockers was feasible, as well as a reduction in loop diuretics, on top of thorough heart failure education with active involvement of the general practitioners. The remaining interventions involved optimization of AV timing interval to the best LV filling efficiency based on transmitral Doppler flow measurements. Importantly, this approach seemed to be associated with improved outcomes with regards to exercise capacity and LV remodeling, as well as a reduced incidence of adverse events during FU, when compared to routine post-implant care. While many of these findings may seem intuitive to the experienced clinician, the concept of a dedicated protocol-driven approach of CRT patients is of high clinical value, with the contemporary tendency for more remote-follow-up of devices where device optimization, rather than patient optimization, is considered the most important goal following device implant.

The design of this protocol-driven FU of ambulatory patients implanted with a CRT pacemaker is unique in several aspects. First, it started straight after the implant in *all* patients implanted with a CRT, thereby not being limited to only non-responders, and thus providing a more accurate measure of the feasibility and impact of such an approach. Secondly, it utilized a combination of a comprehensive clinical and device-based evaluation, combined with an

echocardiographic examination, embedded in a centralized multidisciplinary outpatient evaluation, with continuous efforts made to optimize medical therapy on top of thorough heart failure education appealing for active involvement of the general practitioners. Third, this protocol-driven approach was compared to standard routine care in all consecutive patients implanted before (: routine) and after (: protocol-driven) September 2008, which in turn minimized the likelihood for factors such as selection bias to confound the analysis and allowed to assess the potential benefits of such an approach.

The benefits of CRT are mostly attributed to electrical resynchronization of the heart leading to improved exercise tolerance, cardiac remodeling and a better survival rate in patients showing advanced heart failure symptoms and evidence of ventricular conduction delay (1-3). Just like in any other therapy, the extent of the response to CRT can be heterogeneous, so most studies have focused primarily on refining pre-implantation patient selection to predict a favorable response; or focused on device optimization, lead positioning or arrhythmia treatments in patients with a suboptimal response. In contrast to previous reports about non-responders being examined long after implant, in which a high prevalence of device-related issues was optimized (16), this report indicates that up to two-thirds of patients tolerated uptitration of neurohormonal blockers after CRT implant to dosages previously (pre-CRT) not tolerated.

Importantly, all patients implanted with a CRT device in both groups had fulfilled standard inclusion criteria, including optimal medical therapy as tolerated by their treating cardiologist. Other clinically-related issues, such as presence of rhythm abnormalities (19%) with concomitant inadequate delivery of biventricular pacing, were also treated accordingly, mostly through medication changes. In addition, 42% of patients had improved their compliance towards reduction in salt and fluid intake, after thorough heart failure education. In practice, changes in medical therapy along with the necessity of compliance were explained altogether with written instructions to the patients during every office visit, in close collaboration with the general practitioners who followed the patients' status at home. All patient received ECHO-guided AV optimization, which resulted in a significant amount of device timing optimization as well. These observations highlight the notion that current post-implant approaches to longitudinal monitoring may overlook important issues like optimization of medical therapy and heart failure education.

In essence, the comparison of routine care with protocol-driven care also allowed to assess the potential impact on remodeling and outcomes. Even though positive effects towards improvement in exercise capacity and remodeling were noticeable in both groups, the extent of these positive effects was significantly greater in the protocol-driven approach, ultimately

leading to a reduced incidence of adverse events at FU. Importantly, this was not attributable to a more pronounced reduction in electrical dyssynchrony in the protocol-driven approach. It is therefore most likely that yet unrecognized contributors of CRT response (e.g. optimization of medical therapy, heart failure education,…), which act independently of a reduction in dyssynchrony, may directly influence the clinical and echocardiographic response to CRT.

Therefore, an improvement in clinical or echocardiographic response after successful resynchronization should not imply that a routine FU visit or a remote device FU is sufficient. Instead, the appropriate interpretation of our experience should consider the possibility that a protocol-driven approach is warranted to ensure a more persistent meaningful change in the natural history of heart failure disease progression after CRT pacemaker implant. These observations challenge the prevailing belief that a patient's response to CRT is based solely on electronic resynchronization itself, as uptitration of medical therapy in conjunction with heart failure education also contributed to a better response.

CLINICAL IMPLICATIONS

There might be a reluctance of physicians to use a protocol-driven clinic as part of their routine FU of patients with implanted CRT devices. Indeed, a scarce amount of data to further substantiate these clinical findings, combined with the lack of resources to support the implementation of a dedicated CRT clinic, may all contribute to a physician's lack of enthusiasm in establishing such a protocol. In addition, there might be realistic concerns that such an approach might lead to an increased workload and costs incurred due to excessive investigations and/or procedures. It is, therefore, reassuring to observe a "real-life" experience of a protocol-driven approach, without using needlessly complex and expensive tests, nor invasive procedures, which might result in improved adherence to medical heart failure therapy, eventually resulting in a better response and less adverse events at FU. By combining the imaging-, heart failure-, and electrophysiology evaluation within one centralized outpatient visit, the total cost and time could be contained. As experience shows, a multidisciplinary optimization clinic is the most direct path towards getting the appropriate care and cross-training among subspecialties. It is conceivable that this approach can be performed by any number of practicing cardiologists, knowledgeable and interested in maximizing the potential of CRT for all patients, not only limited to those lacking an optimal response. Furthermore, the time and personnel commitment is likely very acceptable as part of any heart failure disease management program.

STUDY LIMITATIONS

It is important to recognize that this is not a randomized comparison between routine post-implant care versus protocol-driven post-implant care. Also, referral of patients to the CRT optimization clinic was based on the implementation of such a protocol-driven approach over time. Therefore, part of the more positive results might be attributed to improved clinical care secondary to more experienced hospital staff and a physician's expertise in terms of cardiac care, as well as improved medication treatments. However, the fact that similar changes could be made in the patients initially following routine care at the moment of their first visit to the protocol-driven CRT optimization clinic, argues against the argument that the more positive effects in the protocol-driven care group were due to more experience.

V. CONCLUSION

A multidisciplinary protocol-driven approach for all CRT patients started immediately after device implantation, which incorporates routine device checks with concomitant patient education and medication optimization, is associated with more favorable effects on reverse remodeling and clinical outcomes, as well as fewer adverse events when compared to routine post-implant care. These effects seem to be largely driven by changes in device settings, arrhythmia management, heart failure education and uptitration of neurohormonal blockade.

All the data contained within this Master's thesis is supported by the writer and lead to the design of a scientific article titled "*Value of a routine protocol-driven post-implant management cardiac resynchronization therapy clinic*", which has been submitted for publication in a peer-reviewed tier 1 cardiovascular journal (cfr. supplemental data in Appendix I - Abstract).

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APPENDIX I

VALUE OF A ROUTINE PROTOCOL-DRIVEN POST-IMPLANT MANAGEMENT CARDIAC RESYNCHRONIZATION THERAPY CLINIC

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ABSTRACT

Background: A multidisciplinary protocol-driven approach to evaluate ambulatory cardiac resynchronization therapy (CRT) patients who did not exhibit a positive response has been shown to be feasible, and might be associated with fewer adverse events.

Objectives: To investigate if a protocol-driven approach incorporated in a heart failure disease management clinic for all CRT patients, started immediately after implant, would improve outcomes from a clinical or remodeling endpoint compared to routine post-implant care.

Methods: A total of 114 consecutive CRT patients implanted between 2005-2009 were analyzed and stratified in two groups; those that received routine post-implant care (11/2005-07/2008) versus those that underwent the protocol-driven post-implant management CRT clinic (09/2008-02/2010).

Results: Baseline pre-implantation characteristics among the routine vs. protocol-driven care were similar with regards to LV dimension (6.2 vs. 6.4cm), LVEF (26 vs. 25%), QRS width (155 vs. 160ms) and medication usage (89 vs. 90% neurohormonal blockers). Major adjustments during the protocol-driven approach were echo-guided optimization of AV-timing (52%), uptitration of neurohormonal blockers (34% ACE-inhibitors / 49% beta-blocking agents), heart failure education (42%), arrhythmia management (21%) and LV lead repositioning (7%). Though positive LV remodeling was noted in both groups at 6 months, the extent was significantly greater in the protocol-driven approach when compared to routine care (LVIDd: 6.2±0.8cm to 6.0±1cm, p=0.052 vs. 6.4±1cm to 5.8±0.9cm, p<0.001; LVEF: 26±8% to 33±9%, p<0.001 vs. 25±8% to 37±9%, p<0.001) and was associated with less adverse events during FU (29 vs. 12 events; OR: 0.178 ; p < 0.001 ; 95% CI: 0.077 – 0.413).

Conclusions: A routine protocol-driven approach for CRT patients started immediately after their device implantation is associated with more favorable effects on reverse remodeling and fewer adverse events compared to routine post-implant care. These effects appeared to be driven not only by changes in device settings and arrhythmia management but also by concomitant heart failure education and/or medication optimization.

APPENDIX II

SUMMARY - DUTCH

De westerse maatschappij wordt geconfronteerd met een toenemende vergrijzing van de bevolking, dat in direct verband staat met een hoger voorkomen van cardiovasculaire aandoeningen, o.a. hartfalen. Een specifieke groep hartfalenpatiënten vertoont daarnaast geleidingsstoornissen die tot zogenaamde *ventriculaire dissynchronie* leiden, d.w.z. in plaats van gelijktijdig te slaan, kloppen de twee hartkamers licht uit fase. Deze afwijking vermindert in ernstige mate de hartfunctie, daarmee verder bijdragend tot de symptomen. "*Cardiac resynchronization therapy*" [CRT] is een apparaatgebaseerde interventie geïnspireerd door de technologie toegepast in pacemakers. Deze apparaat is in staat is om *beide hartkamers gelijktijdig te stimuleren*, wat zowel hartfunctie verbetert als symptomen verlicht.

Nochtans schijnt tot één derde van patiënten niet te reageren op CRT, ondanks correcte implantatie en programmering van het apparaat. Om dit probleem aan te snijden werd een *multidisciplinair protocol* opgesteld, gebaseerd op studies waarin ambulante CRT patiënten werden geëvalueerd die geen positief respons vertoonden. Dit protocol richtte zich op het verfijnen van postimplantatie zorg om zowel apparaat als non-apparaat bijdragende factoren te optimaliseren, om alsnog een respons op te wekken. Ondanks zeer gunstige resultaten, werd dit protocol nog niet systematisch uitgetest op *alle* CRT patiënten. Om het volledig effect in te schatten werd een totaal van 114 opeenvolgende CRT patiënten geïmplanteerd tussen 2005-2009 om bijkomend onderverdeeld te worden in twee groepen; een eerste groep dat *routine postimplantatie zorg* (11/2005-07/2008) ontving, tegenover een tweede groep patiënten die de *protocolgedreven postimplantatie zorg* (09/2008-02/2010) in een gespecialiseerde hartziektekliniek onderging. Er werd ondermeer rekening gehouden met remodelling (i.e. afname in linkerventrikel diameter) en inspanningscapaciteit, alsook ongunstige eindpunten waaronder mortaliteit en spoedopname na implantatie.

Bijgevolg kan worden gesteld dat een *protocolgedreven aanpak* van *alle* CRT patiënten, opgenomen in een gespecialiseerde kliniek voor hartziekten gestart *onmiddellijk na implantatie*, geassocieerd kan worden met *meer gunstige uitkomsten* op positieve remodelling-vlak alsook *minder ongunstige gebeurtenissen*, wanneer het vergeleken wordt met routine postimplantatie zorg. Deze uitkomsten bleken niet enkel gedreven door veranderingen in specifieke *apparaatinstellingen* en *aritmiebeheer*, maar ook door bijkomend *onderwijs in hartfalen* en/of *optimalisatie van medicatie*.

Auteursrechtelijke overeenkomst

Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
Insights from implementing a routine Cardiac Resynchronization optimization clinic in a tertiary Belgian Hospital

Richting: **master in de biomedische wetenschappen-bio-elektronica en nanotechnologie**
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Voor akkoord,

Kepa, Jacek

Datum: **14/06/2010**