NON-PHARMACOLOGICAL TREATMENT OF CHRONIC SYSTOLIC HEART FAILURE

OPTIMIZATION OF CARDIAC RESYNCHRONIZATION THERAPY FOR THE TREATMENT OF CHRONIC HEART FAILURE: RESPONSE OF PATIENTS AND NEW INDICATIONS

PhD thesis

Annamária Kosztin MD

Semmelweis University
Doctoral School of Basic Medical Sciences

Supervisors: Béla Merkely MD, DSc
Gábor Földes MD, PhD

Reviewers: Lívia Jánoskúti MD, PhD
Róbert Pap MD, PhD

Chairman of the Commitee: Péter Sótonyi MD, DSc
Members of the Commitee : István Lőrincz MD, PhD
Gergely Szabó MD, PhD

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1 ABBREVIATIONS

ACE: Angiotensin Converting Enzyme

AE: Adverse Event

ARB: Angiotensin Receptor Blocker

AV: Atrio-Ventricular

AUC: Area Under the Curve

BNP: Brain Natriuretic Peptide

BUN: Blood Urea Nitrogen

CABG: Coronary Artery Bypass Graft

CI: Confidence Interval

COPD: Chronic Obstructive Pulmonary Disease

CRT: Cardiac Resynchronization Therapy

CRT-D: Cardiac Resynchronization Therapy with defibrillator

CRT-P: Cardiac Resynchronization Therapy - Pacemaker

CT-apelin: C-Terminus Apelin

EDV: End-diastolic Volume

EF: Ejection Fraction

ELISA: Enzyme-linked Immunosorbent Assay

ESV: End-systolic Volume

EDV: End-diastolic Volume

HF: Heart Failure

HR: Heart Rate

HTX: Heart Transplantation

ICD: Implantable Cardioverter Defibrillator

IQR: Interquartile Range

IVCD: Intraventricular Conduction Disorder

LBBB: Left Bundle Branch Block

LVEF: Left Ventricular Ejection Fraction

LVESV: Left Ventricular End-systolic Volume

NYHA: New York Heart Association

NT-proBNP: N-terminal prohormone Brain Natriuretic Peptide

PCI: Percutaneous Coronary Intervention

PM: Pacemaker

PI: Principal Investigator

PTX: Pneumothorax

ROC: Receiver Operating Characteristic Curve

RBBB: Right Bundle Branch Block

RVAP: Right Ventricular Apical Pacing

RV-LV AD: Right to Left Ventricular Activation Delay

SAE: Serious Adverse Event,

TDI: Tissue Doppler Imaging

UADE: Unanticipated Adverse Device Effect

USADE: Unanticipated Serious Adverse Device Effect

VT: Ventricular Tachycardia

VF: Ventricular Fibrillation

VV: Ventriculo-Ventricular

6MWT: 6-minute Walk Test

77-aa apelin peptide: 77-aminoacid apelin peptide

2 INTRODUCTION

2.1 Prevalence and incidence of chronic systolic heart failure

During the past half century, cardiovascular disease has become the largest cause of mortality worldwide (1), the prevalence is approximately 1–2% of the adult population in developed countries, rising to ≥10% among people over 70 years of age (2). Heart failure (HF) is still a major and rising healthcare problem, due to the successful acute coronary syndrome-treatment and ageing, the previously fatal condition turned to a prolonged chronic disease with subsequent hospital admissions (1). Based on data about causes of cardiovascular hospitalization suggests, the ratio of HF hospitalization is decreasing, but primarily in the population with reduced, not with preserved ejection fraction (2). The European Society of Cardiology Heart Failure Registry, where approximately 70% of patients had reduced ejection fraction (<45%), showed that 12-month all-cause mortality rates for hospitalized and ambulatory patients were 17% and 7%, respectively (3), while the 12-month hospitalization rates were 44% and 32%, respectively (3).

2.2 Diagnosis of heart failure

1.1.1 Signs and symptoms of heart failure

Heart failure is a complex clinical syndrome with non-specific signs and symptoms of fluid retention and increased sympathetic activity (2), therefor the most accurate diagnostic tools of HF are supposed to provide objective evidences of a structural or functional cardiac abnormality (2).

2.2.2 Gold standard clinical tools to diagnose heart failure: Echocardiography and NT-proBNP

Echocardiography is the most useful, widely available and easily reproducible test to confirm the diagnosis of HF. It provides immediate information on ejection fraction, systolic and diastolic function, chamber volumes and dimensions and valve function, which are essential for the diagnosis and treatment of HF (2).

The other gold standard diagnostic tool is the B-type natriuretic peptide (BNP) and N-

terminal prohormone BNP (NT-proBNP), which is broken down by an enzyme called neprilysin. The negative predictive values of these peptides are very similar and high (0.94–0.98) during the chronic and acute HF events, however the positive predictive values are lower in chronic (0.44–0.57) and in acute settings (0.66–0.67) as well (4).
Therefor the evaluation of natriuretic peptides is primarily recommended for excluding, not for confirming the diagnosis of HF.

2.3 Treatment of chronic systolic heart failure

2.3.1 Pharmacological treatment

In patients with chronic systolic HF the aim of the treatment includes the improvement of their symptoms and quality of life, decrease the number and duration of hospital admissions and reduce mortality. By evidences of high-volume, randomized trials, the basic pharmacological regime has been confirmed as the most effective therapy which improves these endpoints.
Groups of neurohormonal antagonists reduce all-cause mortality, thus present as IA evidence level in the current guidelines: these are the beta blockers, ACE inhibitors and Mineralocorticoid Receptor Antagonists (2). However a new compound, CLCZ (combination of ARB and the neprilysin inhibitor, sacubitril) has been already shown to be superior to an ACE inhibitor, enalapril (2). Until further evidences are coming, it is recommended as a IB-drug for replacement of an ACE-inhibitor in ambulatory patients with systolic HF who remain symptomatic despite optimal medical treatment.
Angiotensin Receptor Blockers are alternative therapies when ACE inhibitors are contraindicated or not tolerated. Any other pharmacological treatments such as diuretics, ivabradine, direct vasodilators and digoxin can be added for selected patient populations with symptoms (NYHA II-IV)(2).

2.3.2 Non-pharmacological treatment: Implantable Cardioverter Defibrillator (ICD), Cardiac Resynchronization Therapy (CRT)

2.3.2.1 Implantable Cardioverter Defibrillator

A high proportion of deaths among patients with severe systolic HF occur suddenly and unexpectedly due to electrical disturbances, including ventricular arrhythmias, bradycardia or asystole (2). We can account approximately 20% of incidence of sudden cardiac death in patients with lower than 30% of left ventricular ejection fraction (5). To prevent sudden cardiac death and to terminate potentially lethal ventricular arrhythmias, the most effective therapy is the implantable cardioverter defibrillator compared to antiarrhythmic agents.

As a choice of secondary prevention, ICD was investigated in AVID(6), CIDS(7), and CASH(8) trials, where ischemic and non-ischemic patients were enrolled after ventricular tachycardia (VT) or ventricular fibrillation (VF) with syncope and low ejection fraction (except for CASH trial, where the mean ejection fraction was 46 ± 18%). In these trials ICD was compared to amiodarone, sotalol, metoprolol or propafenon. Each trials confirmed that ICD group experienced 20-31% relative risk reduction in all-cause mortality in the first three years compared to groups treated with antiarrhytmic agents.

For primary prevention MADIT I (9), MADIT II (10), MUSTT (11) and SCAD-HeFT (12) trials confirmed the effectivity of ICD compared to conventional therapy. The first, MADIT I trial investigated ischemic HF patients with mild to moderate symptoms (NYHA I-III) with inducible or asymptomatic VT and low ejection fraction. The ICD group experienced a 31% risk reduction in all-cause mortality, while on conventional treatment arm 22% risk reduction was observed during the mean follow up time of 27 months. In MADIT II 1232 patients were enrolled who experienced a myocardial infarction less than 30 days prior to enrolment and had low EF (≤30%) and they were randomized to ICD or non-ICD arm in a 3:2 manner. The study ended with similarly favourable results as MADIT I.

SCD-HeFT (12) was the latest of those studies demonstrating the benefits of ICDs. In the trial 2521 mild to moderate HF patients (NYHA II-III) with low EF (≤35%) were investigated. The results concluded the evidences of studies mentioned above, that ICDs significantly reduce the risk of all-cause mortality (from 31 to 55%) in groups suffering or in potentially risk of sudden cardiac death caused by malignant ventricular

arrhythmias.

Thus by the current guidelines (2) patients have to be implanted an ICD after 3 months of optimal medical treatment with ≤35% ejection fraction and symptomatic HF (NYHA II-IV functional class) with narrow QRS <120ms in primary prevention. In secondary prevention survivors of sudden cardiac death or patients who have experienced sustained symptomatic ventricular arrhythmias should be implanted an ICD. In the decision of performing the implantation we should take into consideration the candidate's co-morbidities, etiology, quality of life, the left ventricular ejection fraction and the expected survival over the following year.(2)

2.3.2.2 Cardiac Resynchronization Therapy

While the ICD reduces only the risk of sudden cardiac death, CRT has been shown to improve cardiac function, HF symptoms, and to reduce hospitalization and all-cause mortality in patients with mild to severe HF and a prolonged QRS (13-15). By implanting an additional left ventricular lead into a side branch of the coronary sinus or by surgical or transseptal technique to the left ventricle directly, it is possible to pace both ventricles simultaneously resolving the intra- and interventricular electromechanical delay.

2.4 Efficacy of cardiac resynchronization therapy

2.4.1 Mechanism of action

Due to the progression of the disease, conduction delay - manifested as prolonged QRS - is frequent in HF patients and associated with increased prevalence of mechanical dyssynchrony. Primarily by pacing along the latest activated part of the left ventricle simultaneously with the right ventricle, results in a better activation pattern. The impact of decreasing the interventicular dyssynchony might be less valuable, by the diminishing of intraventricular dyssynchrony of the left ventricle could CRT mostly exert its beneficial effect.

Secondarily CRT devices with atrial electrodes also allow the optimization of the atrioventricular interval for patients with sinus rhythm, which produces a better filling time.

The acute haemodynamic and electromechanical effect can be observed in the increasing

stroke volume, decreasing mitral regurgitation, pulmonary wedge pressure and narrowing QRS. These actions turn to reverse remodeling which is expressed from cellular to morphological levels, and it is reflected in the beneficial long-term outcome such as reduced mortality and HF hospitalization.

2.4.2 Current indications

There is a conclusive evidence of short- and long-term effect of CRT on symptoms, exercise capacity, left ventricular function and reduced HF hospitalization and all-cause mortality in symptomatic patients (NYHA II-IV functional class) with sinus rhythm and typical LBBB morphology and wide QRS (>150ms). In this patient population, CRT implantation is recommended with IA evidence level. In those patients, whom QRS is between 120-150 ms with Left Bundle Branch Block (LBBB) morphology, the evidence level is B (16).

The benefit in those, whose non-typical LBBB is less pronounced, thus those with wide QRS >150ms, IIa class B level, while in those patients who has QRS of 120-150 ms, CRT is less recommended as IIb class B evidence level. CRT is not recommended in patients with narrow QRS, Class III. (16).

2.4.3 Investigation of response: definition of responder patients

The definition of responder patients is primarily based on echocardiographic parameters, since improvement of left ventricular ejection fraction and left ventricular dimensions are strongly correlated with the clinical outcome and proved to be surrogate endpoints of respond (17). However there has been a mild heterogeneity in defining response to CRT, based on the most frequently used end-systolic volume (ESV) reduction, patients can be classified as super responders (≥30% ESV decrease), responders (30-15% ESV decrease), non-responders (<15% ESV decrease) and negative responders (ESV increase)(18). Defining responder criteria also involve functional parameters in some studies such as NYHA class, 6 minute walk test or quality of life questionnaires, which show less comprehensive results in detecting the positive response to CRT (19). Besides there have been some additional parameters such as detection of the decrease of functional mitral regurgitation or septal dyskinesis (20,21) which might also reflect the beneficial response

(2) to the therapy.

Based on the definitions mentioned above, approximately 22% of patients are super-responders, further 35% are responders, while 43% response less favorably to CRT (non-responders or negative responders)(18). Mainly patients with non-ischemic etiology, women and patients with typical LBBB morphology seem to be the most optimal candidates (2).

2.4.3.1 Before CRT implantation - optimal patient selection

2.4.3.1.1 QRS width and morphology

The prognostic implications of QRS width and morphology are between the main predictors of long-term outcome after CRT implantation although partly still debated.

However either the early haemodynamic, echocardiographic investigations or randomized trials confirmed the poor response to CRT in patients with QRS<150ms, the first recommendations of ESC guidelines were derived from the inclusion criteria of two initial high-volume randomized studies, the COMPANION(22) and CARE-HF(23) studies, which used QRS>120ms. Although 130 or 150 ms cut off values also appeared in some trials (MUSTIC(24) or MIRACLE(25)), the initial 120 ms was accepted continuously year after year. The findings of MADIT CRT (21) were incorporated in the guidelines as the next milestones, confirming patients with mild symptoms also benefit from CRT over 150 ms QRS duration. While most of the clinical trials and meta-analyses suggest a moderate clinical improvement to CRT between 120-150 ms QRS regardless of symptoms, there are limited and controversial data for echocardiographic dyssynchrony parameters, which may additionally help to appoint responder patients in this grey zone (26).

Beside the QRS duration, the morphology is also a crucial parameter. The sub-study of MADIT-CRT(25) showed that the presence of LBBB morphology was associated with 53% reduction in the risk of all-cause mortality and HF events, while patients with non-LBBB morphology did not show any clinical benefit to CRT. These findings were also confirmed by recent meta-analyses, which showed 36% and 24% risk reduction in all-cause mortality in patients with LBBB, whereas no clinical benefit could be observed in non-LBBB respectively(27). However regarding to a recent meta-analysis from Cleland

et al., the impact of QRS morphology is still questionable, while only QRS duration predicted the magnitude of the effect of CRT on outcomes.(28)

The 2013 ESC guideline provides IA evidence level for NYHA II-IVa patients with QRS >150ms and IB with QRS 120-150 ms and LBBB morphology, while III B for narrow QRS (<120ms).

2.4.3.1.2 Ejection fraction

Left ventricular ejection fraction (LVEF) is one of the basic parameters that determine the selection of patients for resynchronization, while the baseline value and its improvement strongly correlate with the outcome, thus regards as a surrogate endpoint in chronic systolic HF (29).

The first large randomized trials – COMPANION (22) and CARE HF(23) included patients with LVEF≤ 35% and NYHA III-IV functional class. Their findings were conclusive in this severely symptomatic patient population, less than 35% patients had a clear benefit from resynchronization. Further studies with higher inclusion criteria for EF and mild symptoms were also designed. In the REVERSE(30) trial patients with ≤40% of EF were included. Based on the core lab measurements, approximately 30% of the patients had >30% EF, which population also showed a significant improvement in echocardiographic parameters and composite clinical endpoint of HF events and all-cause mortality.

In the MADIT-CRT trial(31) despite the inclusion criteria of ≤30% LVEF, patients with higher ejection fraction were also enrolled assessed by the core lab. Kutyifa et al. found the beneficial effect of CRT could be detected regardless of ejection fraction, moreover patients with higher than 30% of LVEF showed the largest echocardiographic reverse remodeling (31). Based on the results of previous trials, the current guidelines recommend CRT for patients with LVEF ≤ 35% and NYHA II-IVa.

However the role of right ventricular function improvement after CRT is less evaluated and described in the literature, there have been evidences about a more favourable clinical outcome and long-term results in those patients who has a better baseline right ventricular function assessed by sophisticated parameters such as longitudinal and global strain (32).

2.4.3.1.3 Symptoms

There is a clear evidence for device implantation in patients with mild to severe symptoms

(NYHA II-IVa). The first randomized trials included patients with severe symptoms (NYHA III-IV), thereafter MADIT-CRT(21), REVERSE(33) ad RAFT(33) trials supported the benefits of CRT in mildly symptomatic patients. Based on MADIT-CRT(21) and REVERSE(33), where 18% and 15% of included patients were asymptomatic - NYHA I respectively, the trials confirmed that CRT did not reduce all-cause mortality or HF events in this patient population. In NYHA II, MADIT-CRT long term follow up results showed 35% risk reduction in patients in NYHA II functional class with ischemic etiology, while 43% risk reduction could be observed in the composite primary endpoint in non-ischemic patients compared to ICD alone patients (34). In a recent meta-analysis Al Majed et al. found that CRT reduces the risk of all-cause mortality and HF hospitalization in patients with NYHA I-II 29% and 17% respectively, which is comparable to patients with severe symptoms, NYHA III-IVa as well(35).

2.4.3.1.4 Predictors of response – biomarkers, CT-apelin

An optimal biomarker in chronic HF should be specific enough to detect the disease, provide an estimation of the prognosis and guide the treatment. The gold standard HF biomarker is the NT-proBNP. However, in patients who underwent CRT implantation, the cross-sectional values are suitable for describing the current status of the patient but prior studies failed to confirm its role as an independent predictor of response to CRT (36,37). Thus novel biomarkers are being investigated, in which inflammatory factors can take a part. Due to the low cardiac output and relating hypoperfusion all over the body, a systematic inflammation can occur during chronic HF. By activating the complement system, its components such as C3a might have an important role and has a predictive value for the response to CRT (38): elevated C3a levels increase the risk of mortality independent of the NT- proBNP levels, while CRT has an anti-inflammatoric effect by reducing the complement activation, thus measuring of the alteration of C3a might be a potential biomarker in the future. There are some other routinely measured laboratory parameters, which might help tailoring the therapy and predict the outcome after CRT implantation. Based on the above mentioned immuno-pathophysiology, the ratio of neutrophil leukocytes to the lymphocytes (39) or due to the congestion, the red blood cell distribution width might be novel prognostic markers in chronic HF (40). From the state-of-art HF biomarkers such as galectin-3, copeptin, NGAL, adrenomedullin or apelin (41,42), the latter has been emerged as a promising biomarker and investigated

comprehensively. Pre-pro-Apelin is expressed as a pro-hormone from several tissues. The apelin and its G-coupled receptor are expressed early during the embryonic development of the heart and affect the angiogenesis and maturation of cardiovascular cells (43). Its expression is also detected in adults where apelin has a paracrine effect as one of the most potent stimulators of cardiac contractility (44), moreover acts as a mediator of blood pressure via nitric-oxide dependent pathways (45). However, the role of apelin in HF is still unclear as changes of plasma levels are controversial in humans during the progression of HF (46-48). In addition, no data was available on its value in predicting or evaluating the response to CRT until now.

2.4.3.2 During the implantation

2.4.3.2.1 The role of intra- and interventricular delay

During the progression of HF, prolonged atrio-ventricular (AV) and ventriculo-ventricular (VV) delay can be observed. Interventricular dyssynchrony refers to prolonged activation between the ventricles, while intraventricular dyssynchrony develops by the late activation of mostly the postero-lateral / lateral region of the left ventricle (49). Several studies tested imaging (transthoracal echocardiography and MRI) and electrophysiological techniques to assess the localization and the role of intra- and interventricular dyssynchrony in CRT response.

The echocardiographic evaluation of interventricular dyssynchrony is based on the delay between the beginning of aortic and pulmonary velocity curves and the QRS, over 40ms delay the dyssynchrony can be confirmed. Intraventricular dyssynchrony can be evaluated by TDI or speckle tracking methods by segments, the latest activated part should contract with at least 50ms delay (49). These methods reflect primarily the mechanical dyssynchrony, thus there might have been differences between dyssynchrony assessed by echocardiogaphic or electrophysiological techniques.

The electroanatomical mapping is a more precise technique, imaging the electrical activation pattern directly (50). In this regard the most often investigated phenomenon is LBBB. Auricchio et al. (50) found that an U-shaped pattern of activation can be observed, where the line of block generally paralleled the septum.

Regardless of the method, the assessment of the latest activated part in the left ventricle

could be essential in order to perform a guided left ventricular lead implantation, thus achieve a better clinical response to CRT.

2.4.3.2.2 Targeting of the LV lead implantation

It has been proposed that optimal LV lead placement is an important determinant of response to CRT. The location of the left and right ventricular leads affects clinical outcome, and the incidence of ventricular tachyarrythmias (51). There have been positive results for echocardiography-guided left ventricular lead implantation. Those who were randomized to planned lead implantation by evaluating the latest site of peak contraction by strain analyses, yielded 15% higher amount of echocardiographic responder patients (52).

Furthermore, few smaller studies have indicated that the electrical delay between the signals sensed by the LV lead and the beginning of QRS duration (Q-LV), or the distance between the electrical signals of the left and right ventricular leads (RV-LV AD) predicted echocardiographic improvement and clinical outcome (53-55).

By measuring LV lead activation time from the beginning of the QRS (Q-LV), Gold et al. showed significant increase in functional and echocardiographic improvement in those patients who had greater Q-LV time.

RV-LV activation delay may also reflect the distance of RV and LV leads, moreover shows the electrical dyssynchrony and prolonged activation pattern derived from the slow conduction due to e.g. a scar tissue. Those studies, which used RV-LV activation delay (55,56), also showed significant improvement in echocardiographic response and in clinical outcome in patients with longer measured activation delay. However, none of these studies looked specifically at sub-groups of LBBB and non-LBBB patients.

Based on these prior studies the assessment the RV-LV delay during the implantation seems essential in the terms of the further response.

2.4.3.2.3 Multipolar pacing

However in novel therapeutic attempts multiple right and left ventricular stimulations are performed by multiple leads, in the recent thesis we are focusing on the comparison of bipolar and quadripolar left ventricular pacing.

During the implantation procedure, it can happen that only suboptimal target vein can be found for LV lead implantation or difficult to avoid phrenic nerve stimulation. By using multipolar pacing, a better clinical response and lower number of phrenic nerve stimulation (57) can be observed. Several investigations (58-60) confirmed a more pronounced improvement by quadripolar lead implantation and optimization of the pacing site compared to bipolar stimulation. This effect was reflected either in haemodynamic (58,60) or echocardiographic response (59).

2.4.3.3 Follow up - patient management and device optimization

2.4.3.3.1 AV and VV delay

The proper programming of the device such as AV and VV delay seems slightly controversial, while prior studies (61,62) found that it has an impact on better response to CRT. However large randomized trials (63,64) could not confirm these data, therefor in the current guidelines, it is not recommended routinely, but supported to use in non-responder patients (65).

The optimization is classified into two groups: echocardiography-based and device-specific measurements and settings. Regarding the AV delay, a suboptimal AV programming can result in a 10-15% decrease in cardiac output. The optimal setting was investigated by a large randomized trial (63), where no difference was found in the echocardiographic response in cases of fix 120ms AV delay, echocardiographic optimization or a device-specific optimization (SMART AV function).

The VV delay optimization can also be controlled by echocardiography-based higher stroke volume, ECG-based QRS narrowing or device-specific programs. However, these methods are not corroborated by tough evidences.

2.4.3.3.2 Remote monitoring

Remote monitoring is presented as IIa A evidence in the current ESC guidelines (65). By home monitoring it is considered to detect the arrhythmias or technical issues earlier, moreover HF hospitalizations or malignant arrhythmias can be prevented (66,67).

2.4.4 New indications:

2.4.4.1 Non-Left Bundle Branch Block morphology

Recent studies have suggested that patients with LBBB derive a significant benefit from CRT implantation, while in patients with a non-LBBB (as Right Bundle Branch Block - RBBB or intraventricular conduction delay - IVCD) the benefit is less if at all discernible (68,69). In non-LBBB patients with a prolonged PR interval, resynchronization with ICD treatment (CRT-D) was also associated with a 73% reduction in the risk of heart failure/death and 81% decrease in the risk of all-cause mortality compared with implantable cardioverter defibrillator therapy without CRT (70). In non-LBBB patients with normal PR, CRT-D therapy was associated with a trend toward an increased risk of heart failure/death (HR 1.45; 95%, CI 0.96-2.19; P=0.078; P<0.001) and a more than 2-fold higher mortality (HR 2.14; 95%, CI 1.12-4.09; P=0.022; P<0.001) compared with implantable cardioverter defibrillator therapy without CRT(70).

2.4.4.2 Upgrading to Cardiac Resynchronization Therapy

2.4.4.2.1 Lack of evidences

Since chronic right ventricular pacing is thought to be deleterious by increasing the risk of atrial fibrillation, HF and all-cause mortality (71,72), patients already carrying conventional pacemaker (PM) or ICD systems are often considered for upgrading to CRT. Recent studies have suggested that only patients with typical LBBB ECG morphology derive a significant benefit from CRT(68,69). Although right ventricular pacing could reveal ventricular dyssynchrony similar to LBBB, data are scarce regarding the benefit of upgrade CRT in patients with previously implanted cardiac pacemaker or ICD systems.

The latest ESC guidelines on cardiac pacing and resynchronization therapy recommended CRT upgrade as a class I indication (level B) for symptomatic patients (NYHA III-IV) with low ejection fraction (LVEF≤35%)(65), while the most recent European heart failure guidelines restrict this indication as a class IIb (level B)(2). The ACC guidelines focused on the percentage of pacing rather than symptoms.

2.4.4.2.2 The BUDAPEST CRT upgrade study

About 28% of CRT implantations in Europe are upgrade procedures after previously implanted cardiac devices(73). To date, there are no conclusive results on the outcome of patients who underwent CRT-D upgrade from having previously implanted pacemaker or ICD devices, symptomatic HF, reduced ejection fraction and relatively high percentage (>20%) ventricular pacing. Furthermore, recent data indicate that upgrade procedures to biventricular pacing are associated with a relatively high complication rate (74), suggesting that a large, multicenter, randomized trial is required. We have designed an investigator initiated, prospective, randomized, multicenter trial, the BUDAPEST CRT upgrade study to clarify the question with 21 European and Israeli sites' participation. The study is conducted in accordance with the Helsinki Declaration, the Good Clinical Practice and the applicable regulatory requirements (75).

3 OBJECTIVES

Our aim was to determine novel parameters that might improve the clinical outcome after CRT implantation in regard of optimal patient selection and special methods during the implantation or early detection of response.

In order to optimize the patient selection and early assessment of the response to CRT, the serum levels of a novel biomarker, CT-apelin were measured. Its predictive value for the echocardiographic response was investigated and compared to the gold standard NT-proBNP levels at baseline and 6 months after resynchronization.

Moreover we examined the impact of an easily measured parameter during the implantation, the RV-LV activation delay. Its predictive role in the functional, echocardiographic and clinical outcome such as heart failure, all-cause mortality or laboratory parameters including NT-proBNP and renal function was assessed by the baseline QRS morphology of patients who underwent CRT implantation.

We would also focus on those questions, which are not entirely covered by the current ESC guidelines: patients who have an already implanted conventional pacemaker or ICD and referred to CRT upgrade. By concluding the available evidences of the literature, we analysed the clinical outcome, adverse events and long-term survival after upgrading compared to de novo implantation. However conclusive data will be provided by the BUDAPEST-CRT Upgrade Study, which investigates the all-cause mortality, heart failure events and echocardiographic response as primary endpoint besides functional response and safety after 12 months. In the current thesis the actual status, rationale and design of this investigator initiated trial is discussed in details.

4 METHODS

For a better interpretation, those studies in which optimal patients selection and intraoperative parameters were evaluated, are shown separately (Part 1) in the Methods and Results sections. In Part 2 the questions of CRT upgrade are shown by concluding the results of the currently available data in the literature in a meta-analysis and the rationale and status of the BUDAPEST CRT upgrade study.

4.1 Patient population

4.1.1 Inclusion and exclusion criteria of patients in Part 1.

Between September 2009 and December 2010 a prospective, observational, cohort study was designed to investigate patients undergoing successful CRT implantation at the Heart and Vascular Center, Semmelweis University, Budapest, Hungary. Patients with both ischemic and non-ischemic etiology were enrolled. Inclusion criteria were low left ventricular ejection fraction (EF≤35%), a prolonged baseline QRS interval (≥120 ms) and symptoms of HF (NYHA II-IVa functional class) despite optimal medical treatment. Before the enrolment all patients underwent diagnostic coronarography or recoronarography in order to tailor the implantation by images of coronary sinus, moreover atherosclerosis as a secondary cause of HF could be verified. In those cases, where a percutaneous coronary intervention (PCI) was performed, patients were enrolled after 3 months of the procedure.

Exclusion criteria were patients with genetic HF, known malignant or inflammatory disease or severely reduced life expectancy, less than 1 year. We did not include those patients who were geographically unstable, or unwilling to attend regular follow ups or did not consent to the study.

In the investigation of optimal patient selection by serum biomarker measurements, from the total included patient cohort those who died before 6 month-follow up or unable or unwilling to give serum samples for biomarker assessments were censored due to the lack of ability to classify them according to response criteria and further biomarker measurements. Therefor it can be viewed as a substudy in the current thesis.

The study was approved by the Institutional Scientific Ethics Committee. All patients provided written informed consents and all data were anonymized prior to utilization.

4.1.2 Patient population and randomization in BUDAPEST CRT upgrade study

This prospective, multicenter, randomized trial was prepared and designed in 2013 by the principal investigator (PI), Professor Bela Merkely, co-PIs as Dr. Valentina Kutyifa and Professor Ilan Goldenberg and members of Steering Committee. High-volume, experienced centers were contacted in Europe and Israel, each sites which would participate got the opportunity to enroll patients after contracting and initiation.

From November 2014 patients are enrolled to the study regardless of the HF etiology with reduced LVEF (≤ 35%), symptoms (NYHA functional class II-IVa) despite optimal medical treatment with single or dual chamber pacemakers or ICD devices implanted at least 6 months before the inclusion (with ≥20% RV pacing over 90 days prior to enrolment and wide paced QRS duration ≥150 ms) with sinus rhythm, atrial fibrillation/flutter or atrial tachycardia as per protocol. The rate or frequency or rhythm control management is based on the physician's discretion. Patients are excluded with typical LBBB intrinsic QRS morphology, severe right ventricular dilatation (>50mm), severe renal disease (serum creatinine >200umol/l) or other co-morbidities, which might influence the outcome of the patient. Those who had acute events (e.g. PCI, myocarditis, Coronary Artery Bypass Graft - CABG) or in those cases where heart transplantation (HTX) is planned. Detailed inclusion and exclusion criteria are listed in Table 1.

In the Semmelweis University after physicians pre-screened their patients and those who are thought to be eligible for the study, are referred to Annamaria Kosztin for screening and consent.

Those subjects, who proved to be eligible for the study, could be randomized in a 3:2 manner (CRT-D:ICD). Altogether a total of 360 patients are planned to be enrolled.

Table 1. Inclusion and exclusion criteria of the BUDAPEST CRT upgrade study

Inclusion criteria	Exclusion criteria
1. Age: over 18 years 2. Cardiomyopathy with LVEF ≤35%, ischemic or non-ischemic 3. Single or dual chamber PM or ICD implanted ≥6 months prior to enrolment (battery depletion or another indication for upgrade is not required) 4. RV pacing ≥20% in the prior ≥90 days (use of algorithms to avoid ventricular pacing is recommended, per discretion of the clinician) 5. Paced QRS duration ≥150 ms 6. Symptomatic heart failure with NYHA functional class II-IVa ≥3 months prior to enrolment, despite optimized medical therapy 7. Informed consent	1. CABG or PCI ≤3 month ago or planned 2. AMI ≤3 month ago 3. Unstable angina 4. Planned cardiac transplant 5. Acute myocarditis 6. Infiltrative cardiomyopathy 7. Hypertrophic cardiomyopathy 8. Severe primary mitral, aortic or tricuspid valve stenosis or insufficiency 9. Tricuspid valve prosthesis 10. Severe right ventricular dysfunction (RV basal diameter > 50mm) 11. Chronic severe renal dysfunction (creatinine >200 μmol/l) 12. Pregnant women or planned pregnancy 13. Subjects who are unable or unwilling to cooperate with the study protocol 14. Any comorbidity that is likely to interfere with the conduct of the study 15. Participation in another trial 16. Patients geographically not stable or unavailable for follow-up 17. Intrinsic QRS with typical LBBB morphology

AMI= Acute Myocardial Infarction; CABG= Coronary Artery Bypass Graft; ICD= Implantable Cardioverter Defibrillator; LBBB= Left Bundle Branch Block; LVEF= Left Ventricular Ejection Fraction; NYHA= New York Heart Association; PCI= Percutaneous Coronary Intervention; RV= Right Ventricle

4.2 Follow up and investigations

4.2.1 Follow up

4.2.1.1 Baseline and follow up visits in Part 1

Each visits were performed by Annamaria Kosztin and Vivien Klaudia Nagy, which included a physical examination, assessment of the NYHA functional class, transthoracic echocardiography, detailed laboratory tests, 6 minute walk test and EQ5D quality of life measurements extended with device interrogations after the implantation. Investigations were performed at the baseline visit and 6 months after CRT/ICD implantation. Beyond regular outpatient visits, patients were contacted via telephone and the Hungarian National Database was used to obtain vital information at 3 years after CRT implantation (Figure 1) .

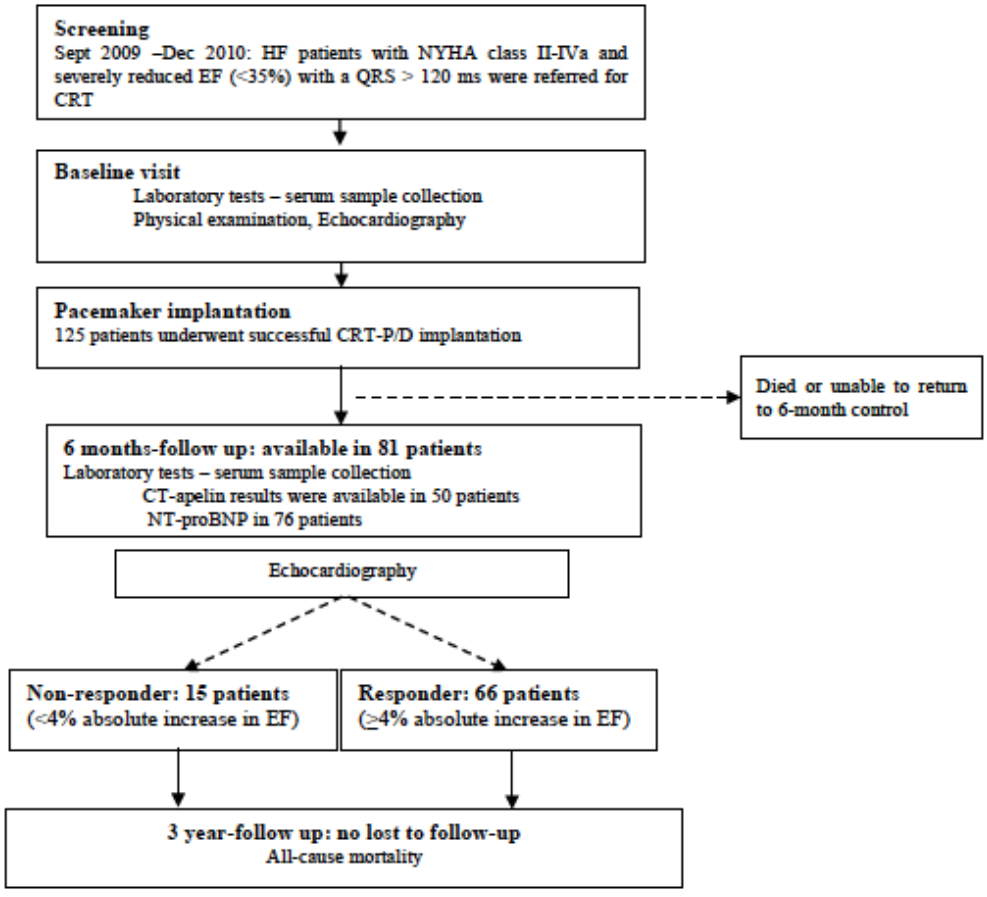

Figure 1. Flowchart of patient enrolment and follow up of optimal patient selection by biomarkers

4.2.1.2 Follow up in the BUDAPEST CRT upgrade study

Eligible patients undergo a baseline evaluation including clinical history, physical examination, NYHA class, 12-lead ECG with paced (paced VVI or DDD 70 bpm and non-paced QRS complexes using VVI 40 bpm settings), transthoracic echocardiography, device interrogation (RV pacing percentage and Holter data), quality of life assessment (EQ5D), 6 minute walk test and optional NT-pro-BNP measurement. Patients are followed up for 12 months after randomization. Regular, in-office follow-ups will be performed at 1, 6 and 12 months (Table 2), which are performed by Annamaria Kosztin (each investigations except for echocardiography) and Attila Kovacs (echocardiography). While Semmelweis University is responsible for the maintenance of echocardiography core lab and Biobankok server, each PM interrogation files, ECGs and echocardiographic images that are performed during the patient follow ups from active centers, are uploaded to our Biobankok Server and will be analysed centrally.

4.2.2 ECG

By performing a 12-lead analog ECG, the assessment of QRS width and morphology were mandatory in each study. After all of the ECGs has been recorded, the same person assessed the data and fill our electronical database retrospectively.
LBBB was defined on 12-lead ECG as QRS duration >120 ms; QS or rS in lead V1; broad R waves in leads I, aVL, V5, and/or V6; and absent q waves in leads V5 and V6. RBBB required QRS duration >120 ms; rsr, rsR, rSR, or qR in leads V1 or V2; and occasionally, wide R waves and wide S waves in leads I, V5, and V6. Intraventricular conduction delay was defined as QRS >120 ms without typical features of LBBB or RBBB.
During BUDAPEST CRT study, the assessement of presence of intrinsic LBBB is based on the physicians' discretion. The digital formation of ECGs are uploaded to the Biobankok server and will be analysed retrospectively.

4.2.3 Echocardiography

Echocardiography was performed according to current standards in a left lateral position using Philips iE33 echocardiography system equipped with an S5-1 transducer (Philips Healthcare, Best, The Netherlands). Image acquisition was performed according to current recommendations (76). Measurements were performed by the same person offline using the QLAB software (Philips Healthcare). Left ventricular end-systolic and end-diastolic volumes were measured and ejection fraction was calculated by the biplane Simpson method (76).

Table 2. Follow up visits of the BUDAPEST CRT upgrade study

Visit/evaluation	**Patient Enrolment Visit Day 0**	**Device Implantation and Programming Within 14 days**	**1 month FU visit Day 30**	**6 months FU visit Day 180**	**12 months FU visit Day 365**
Inclusion criteria	x				
Exclusion criteria	x				
Signed Informed Consent	**x**				
clinical history	x		x	x	x
physical examination	x		x	x	x
assessment of NYHA class	x		x	x	x
12-lead ECG (paced)	x				x
12-lead ECG (at VVI 40 bpm)	x				x
Echocardiography	**x**				**x**
device interrogation (print, save, upload)	x		x	x	x
blood test (NP-pro-BNP)	x[1]				x[1]
6 minute walk test	x[2]				x
Randomization	x				
Assessment of clinical end-points			**x[3]**	**x[3]**	**x[3]**
Assessment of post-implantation complications			x		
SAE, AE, UADE, USADE	x	x	x	x	x
Quality of life assessment using EQ-5D	x[2]				x

1: Optional, 2: After the randomization but before implantation, 3: Clinical end-points;

SAE= Serious Adverse Event; AE= Adverse Event; UADE= Unanticipated Adverse Device Effect; USADE= Unanticipated Serious Adverse Device Effect

4.2.4 Serum biomarker measurements

Human CT-apelin was measured by Annamaria Kosztin using C-terminus Enzyme Immunoassay competitive ELISA method (RayBiotech, Inc., Norcross, USA) which is designed to target the C-terminus of the 77-aminoacid apelin peptide. By this kit all active forms (apelin-13, -31, -28, and apelin-36) of the pre-prohormone 77-aa apelin peptide can be measured. NT-proBNP was measured with Cobas proBNP II kit (Roche Diagnostics Gmbh, Mannheim, Germany). Serum samples were stored at -80 ^{o}C until sample collection was completed.

Rutine laboratory measurements (ions, renal function, haematology parameters) were performed by Eva Forizs using automatic kits (Roche kit, Roche Diagnostics Gmbh, Mannheim, Germany) as routine clinical practice in our hosital.

4.3 Device implantation and programming

4.3.1 Device implantation procedure in Part 1

Device implantations were performed according to current standards by using a transvenous approach. By performing a coronary sinus angiogram LV lead implantation was tailored during device implantation. After positioning of each leads, pacing, sensing and impedance parameters were measured. In patients with intraoperative LV lead dislocation or phrenic nerve stimulation, coronary sinus stent implantation was performed in the CS side branch after repositioning of the LV lead (77,78). Right ventricular lead was primarily implanted into a septal position, while left ventricular lead into a posterolateral or lateral side branch. LV and RV lead positions were assessed by the implanting physician based on the right and left anterior oblique (RAO and LAO) views.

4.3.2 Upgrade procedure in BUDAPEST CRT Upgrade study

Upgrade procedures need to be performed within 14 business days after randomization. (Table 2). During the procedure, duration time of the upgrade, X-ray dosage, details of

the implanted leads, adverse events and RV-LV AD are mandantory to report. Patients with an existing ICD, who are randomized to the ICD arm, may not need a procedure unless a generator replacement, a system revision is necessary or the PI decides on upgrading to CRT-D in RV only pacing mode. The optional study interventions are listed in Table 3. Decisions about lead extraction are based on the physicians' discretion by actual recommendations. (79) Use of Boston Scientific Corporation (Marlborough, MA, USA) ICDs or CRT-D is preferred, but not mandatory. In the ICD arm, choosing single or dual chamber device is left to the physician decision. In the CRT-D arm, the left ventricular lead is recommended to be implanted in the lateral or postero-lateral side branch of the coronary sinus. Transvenous implantation is strongly preferred; however, alternative methods are also accepted if the transvenous attempt fails.

Table 3. Optional study interventions in BUDAPEST CRT upgrade study

CRT-D group	ICD group
1. Existing PM Addition of RV defibrillator lead Addition of RA pacing lead (unless already has one or has permanent AF) Addition of LV pacing lead Extraction of old RV PM lead optional (physician's judgment) Any revision of the old lead(s) and device pocket, as necessary Generator change to CRT-D	1. Existing PM Addition of RV defibrillator lead Addition of RA pacing lead optional (physician's judgment, unless already has one or has permanent AF) Extraction of old RV PM lead optional (physician's judgment) Any revision of the old lead(s) and device pocket, as necessary Generator change to VVI or DDD ICD,
2. Existing ICD Addition of RA pacing lead (unless already has one or has permanent AF) Addition of LV pacing lead Any revision of the old lead(s) and device pocket, as necessary Generator change to CRT-D	1. Existing ICD Continue with existing device Addition of RA pacing lead and upgrading to a DDD ICD is optional (physician's judgment, unless already has one or has permanent AF)

AF= Atrial Fibrillation; CRT-D= Cardiac Resynchronization Therapy with Defibrillatior; ICD= Implantable Cardioverter Defibrillator; PM= Pacemaker; RA= Right Atrium; RV= Right Ventricle

4.3.3 RV-LV AD measurement at implantations

After positioning both ventricular leads, intraoperative RV-LV activation delay measurements were performed by connecting to an electrophysiology system (Biotronik pacemaker interrogation device, Berlin, Germany). The right to left interventricular sensed delay was measured by the time delay of the peak activation in the right and left ventricular sensed signals phrased in milliseconds (Figure 2).

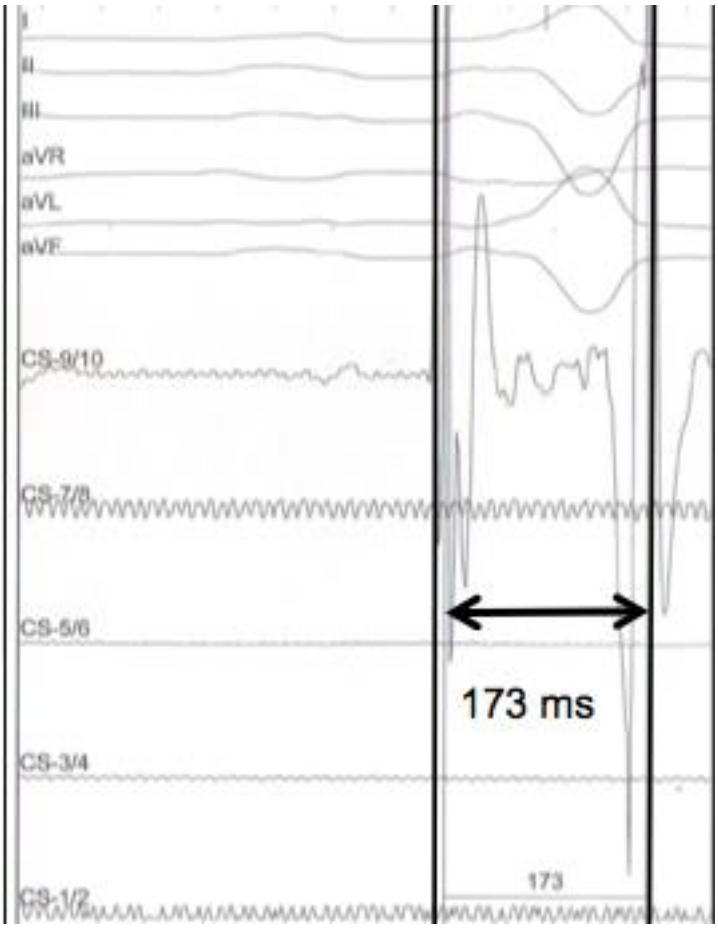

Figure 2. RV-LV AD measurement by assessment of the time delay between the peak activation in the right and left ventricular sensed signals

4.3.4 Device programming during BUDAPEST CRT UPGRADE study

Regarding bradycardia parameters DDD(R) or VVI(R) mode is required with base rate setting between 40-70 bpm. In order to achieve the optimal AV-delay, SMART AV (63) or echocardiographic optimization or fixed values (sensed AV delay 120-140 ms/ paced AV delay 140-160 ms) can be used. Regarding antitachycardia parameters, two zones are recommended: VT1 as a monitor zone between 170-200 bpm without programmed therapy and VF zone over 200 bpm with a 2.5 sec delay, ATP during charging (8 pulses at 88% of the tachycardia cycle length) and subsequent shocks (first : DFT + 10J or 30 J, subsequent shocks should be maximum energy shocks).

4.4 Endpoints

4.4.1 Endpoints of Part 1.

4.4.1.1 Endpoints in assessing the predictive value of NT-proBNP and a novel biomarker, CT-apelin

The primary endpoint of the study was non-response to CRT defined as an absolute increase of less than 4% in ejection fraction (80) at 6 months, compared to baseline measurements. Secondary endpoint was all-cause mortality during the three years follow-up.

4.4.1.2 Endpoints in evaluating the effect of RV-LV AD specified by QRS morphology

The primary composite endpoint was heart failure hospitalization or all-cause mortality. Secondary endpoint was death from any cause.

Heart failure events were defined as symptoms and signs of heart failure that required intravenous diuretic treatment during an in-hospital stay. All-cause mortality was assessed by the National Health Fund Death Registry.

We also evaluated the clinical outcome as changes of ejection fraction, distance walked during the 6-minute walk test and NT-proBNP serum levels after 6-month.

First the recent endpoints were assessed by RV-LV AD as a continuous variable in the total patient cohort, then patients were dichotomized by the lower quartile of RV-LV AD (86 ms)

1) patients with RV-LV AD < 86 ms
2) and those with RV-LV AD ≥ 86 ms

Thereafter they were further grouped by their baseline LBBB morphology:

1) patients with RV-LV AD < 86 ms and LBBB
2) patients with RV-LV AD ≥86 ms and LBBB
3) patients with RV-LV AD < 86 ms and non-LBBB
4) patients with RV-LV AD ≥ 86 ms and non-LBBB

Finally we also investigated the outcomes of two subgroups: patients with LBBB and RV-LV AD < 86 ms together with patients with non-LBBB ("expected CRT non-responders") and compared them to patients with LBBB but RV-LV AD ≥ 86 ms ("expected CRT responders").

Our analyses were extended by RV-LV AD to QRS duration (RV-LV AD /QRS), moreover in order to further assess the effects of RV-LV AD as a continuous parameter on NT-proBNP and clinical outcome of HF/death, we evaluated the changes in NT-proBNP at 6-month by RV-LV AD quartiles along with the incidence of HF/death.

4.4.2 Endpoints of Part 2.

4.4.2.1 Endpoints in the meta-analysis of patients after CRT upgrade compared to de novo CRT implantation

We report data about all-cause-mortality, heart failure events, echocardiographic (LVEF, EDV), clinical (change of NYHA functional class) and ECG (change of QRS width) parameters of reverse remodeling.

4.4.2.2 Endpoints in the BUDAPEST-CRT upgrade study

The primary endpoint of the study is a composite endpoint of heart failure events, all-cause mortality, or less than 15% reduction in echocardiography determined left ventricular end-systolic volume from baseline to 12-month.
Secondary end points are the composite of heart failure events and all-cause mortality, all-cause mortality alone, the changes of echocardiographic parameters (left ventricular end-diastolic volume or left ventricular ejection fraction) from baseline to 12 month.
Tertiary endpoints are the success and safety of implantation procedures, the change of NYHA class, quality of life assessed by EQ-5D questionnaire, 6-minute walk test and the changes of NT-pro-BNP serum levels from baseline to 12 months.

4.5 Statistics and methods for analyses

4.5.1 Statistical analysis

Statistical analyses were performed by Graph Pad version 6.0 and 7.0 (Graph Pad Inc., CA, USA), SPSS version 9 (IBM, NY, USA) or Comprehensive Meta-Analysis 3.3 (Biostat, Inc., USA).
Continuous variables with normal distributions are expressed as mean±SD, while those with non-normal distributions as medians with interquartile range (IQR). Categorical variables are shown with numbers and percentages (n, %). Baseline clinical characteristics of Part 1 were compared by unpaired t-test for normally distributed continuous variables, the Mann–Whitney U-Test for non-normally distributed variables, while χ^2 - test or Fisher exact test was used for dichotomous variables, as appropriate.

Time-to-event data were presented by Kaplan-Meier curves. Unadjusted hazard ratios (HR) with 95 confidence intervals (95% CI) were calculated for mortality in Cox proportional hazards models, while adjusted HR in forward stepwise Cox proportional model adjusting for relevant clinical parameters as appropriate. A two-sided p-value of <0.05 was considered as statistically significant.

Univariate and multivariable receiver-operating characteristic (ROC) curve analyses were also used to determine the discriminatory capacity of biomarkers on non-response and were shown as the area under curve (AUC) and p values. In case of a significant p value, an optimal cutoff was assessed for the continuous variable based on maximal sensitivity and specificity. Using these cutoffs, patients were separated to low and high biomarker level groups for logistic regression analyses. Multivariate logistic regressions were performed with variables showing a p value less than 0.05 in univariate analyses.

In the meta-analyses heterogeneity between individual trial estimates was assessed by the Q statistic and I^2 statistic (81). Since, there was significant heterogeneity in the design and patient's characteristics of the studies included into the meta-analyses, it was assumed that the true effect size varies from one study to the next, and hence the random-effect model was used(82). A forest plot was created with individual trials and the pooled estimates. Publication bias was assessed using the funnel plot, the trim and fill method of Duval and Tweedie (83) and an adjusted rank-correlation test according to Begg and Mazumdar(84). Since we did not have access to individual patient data from all studies reviewed, the median of delta values for LVEF, EDV, NYHA and QRS were calculated and compared between the two patient groups separately by using the Mann-Whitney U test. Methodological quality of all studies was assessed using the Methodological Index for Non-Randomized Studies (MINORS)(85). Studies were defined to be low, moderate and high quality studies based on their MINORS scores of <8, <16, and ≥16 points (data are not shown).

4.5.2 Study selection for systematic review and meta-analyses

The systematic review was performed according to the PRISMA Statement (86) and a predefined review protocol was published in the PROSPERO database under the registration number of CRD42016043747. A comprehensive search of PubMed, Research Gate, and Google Scholar databases was performed from January 2006 to June 2016

focusing on full-sized, peer-reviewed, English language papers reporting data on patient outcomes after upgrade CRT vs. de novo implantations as a comparator group. Abstracts were only included when critically relevant and not available as full-text articles. In order to identify all potentially relevant articles, the search was performed by using the terms of 1. “upgrade” AND “CRT”; 2. “upgrade” AND “cardiac resynchronisation therapy”. The search was also extended by using the name of the most frequently cited authors of the identified studies. In addition, references of relevant review articles were also searched to find appropriate manuscripts. Potentially relevant articles were evaluated by three independent reviewers and additional manuscripts were retrieved that either reviewer felt were potentially relevant. According to our review protocol studies were accepted for analysis if (i) including heart failure patients with reduced ejection fraction (HFrEF) with de novo and upgrade CRT implantations (ii) reporting all-cause-mortality data or heart failure events; (iii) reporting echocardiographic (i.e. LVEF, EDV) or clinical (NYHA class) or ECG (QRS width) parameters of reverse remodeling (Table 4). Heart failure events were defined as hospitalization due to progression of heart failure. In order to evaluate the heterogeneity of patients who were enrolled into each therapy groups, the most important baseline clinical characteristics were collected. Data on procedure related complications were also investigated if available.

Table 4. Searching methodology and eligibility criteria for the meta-analysis

Eligibility criteria

Criteria	Included	Excluded
Participants	wide QRS, NYHA II – ambulatory IV and EF≤ 35%	No indication for CRT
Intervention	CRT upgrade	Unsuccessful LV lead implantation
Comparator	de novo CRT implantation	No comparator group
Primary Outcome	All-cause mortality	Only cause specific mortality data or composit endpoints provided
Secondary outcomes	Changes in NYHA class, Echocardiographic parameters of reverse remodeling, QRS narrowing	NA
Study Design	Randomized controlled trials Non-randomized trials Observational cohort studies	Case reports Reviews Meta-analyses
Languages	English	Any other languages
Publication status	Published or accepted manuscripts or abstracts	Non peer-reviewed, unpublished

CRT= Cardiac Resynchronization Therapy; LV= Left Ventricle; NA= not applicable; NYHA= New York Heart Association

4.5.3 Sample size calculation and statistical methods in the BUDAPEST CRT UPGRADE study

Altogether 360 patients are planned to enroll to the study. The main objective is to investigate the primary composite clinical and echocardiographic endpoint after CRT upgrade (superiority of CRT-D upgrade vs. ICD only). Analyses will be performed (i) on an intention-to-treat-basis (without regard to device actually implanted/revised), (ii) and on efficacy basis, censoring follow-up when a patient crosses over to a different device. The primary analyses will be stratified by the percentage of baseline RV pacing as pre-specified in the study. The null hypothesis for the primary endpoint is that the hazard rate, which is assumed to be constant across all study intervals, is identical in the two groups (CRT-D v. ICD). The hypothesis will be tested in a study in which subjects are entered and followed up until (i) the primary composite endpoint occurs, (ii) the patient drops out of the study, (iii) or the study ends while the patient is still being followed, in which case the patient is censored.

Power was calculated a priori based on a hazard ratio of 0.7 and a primary composite endpoint event rate of 80% in the ICD group over 12 months. The power calculation was based on higher RV pacing rates, while no data is available <40%. Although the risk seems to correlate with RV pacing, the exact correlation is unclear. The attrition (drop out) rate was assumed at 0.01/interval. An instantaneous hazard rate of 0.134 for the ICD group and 0.094 for the CRT-D group was assumed – this equals to a median survival time of 5.17 intervals in the ICD group and 7.38 intervals in the CRT-D group, a cumulative event free survival at 12 intervals of 0.2 for the ICD group and 0.32 for the CRT-D group. The two-tailed alpha was set at 0.05. A total of 144 patients will be entered into the ICD group and 216 into the CRT-D group to achieve a power of 80.1% to yield a statistically significant result.

5 RESULTS

5.1 Part 1 – Optimization of patient selection and intraoperative techniques in order to achieve a more beneficial clinical response

5.1.1 Optimal patient selection by measuring NT-proBNP and a novel biomarker, serum CT-apelin

5.1.1.1 Baseline clinical characteristics

From those patiens who underwent a successful CRT implantation between September 2009 and December 2010, 81 patients were included in the current study. Mean age of the recruited patients was 64.9±10.5 years, with a mean ejection fraction of 28.5±6.5%, and mean QRS width of 167.7 ± 29.8 ms. Eighty-six percent of the patients had typical LBBB morphology and 59% had CRT-D device. Seventy-five percent of the patients were in NYHA class III functional state and 59 % had ischemic etiology before CRT implantation (Table 5a).

5.1.1.2 Response and prognosis

During the mean follow-up time of 795 ± 99 days, 7 (9%) patients died. Based on the pre-defined classification of response, 15 (18.5%) patients proved to be non-responders, of which 4 died during the follow up. Baseline clinical characteristics, medical therapy and echocardiographic findings were similar between responders and non-responders (Table 5a, 5b, 5c). In line with the definition of response, left ventricular volumes significantly decreased (ESV: 179.1 ± 64.9 vs. 117.9 ± 58.9, $p<0.0001$, EDV: 248.6± 80.2 vs. 196.7 ± 77.5, $p<0.0001$) and left ventricular function significantly improved (EF: 28.1 ± 6.0 vs. 41.3 ± 7.9) in responder patients after CRT implantation, while these parameters remained unchanged in the non-responder group after 6 months (Table 6).

Table 5a. Baseline clinical variables in the responder and non-responder patients

Baseline clinical variables	**All patients (n=81)**	**Responders (n=66)**	**Non-responders (n=15)**	**p value**
Age (yrs, mean±SD)	64.9 ± 10.49	64.1± 10.8	68.5 ± 8.4	0.14
Gender (female, n, %)	15 (18.5%)	14 (21%)	1 (7%)	0.28
Ischemic etiology (n, %)	48 (59%)	39 (59%)	9 (60%)	1.00
NYHA II. st (n, %)	11 (14%)	9 (14%)	2 (13%)	1.00
NYHA III. st (n, %)	61 (75%)	49 (74%)	12 (80%)	0.75
NYHA IV. st (n, %)	9 (11%)	8 (12%)	1 (7%)	1.00
QRS (ms, mean±SD)	167.7 ± 29.8	166.6 ± 28.8	172.0 ± 34.3	0.53
typical LBBB morphology (n, %)	70 (86%)	57 (86%)	13 (87%)	1.00
not typical LBBB (n, %)	11 (14%)	9 (14%)	2 (13%)	1.00
6 minutes walk test (m, mean±SD)	311.4 ±117.1	307.3 ± 127.6	329.2 ± 54.1	0.56
RR systolic (mmHg, mean±SD)	120.4 ± 18.8	121.1 ± 17.4	117.5 ± 24.8	0.51
RR diastolic (mmHg, mean±SD)	76.2 ± 10.7	76.9 ± 10.2	73.1 ± 12.3	0.21
Heart rate ($min^{-1,}$ mean±SD)	75.6± 14.5	75.6 ± 14.1	75.3 ± 16.5	0.93
Atrial fibrillation (n, %)	20 (25%)	14 (21%)	6 (40%)	0.18
Body mass index (BMI; med, IQR)	27.0 (24 / 30)	27.0 (24 / 30)	29.0 (26 / 31)	0.16

LBBB = left bundle branch block; NYHA class = New York Heart Association class; PCI= percutaneous coronary intervention; CABG = coronary artery bypass grafting; VF= ventricular fibrillation

Table 5b. Baseline medical history, echocardiographic parameters and serum peptides in the responder and non-responder patients

Medical history				
Hypertension (n, %)	63 (78%)	51 (77%)	12 (80%)	1.00
Type 2 DM (n, %)	25 (31%)	22 (33%)	3 (20%)	0.37
Prior PCI (n, %)	25 (31%)	20 (30%)	5 (33%)	1.00
Prior CABG (n, %)	14 (17%)	11 (17%)	3 (20%)	0.72
Prior stroke (n, %)	8 (10%)	6 (9%)	2 (13%)	0.64
Prior COPD (n, %)	10 (12%)	8 (12%)	2 (13%)	1.00
Prior dyslipidaemia (n, %)	28 (35%)	20 (30%)	8 (53%)	0.13
Prior major arrhythmia - VF (n, %)	3 (4%)	2 (3%)	1 (7%)	0.46
Prior ICD implantation (n, %)	7 (9%)	4 (6%)	3 (20%)	0.11
Echocardiographic parameters				
LV ejection fraction (Simpson%, mean±SD)	28.5 ±6.5	28.1 ± 6.0	30.4 ± 8.2	0.23
LV end-systolic volume (ml, mean±SD)	183.5 ± 63.3	179.1 ± 64.9	203.0 ± 51.5	0.22
LV end-diastolic volume (ml, mean±SD)	254.7 ± 79.1	248.6± 80.2	281.5 ± 67.9	0.18
Serum peptides				
NT-proBNP (pg/ml; med, IQR)	2573 (1207 /4611)	2561 (1173 / 4616)	3126 (1238 / 4492)	0.61
CT-apelin (ng/ml; med, IQR)	512.0 (288.3 / 808.8)	549.5 (279.0/868.8)	472.5 (307.8 / 700.3)	0.74

DM = diabetes mellitus; PCI= percutaneous coronary intervention; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; VF= ventricular fibrillation

Table 5c. Baseline medical therapy in the responder and non-responder patients

Baseline medical therapy (n, %)				
Beta blocker (n, %)	74 (91%)	60 (91%)	14 (93%)	1.00
ACE inhibitor or ARB (n, %)	77 (95%)	63 (96%)	14 (93%)	0.57
Spironolactone (n, %)	56 (69%)	46 (70%)	10 (67%)	1.00
Eplerenone (n, %)	7 (9%)	5 (8%)	2 (13%)	0.61
Furosemide (n, %)	62 (77%)	49 (74%)	13 (87%)	0.50
Hydrochlorotiazide (n, %)	9 (11%)	7 (11%)	2 (13%)	0.67
Hydralazine (n, %)	5 (6%)	4 (6%)	1 (7%)	1.00
Digoxin (n, %)	23 (28%)	20 (30%)	3 (20%)	0.54
Amiodarone (n, %)	23 (28%)	19 (29%)	4 (27%)	1.00
Statin (n, %)	50 (62%)	38 (58%)	12 (80%)	0.15
Aspirin (n, %)	38 (47%)	34 (52%)	4 (27%)	0.10
Clopidogrel (n, %)	20 (25%)	17 (26%)	3 (20%)	0.75
Oral anticoagulant therapy (n, %)	26 (32%)	19 (29%)	7 (47%)	0.22

ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker

Table 6. Changes in echocardiographic parameters 6 months after CRT compared to baseline

Responder patients	**Baseline**	**Follow up**	**p value**
LV ejection fraction (Simpson%, mean±SD)	28.1 ± 6.0	41.3 ± 7.9	**<0.0001*** **
LV end-systolic volume (ml, mean±SD)	179.1 ± 64.9	117.9 ± 58.9	**<0.0001*** **
LV end-diastolic volume (ml, mean±SD)	248.6± 80.2	196.7 ± 77.5	**<0.0001** **
Non-responder patients			
LV ejection fraction (Simpson%, mean±SD)	30.4 ± 8.2	29.3 ± 7.1	0.34
LV end-systolic volume (ml, mean±SD)	203.0 ± 51.5	194.8 ± 46.9	0.38
LV end-diastolic volume (ml, mean±SD)	281.5 ± 67.9	271.6 ± 56.1	0.43

LV= Left Ventricle

According to Cox-regression analysis, non-responders had an almost four-fold higher risk for mortality compared with responders (HR: 3.75; 95% CI: 1.00-13.97; p=0.049) (Figure 3). This impact on mortality persisted also in the multivariate model, with non-response to CRT prevailing as an independent predictor of mortality (adjusted HR: 4.54, 95% CI: 1.14-18.15, p=0.03).

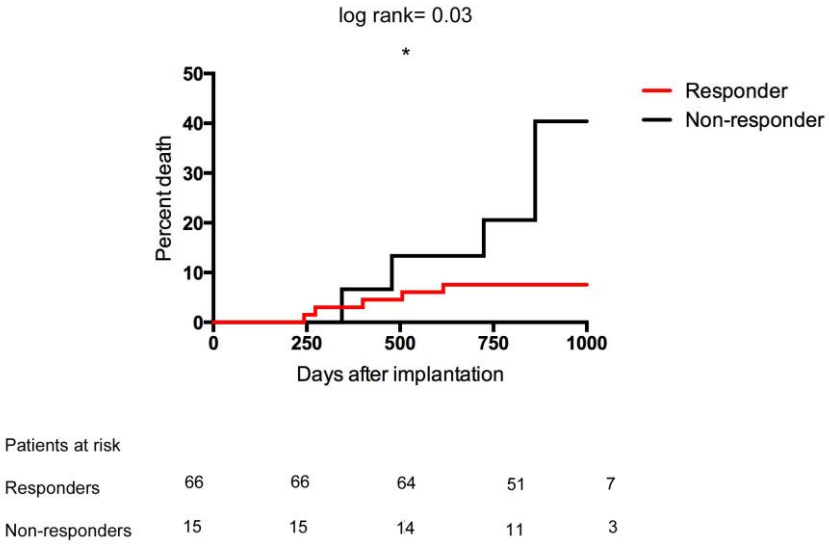

Figure 3. All-cause mortality in responder and non-responder patients to CRT

5.1.1.3 Biomarkers to identify non-responders

At baseline, serum CT-apelin and NT-proBNP levels were similar in both responders and non-responder patients (p=0.74), (Table 5) and ROC testing showed that these parameters are not predictors of non-response (apelin: AUC 0.48; 95%CI: 0-29-0.70; p=0.87, NT-proBNP: AUC 0.53; 95%CI: 0-37-0.70; p=0.73).

At six months, serum CT-apelin significantly decreased in responders (from 549.5 ng/ml [IQR: 279.0-868.8] to 211.0 ng/ml [IQR: 113.8-416.8]; p<0.0001), while it remained unchanged in non-responder patients (from 472.5 ng/ml [IQR: 307.8-700.3] to 541.0 ng/ml [IQR: 278.3-831.0]; p=0.80)(Table 7).

Table 7. Changes in serum peptide levels between responder and. non-responder patients after CRT implantation

Responder patients	**Baseline**	**Follow up**	**p value**
CT-apelin (ng/ml, med, IQR)	549.5 (279.0/868.8)	211.0 (113.8/416.8)	**<0.0001*** **
NT-proBNP (pg/ml, med, IQR)	2561.0 (1173.0 / 4616.0)	1253.0 (516.0 /2519.0)	**0.007*** **
Non-responder patients			
CT-apelin (ng/ml, med, IQR)	472.5 (307.8 / 700.3)	541.0 (278.3/831.0)	0.80
NT-proBNP (pg/ml, med, IQR)	3126.0 (1238.0 / 4492.0)	2676.0 (1947.0/4354.0)	0.91

CT-apelin= C-Terminal Apelin; NT-proBNP= N-terminal prohormone Brain Natriuretic Peptide

Similarly, NT-proBNP levels significantly decreased in responders at 6 months (median: 2561 pg/ml, IQR: 1173-4616 to 1253 pg/ml IQR: 516-2519; p=0.007), while it remained unchanged in non-responder patients (median: 3126 pg/ml [IQR: 1238-4492] to 2676 pg/ml [IQR: 1947-4354]; p=0.91)(Table 7)(Figure 4).

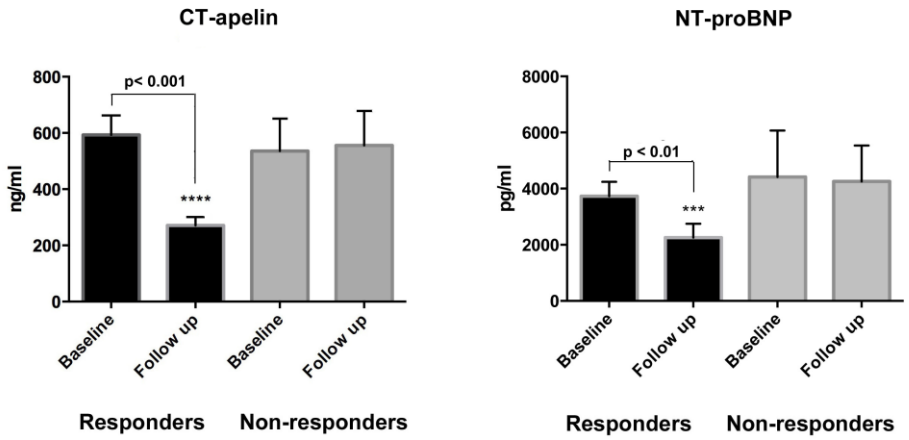

Figure 4. Changes in CT-apelin and NT-proBNP levels according to response to CRT

In ROC analysis, both 6-month CT-apelin and NT-proBNP levels significantly discriminated between responder and non-responder patients (CT-apelin: AUC 0.78; 95%CI: 0.59-0.97; p<0.01, NT-proBNP: AUC 0.75; 95%CI: 0.62-0.88; p=0.005). According to the highest sensitivity and specificity, the optimal cutoffs to diagnose non-response were 268.5 ng/ml for CT-apelin and 1348.5 pg/ml for NT-proBNP, respectively. When patients were classified into groups according to optimal cutoff values, patients with high serum CT-apelin showed a 10 times higher odds for non-response (OR: 10.3, 95% CI; 1.16-91.43; p=0.04), while higher NT-proBNP levels indicated a 16-fold odds for non-response in our patient cohort (OR: 16.0, 95% CI; 1.96-130.68 ; p=0.01).
However, Multivariate ROC testing suggested the superiority of CT-apelin over NT-proBNP (CT-apelin: AUC 0.78; 95%CI: 0-59-0.97; p=0.013 vs. NT-proBNP: AUC 0.67; 95%CI: 0.49-0.85; p=0.13, Figure 5) that was also confirmed in multivariate logistic regression analysis (CT-apelin: p=0.01, NT-proBNP: p=0.41).

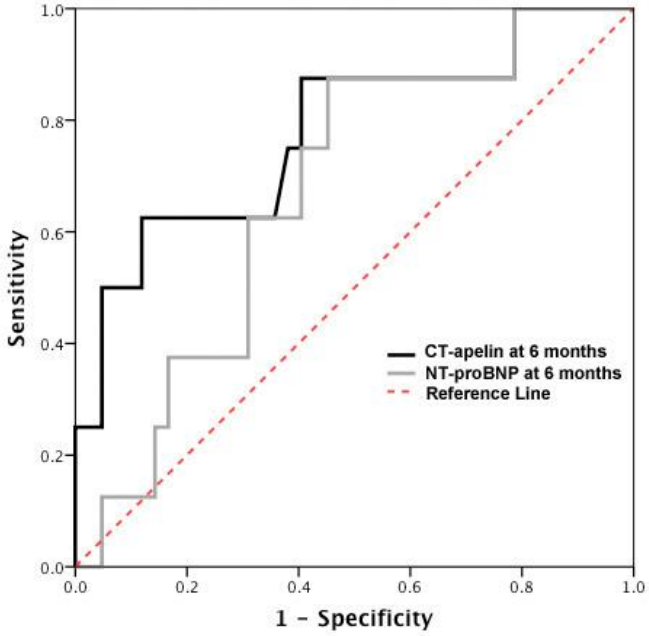

Figure 5. Receiver–Operator Characteristic Curve analysis comparing the diagnostic performance of 6-month serum CT-apelin and NT-proBNP levels on identifying non-responders to CRT

5.1.2 The role of an intraoperative parameter, the RV-LV AD measuring during CRT implantation

5.1.2.1 Baseline clinical characteristics

Between September 2009 and December 2010, 125 patients were enrolled in this study, 73 patients (58%) received CRT-D, while 52 patients (42%) were implanted with a CRT with pacemaker (CRT-P). The mean age of the study participants was 67.0 ± 8.6 years, the mean EF was 28.2 ± 6.5%. Majority of the patients (71%) were in NYHA functional class III, 62% of them had LBBB and 60% had ischemic cardiomyopathy. The RV-LV AD measurements were ranged between 40 and 175ms, the mean value was 106.10 ± 29.98 ms in the entire patient cohort, 109.80 ± 30.31 ms in the LBBB group, 100.0 ± 28.72 ms in the non-LBBB group (p=0.07).

Baseline clinical characteristics of patients with an RV-LV AD below or equal and above 86 ms (lower quartile) are listed in Table 8a and Table 8b. Notably, there were no major differences among patients with a shorter or longer RV-LV AD in clinical or echocardiographic parameters.

After we further dichotomized the patient cohort by LBBB morphology, we assessed the baseline clinical characteristics in patients with LBBB and RV-LV AD $\geq$ 86 ms and compared to the group of remaining patients such as LBBB and RV-LV AD < 86 ms and patients with non-LBBB together. In the group of LBBB and RV-LV AD $\geq$ 86 ms, lower percent of the patient population had ischemic etiology (50% vs. 69%; p=0.04) or prior CABG (12% vs. 26%; p=0.04), had higher mean LV ESV (194.5±70.0ml vs. 168.3±56.4 ml; p= 0.04), less patients were in ambulatory NYHA IV functional class (8% vs. 3%; p= 0.01), and more had sinus rhythm (82% vs. 51%; p= 0.001) at enrolment compared to the group of LBBB and RV-LV AD < 86 ms and patients with non-LBBB together (Table 8c and Table 8d).

Table 8a. Baseline clinical characteristics of CRT patients by RV-LV AD of 86 ms at device implantation

	RV-LV AD ≥ 86ms (n=95)	**RV-LV AD < 86 ms (n=30)**	**p-value**
Age in years (mean±SD)	67.1±8.3	66.5±9.7	0.73
Female gender (n, %)	18 (19%)	6 (20%)	1.00
CRT-D (n, %)	53 (56%)	20 (67%)	0.39
RV-LV AD (ms; mean±SD)	117±23	69±13	NA
Baseline medical history			
Ischemic etiology (n, %)	56 (60%)	19 (63%)	0.25
Diabetes mellitus (n, %)	31 (32%)	6 (20%)	0.25
Secondary prevention (n, %)	5 (4%)	5 (17%)	0.06
Prior myocardial infarction (n, %)	31 (32%)	14 (47%)	0.19
CABG (n, %)	17 (18%)	7 (23%)	0.60
Baseline clinical assessment			
Sinus rhythm at enrolment (n, %)	64 (67%)	18 (60%)	0.51
QRS at baseline (ms, mean±SD)	166.4±27.7	170.0±33.9	0.57
LBBB ECG morphology (n, %)	60 (63%)	18 (60%)	0.23
RBBB ECG morphology (n, %)	0 (0%)	2 (7%)	0.06
IVCD ECG morphology (n, %)	35 (37%)	10 (33%)	0.83
NYHA II (n, %)	16 (17%)	2 (6%)	0.24
NYHA III (n, %)	69 (73%)	23 (77%)	0.81
NYHA IVa (n, %)	10 (10%)	5 (17%)	0.35
6-minute walk test (m, mean±SD)	307.4±128.8	268.1±128.6	0.22
Systolic blood pressure (mmHg, mean±SD)	119.9±17.5	122.5±20.8	0.52
Heart rate at baseline (bpm, mean±SD)	75.8±46.4	73.7±11.3	0.59

RV-LV AD= Right to left ventricular activation delay; CABG= coronary artery bypass graft; LBBB= left bundle branch block; RBBB= right bundle branch block; IVCD= intraventricular conduction delay

Table 8b. Baseline medical therapy, laborator and echocardiographic parameters of CRT patients by RV-LV AD of 86 ms at device implantation

Baseline medical therapy			
Beta blocker (n, %)	86 (91%)	24 (83%)	0.19
ACE inhibitor or ARB (n, %)	91 (96%)	27 (93%)	0.36
Spironolactone (n, %)	69 (74%)	18 (62%)	0.25
Loop diuretics (n, %)	77 (82%)	23 (80%)	0.61
Laboratory parameters			
NT-proBNP (ng/ml; med, IQR)	2608.0 (1596/4945)	2815.0 (1232/4732)	0.88
Creatinine (umol/L; med, IQR)	106.8 ±34.8	118.0 ±41.6	0.20
BUN (mmol/L; mean±SD)	9.2 ± 1.4	10.7 ± 7.0	0.18
Echocardiography parameters			
LVEF (%, mean±SD)	28.5±5.5	28.1±6.9	0.82
LV end-diastolic volume (ml, mean±SD)	249.6±49.3	253.4±82.7	0.86
LV end-systolic volume (ml, mean±SD)	181.4±50.4	184.0±67.4	0.85

ACE= angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blocker; LV= left ventricular; LVEF= left ventricular ejection fraction; BUN= blood urea nitrogen.

Table 8c. Baseline clinical characteristics of CRT patients by RV-LV AD of 86 ms and LBBB morphology

	RV-LV AD ≥ 86ms LBBB patients (n=60)	**RV-LV AD < 86 ms LBBB and nonLBBB patients (n=65)**	**p-value**
Age in years (mean±SD)	67.5±7.9	66.3±9.6	0.49
Female gender (n, %)	16 (27%)	8 (12%)	0.07
CRT-D (n, %)	32 (53%)	41 (63%)	0.28
RV-LV AD (ms; mean±SD)	121±23	92±28	NA
Baseline medical history			
Ischemic etiology (n, %)	30 (50%)	45 (69%)	**0.04***
Diabetes mellitus (n, %)	16 (27%)	21 (32%)	0.23
Secondary prevention (n, %)	2 (3%)	8 (12%)	0.10
Prior myocardial infarction (n, %)	17 (28%)	28 (43%)	0.10
CABG (n, %)	7 (12%)	17 (26%)	**0.04***
Baseline clinical assessment			
Sinus rhythm at enrolment (n, %)	49 (82%)	33 (51%)	**0.001*****
QRS at baseline (ms, mean±SD)	167.3±24.5	167.2±33.3	0.98
LBBB ECG morphology (n, %)	N/A	18 (28%)	N/A
RBBB ECG morphology (n, %)	N/A	2 (3%)	N/A
IVCD ECG morphology (n, %)	N/A	45 (69%)	N/A
NYHA II (n, %)	9 (15%)	6 (9%)	0.41
NYHA III (n, %)	46 (77%)	44 (68%)	0.32
NYHA IVa (n, %)	5 (8%)	15 (23%)	**0.01***
6-minute walk test (m, mean±SD)	316.0±132.6	282.9±125.2	0.22
Systolic blood pressure (mmHg, mean±SD)	119.8±18.9	121.1±17.8	0.70
Heart rate at baseline (bpm, mean±SD)	76.8±13.8	77.0±20.8	0.97

RV-LV AD= Right to left ventricular activation delay; CABG= coronary artery bypass graft; LBBB= left bundle branch block; RBBB= right bundle branch block; IVCD= intraventricular conduction delay

Table 8d. Baseline medical therapy, laboratory and echocardiographic parameters of CRT patients by RV-LV AD of 86 ms and LBBB morphology

Baseline medical therapy			
Beta blocker (n, %)	54 (90%)	56 (88%)	0.59
ACE inhibitor or ARB (n, %)	58 (97%)	60 (94%)	0.44
Spironolactone (n, %)	42 (70%)	45 (70%)	1.00
Loop diuretics (n, %)	45 (75%)	55 (86%)	0.19
Laboratory parameters			
NT-proBNP (ng/ml; med, IQR)	2608 (1063/4664)	2612.0 (1739/5049)	0.21
Creatinine (umol/L; med, IQR)	101.9 ±45.0	116.1 ±36.8	0.06
BUN (mmol/L; mean±SD)	9.0 ± 4.7	10.1 ± 5.4	0.21
Echocardiography parameters			
LVEF (%, mean±SD)	27.6±7.6	28.0±6.6	0.77
LV end-diastolic volume (ml, mean±SD)	263.1±86.1	233.5±69.1	0.08
LV end-systolic volume (ml, mean±SD)	194.5±70.0	168.3±56.4	**0.04***

ACE= angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blocker; LV= left ventricular; LVEF= left ventricular ejection fraction; BUN= blood urea nitrogen.

N/A: not applicable due to the definition of the groups

5.1.2.2 RV-LV activation delay and functional outcome 6 months after CRT implantation

At 6-month follow up, 33 (55%) of the patients with RV-LV AD ≥ 86 ms and LBBB performed their 6-minute walk test over 300 meters, compared to 23 of those patients (35%) with RV-LV AD < 86 ms or with a non-LBBB (55% vs. 35%; p=0.03) (Table 9). In patients with RV-LV AD ≥ 86 ms and LBBB, better laboratory parameters were observed at 6-month after CRT implantation with an NT-proBNP median value of 1216 (IQR: 326.9 / 2630) vs. 1887 (IQR: 1140 / 3300); p = 0.03, a creatinine value of 96.3 ± 56.6 vs. 122.1 ± 46.9; p = 0.01 and a blood urea nitrogen value of 7.6 ± 4.7 vs. 10.9 ± 5.6; p = 0.001, as compared to non-LBBB patients or to those with LBBB and RV-LV AD < 86 ms (Table 9). Patients with RV-LV AD ≥ 86 ms and LBBB showed the greatest improvement in left ventricular ejection fraction (EF: 28.0 ± 7.1 to 36.3 ± 12.3; p < 0.001) 6-month after CRT implantation.

5.1.2.3 RV-LV activation delay and clinical outcome in the total patient cohort

During the median follow-up of 2.2 years, 44 (35%) patients had heart failure events or death, out of them 36 (29%) patients died. Sixteen (53%) patients had HF or death with RV-LV AD < 86 ms, and 28 (29%) with RV-LV AD ≥ 86 ms, while 11 (37%) patients died with RV-LV AD < 86 ms, and 25 patients (26%) with RV-LV AD ≥ 86 ms.

Patients with RV-LV AD ≥ 86 ms had significantly lower cumulative probability of HF/death when compared to those with RV-LV AD < 86 ms (p=0.003) (Figure 6a). The cumulative probability of all-cause mortality was significantly lower in patients with a longer activation delay (RV-LV AD ≥ 86ms) compared to those with shorter delay (RV-LV AD < 86ms, p=0.004) (Figure 6b).

Table 9. Clinical parameters at 6-month after CRT implantation

Clinical assessment	**RV-LV AD ≥ 86ms LBBB patients (n=60)**	**RV-LV AD < 86 ms LBBB and nonLBBB patients (n=65)**	**p value**
6-minutes walk test > 300 m (n; %)	33 (55%)	23 (35%)	**0.03***
Systolic blood pressure (Hgmm, mean±SD)	127.4 ± 19.3	122.2 ± 24.8	0.27
Diastolic blood pressure (Hgmm, mean±SD)	77.2 ± 9.4	73.2 ± 12.0	0.08
Laboratory parameters			
NT-proBNP (ng/ml; med, IQR)	1216 (326.9 / 2630)	1887 (1140 / 3300)	**0.03***
Creatinine (umol/L; med, IQR)	96.3 ± 56.6	122.1 ± 46.9	**0.01***
Blood Urea Nitrogen (mmol/L; mean±SD)	7.6 ± 4.7	10.9 ± 5.4	**0.001****

NT-proBNP= N-terminal prohormone Brain Natriuretic Peptide

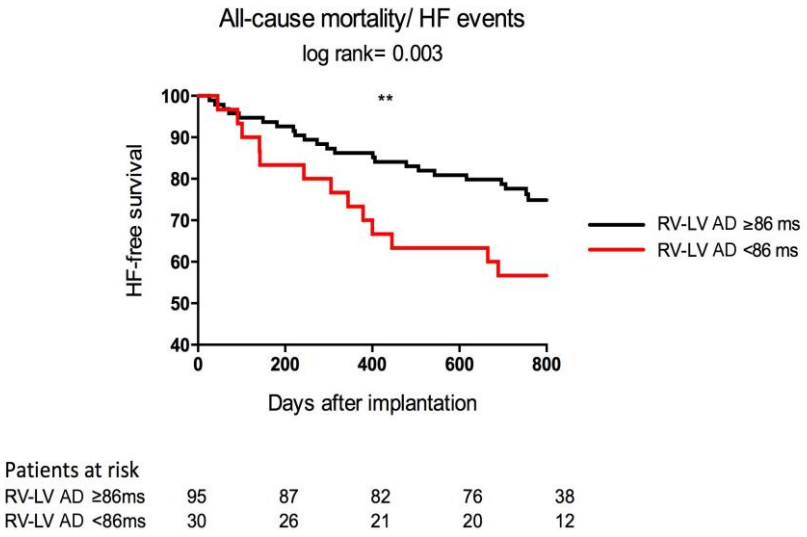

Figure 6a. Kaplan-Meier Cumulative probability of HF/Death by RV-LV AD

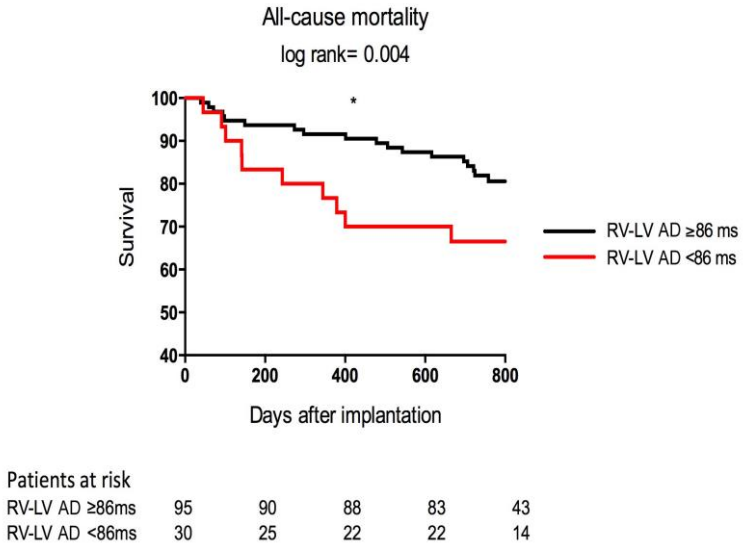

Figure 6b. Kaplan-Meier Cumulative probability of Death by RV-LV AD

Multivariate Cox-regression analysis confirmed the independent role of RV-LV AD first as a continuous parameter (Table 10a) and then by 86 ms (Table10b) in predicting HF or death or all-cause mortality in the total patient population after adjustment for relevant clinical covariates, namely for LBBB ECG morphology, heart failure etiology and age at enrolment. Patients with RV-LV AD ≥ 86ms had a 56% significantly lower risk of HF or death (HR: 0.44; 95% CI: 0.23-0.82; p=0.001) and a 52% lower risk of all-cause mortality (HR: 0.48; 95% CI: 0.23-1.00; p=0.05), compared to those with a shorter RV-LV activation delay at CRT implantation (Table 10b).

Table 10a. Univariate models to evaluate the clinical outcome of CRT patients by continuous value of RV-LV AD and LBBB ECG morphology at baseline

Primary end point: HF event or death	**Hazard Ratio**	**95% confidence interval**	**p-value**
RV-LV AD in all patients (125 patients)	0.98	0.97 – 0.99	**0.015***
RV-LV AD in LBBB (78 patients)	0.98	0.96-0.99	**0.029***
RV-LV AD in non-LBBB (47 patients)	0.99	0.97 – 1.00	0.36
Secondary end point: all-cause mortality	**Hazard Ratio**	**95% confidence interval**	**p-value**
RV-LV AD in all patients (125 patients)	0.98	0.97-0.99	**0.0001*****
RV-LV AD in LBBB (78 patients)	0.97	0.96-0.99	0.03
RV-LV AD in non-LBBB (47 patients)	0.12	0.97 – 1.00	0.98

LBBB= Left Bundle Branch Block; LV= Left Ventricle; RV= Right Ventricle; RV-LV AD= Right to Left Ventricular Activation Delay

Table 10b. Multivariate models of primary endpoint to evaluate the clinical outcome of CRT patients by RV-LV AD and LBBB ECG morphology at baseline

Primary end point: HF event or death	**Hazard Ratio**	**95% confidence interval**	**p-value**
RV-LV AD ≥86ms vs. <86ms in all patients (95 vs. 30 patients)	0.44	0.23 – 0.82	**0.001***
RV-LV AD ≥86ms vs. <86ms in LBBB (60 vs. 18 patients)	0.18	0.63-0.52	**0.001***
RV-LV AD ≥86ms vs. <86ms in non-LBBB (35 vs. 12 patients)	0.63	0.26 – 1.49	0.29
RV-LV AD ≥86ms in LBBB vs. Others (60 vs. 65 patients)	0.23	0.11 – 0.49	**<0.001***

LBBB= Left Bundle Branch Block; LV= Left Ventricle; RV= Right Ventricle; RV-LV AD= Right to Left Ventricular Activation Delay

*Models are adjusted for age at enrolment, ischemic etiology of heart failure, and for LBBB ECG pattern in the model on the total patient population.

Table 10c. Multivariate models of secondary endpoint to evaluate the clinical outcome of CRT patients by RV-LV AD and LBBB ECG morphology at baseline

Secondary end point: all-cause mortality	**Hazard Ratio**	**95% confidence interval**	**p-value**
RV-LV AD ≥86ms vs. <86ms in all patients (95 vs. 30 patients)	0.48	0.23-1.00	**0.05***
RV-LV AD ≥86ms vs. <86ms in LBBB (60 vs. 18 patients)	0.37	0.12-1.18	0.09
RV-LV AD ≥86ms vs. <86ms in non-LBBB (35 vs. 12 patients)	0.43	0.15 – 1.20	0.11
RV-LV AD ≥86ms in LBBB vs. Others (60 vs. 65 patients)	0.35	0.16 – 0.75	**0.007***

LBBB= Left Bundle Branch Block; LV= Left Ventricle; RV= Right Ventricle; RV-LV AD= Right to Left Ventricular Activation Delay

*Models are adjusted for age at enrolment, ischemic etiology of heart failure, and for LBBB ECG pattern in the model on the total patient population.

5.1.2.4 RV-LV activation delay and clinical outcome by LBBB ECG pattern

The findings were even more pronounced in patients with an LBBB ECG pattern. Patients with an LBBB and an RV-LV AD ≥ 86 ms at implantation had a significantly lower cumulative probability of HF/death when compared to those with shorter activation delay (RV-LV AD < 86 ms) and to those patients with non-LBBB ($p<0.001$) (Figure 7a). This difference was translated into a 77% reduction in the risk of HF or death (HR: 0.23; 95% CI: 0.11-0.49; $p < 0.001$), after adjustment for relevant clinical covariates (Table 10b).
Furthermore, there was a significantly lower cumulative probability of all-cause mortality in LBBB patients with a longer RV-LV activation delay at implantation (RV-LV AD ≥ 86ms), compared to those with shorter activation delay (RV-LV AD <86ms) and to those patients with non-LBBB ($p=0.01$) (Figure 7b). This translated into a 65% risk reduction in all-cause mortality in the multivariate models (HR: 0.35; 95% CI: 0.16-0.75; $p=0.007$) (Table10c).
In patients with non-LBBB, there was no significant difference in HF or death or in all-cause mortality by RV-LV AD groups measured at CRT implantation (HF/death HR=0.63; 95% CI: 0.26-1.49; $p=0.29$, death HR=0.43; 95% CI: 0.15-1.20; $p=0.11$) (Table 10b and Table 10c).

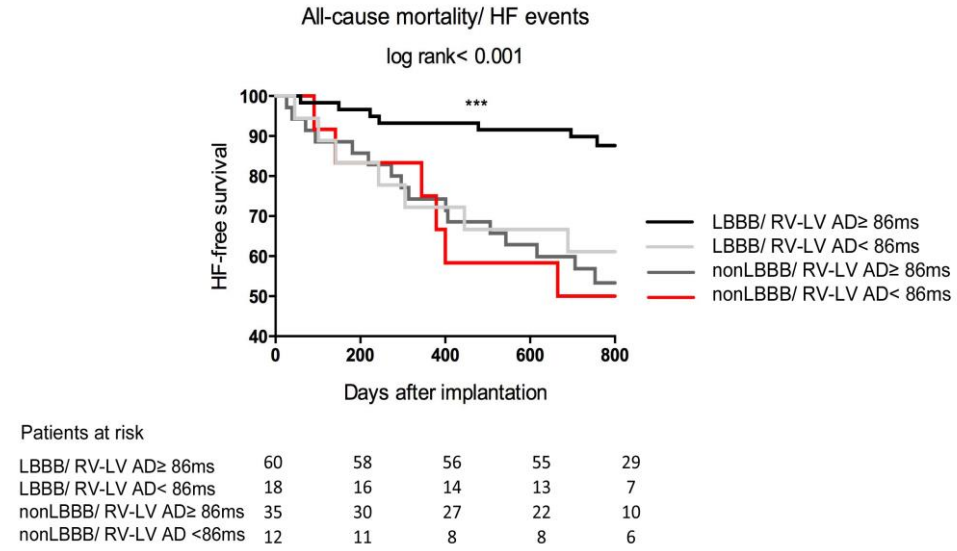

Figure 7a. Kaplan-Meier Cumulative probability of HF/Death by LBBB ECG morphology and RV-LV activation delay**.**

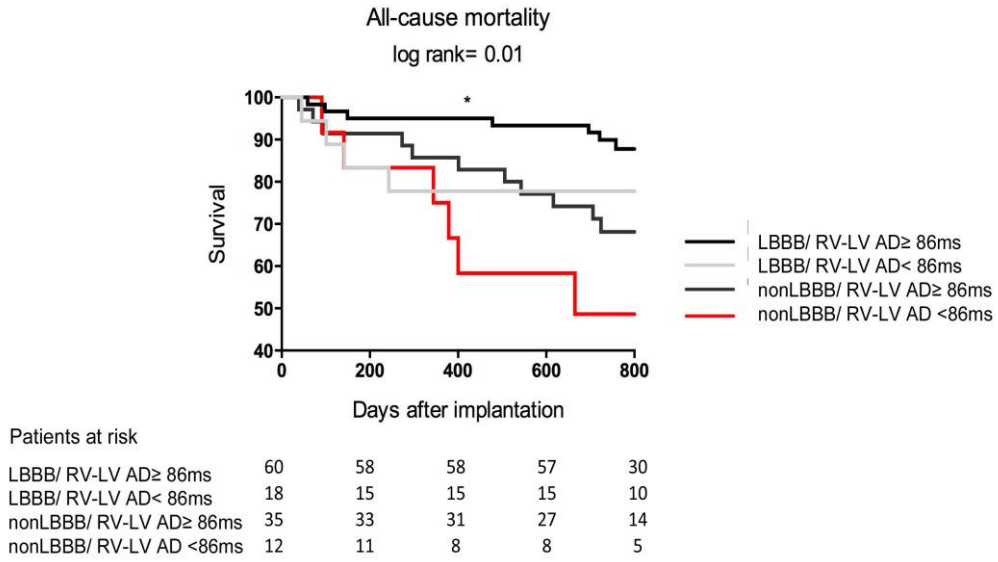

Figure 7b. Kaplan-Meier Cumulative probability of Death by LBBB ECG morphology and RV-LV AD

5.1.2.5 Clinical outcome by RV-LV activation delay after normalization to QRS

The univariate model showed that RV-LV AD /QRS is also an independent factor of the primary endpoint of heart failure and death in LBBB patients (HR: 0.08; 95% CI 0.01-1.02; p=0.05). These results were also confirmed by multivariate Cox regressional analysis: by using the optimal cutoff value of percentage RV-LV AD /QRS which was 64%. Those who had higher RV-LV AD to QRS $\geq$ 64% have lower risk for heart failure events or death in the total patient cohort (HR: 0.43; 95% CI 0.23-0.81; p=0.01) and in LBBB patients as well (HR: 0.28; 95% CI 0.10-0.80; p=0.01). The lowest cumulative probability of HF/death was observed in patients with higher percentage of RV-LV AD /QRS and LBBB morphology (HR: 0.21; 95% CI 0.08-0.54; p=0.001) compared to nonLBBB or low RV-LV AD /QRS patients. In multivariate analyses models were adjusted for age and ischemic etiology. (Data are not shown).

5.1.2.6 Functional outcome, NT-proBNP 6-month after CRT implantation and clinical outcome by RV-LV activation delay quartiles

When we assessed the effects of RV-LV AD on changes of NT-proBNP and incidence of HF/death by RV-LV quartiles, we found a linear increase in the degree of reduction in NT-proBNP 6-month after CRT towards the longer RV-LV AD quartile sub-groups. In parallel with the improvement in NT-proBNP, there was a linear decrease in the incidence of HF/death (Figure 8).

Besides the beneficial changes in NT-proBNP, the better clinical outcome was reflected in the improvement of renal function between patients with longer RV-LV AD and LBBB morphology compared to those, who had shorter activation delay or nonLBBB morphology (Table 9). Significant differences were found in changes of serum creatinine levels after 6 months (96.3±56.6 umol/L vs. 122.1±46.9 umol/L; p=0.01), and more pronounced in Blood Urea Nitrogen (BUN) (7.6±4.7mmol/L vs. 10.9±5.4mmol/L; p=0.001).

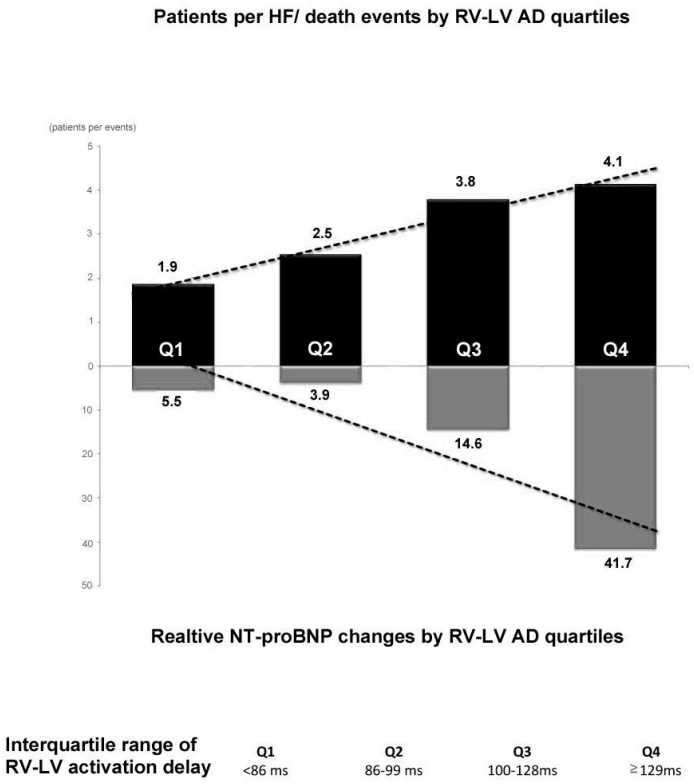

Figure 8. Incidence of patients per HF/death events and relative changes of NT-proBNP by RV-LV AD quartiles

5.2 Part 2 - The question of CRT upgrade

5.2.1 A systematic review and meta-analyses from the literature about the outcome of patients after CRT upgrade vs. de novo CRT implantation

5.2.1.1 Study characteristics

A total of 17 reports were selected for the current analysis comprising 6628 CRT recipients, of whom 4549 patients had de novo resynchronization therapy and 2079 patients underwent an upgrade procedure (Figure 9).

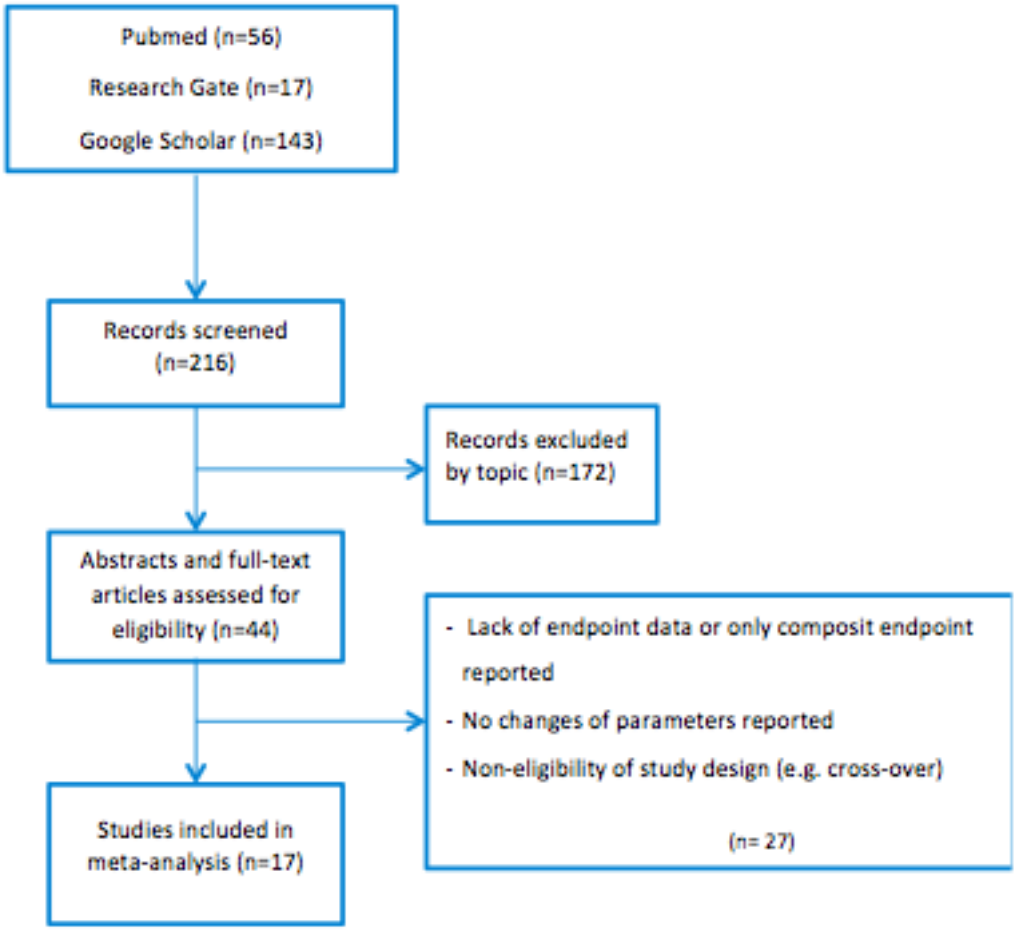

Figure 9. Flow chart of searching for publications to the meta-analyses of CRT upgrade vs. de novo CRT implantation

The characteristics of all included studies are shown in Table 11a. None of the identified studies was a randomized, controlled trial. Most of them were observational, retrospective (87-98)(99) or observational prospective (100-102)(103) cohort studies. The vast majority were single-center observations (89,91-93,95-98,100,101) with the exception of four dual/multicenter studies(88,90,94)(88) and one based on a European survey(87). Four(98,100,102)(88) from the 17 studies proved to be high quality reports with an average MINORS score 13.9 (data are not shown).

The most important published patient characteristics of the included studies, such as age, gender, etiology, baseline QRS duration (paced in upgrade and intrinsic in de novo group), baseline NYHA functional class, baseline left ventricular ejection fraction and dimensions are summarized in Table 11b. In summary, the mean ejection fraction was by definition lower than 35% in all studies and there were no significant differences between the de novo and upgrade groups in most of the individual studies. Most of the trials enrolled patients with severe symptoms (NYHA III-IVa), a smaller extent of the studies investigated patients without depicting functional class. More than 50% of the studies found significant differences in the following baseline parameters between the two patient groups: age, atrial fibrillation and QRS duration. In the upgrade group, patients were generally older, more likely to have atrial fibrillation and they had wider (paced) QRS.

Table 11a: Study design characteristics of included studies to the meta-analyses of CRT upgrade vs. de novo CRT implantation

Study, Year	Design	Number of Patients			Follow up	Endpoints	Type of devices before upgrade	% of ventricular pacing before upgrade	Study quality – MINORS score
		Total	De novo	Upgrade					
Marai et al., 2006	Single-centre, prospective observational cohort	98	73	25	3 months	**ΔEF** **ΔNYHA** (6 MWT)	PMs (VVI / VDD / DDD)	PM dependent patients with constant RVAP for 4.7 ± 2.5 years	moderate
Witte et al., 2006	Single-centre, retospective observational cohort	71	39	32	3 months	**ΔEF** **ΔEDV** **ΔQRS** (dyssynchrony parameters)	PMs (further details are NA)	>50%	moderate
Duray et al., 2008	Single-centre, prospective observational cohort	79	61	18	6 months	**All-cause mortality** (procedural parameters, NYHA / LVEF / NT-proBNP)	PMs / ICDs	NA	high
Nagele et al., 2008	Retrospective population-based cohort	328	221	107	12 / 30 months	**All-cause mortality** **ΔEF** **ΔNYHA** **ΔQRS** (QoL, peak Vo2, dyssynchrony parameters)	81% DDD 19% VVI	96 ± 4%	moderate

Table 11a: Study design characteristics of included studies to the meta-analyses of CRT upgrade vs. de novo CRT implantation (continuation)

Study, Year	Design	Number of Patients			Follow up	Endpoints	Type of devices before upgrade	% of ventricular pacing before upgrade	Study quality – MINORS score
		Total	De novo	Upgrade					
Foley et al., 2009	Single-centre, retrospective observational cohort	394	336	58	12 / 25 months	**ΔEF** **ΔEDV** **ΔNYHA** **All-cause mortality**, (CV death or HF hospitalization, 6 MTW, QoL)	VVI or DDD	81±31.0%	moderate
Wokhlu et al., 2009	Single-center, retrospective observational cohort	505	338	167	7 .1 / 31.2 months	**All-cause mortality** **ΔEF** **ΔEDV** **ΔNYHA**	54.5% ICD 45.5% PM	<40% in 25% of pts 40-80% in 21% of pts >80% in 54% of pts	high
Frohlich et al., 2010	Retrospective population-based cohort	172	102	70	21 months	**ΔEF** **ΔQRS** (NYHA)	Bradycardia indication, no further details	>50% for at least 6 months before including	moderate

Table 11a: Study design characteristics of included studies to the meta-analyses of CRT upgrade vs. de novo CRT implantation (continuation)

Study, Year	Design	Number of Patients			Follow up	Endpoints	Type of devices before upgrade	% of ventricular pacing before upgrade	Study quality – MINORS score
		Total	De novo	Upgrade					
Paparella et al., 2010	Single-centre, retrospective population based cohort	82	43	39	1.3, and every 6 months thereafter / 35 months	**Heart failure events** **ΔEF** **ΔEDV** **ΔNYHA** **ΔQRS** (6 MWT, dyssynchrony parameters, MR)	31% VVI 43% DDD 25% VDD	91 ± 7%	moderate
Kabutoya et al., 2010	Single-centre, retrospective observational cohort	48	33	15	6 months	**ΔEF** (LV dP/dt)	47% PM 53% ICD	94 ± 11%	moderate
Bogale et al., 2011	Multicenter, survey registry	2090	1489	601	12 months	**All-cause mortality** **Heart failure events** (NYHA, QRS, procedural parameters)	30.1% PM 69.9% ICD	62% paced rhythm at inclusion, no further details	moderate

Table 11a: Study design characteristics of included studies to the meta-analyses of CRT upgrade vs. de novo CRT implantation (continuation)

Study, Year	Design	Number of Patients			Follow up	Endpoints	Type of devices before upgrade	% of ventricular pacing before upgrade	Study quality – MINORS score
		Total	De novo	Upgrade					
Gage et al., 2014	Single-centre, retrospective observational cohort	655	465	190	12 months	**All-cause mortality** **Heart failure events** **ΔEF** **ΔEDV** **(**dyssynchrony parameters, MR, RV dysfunction)	58% PM 42% ICD	> 40%	moderate
Tayal et al., 2016	Single-centre, prospective observational cohort	135	85	50	6 / 48 months	**All-cause mortality** **ΔEF** (MR, Global long. strain)	PMs	>40%	high
Horst et al., 2016	Single-centre, retrospective observational cohort	268	134	134	12 months	**All-cause mortality** (procedural parameters)	PMs and ICDs; 60% DDD, 40% VVI	NA	moderate
Tondato et al., 2016	Single-centre, retrospective observational cohort	220	120	100	62 months	**All-cause mortality** (NYHA, QRS, Responders by echocard. parameters)	NA	NA	moderate

Table 11a: Study design characteristics of included studies to the meta-analyses of CRT upgrade vs. de novo CRT implantation (continuation)

Study, Year	Design	Number of Patients			Follow up	Endpoints	Type of devices before upgrade	% of ventricular pacing before upgrade	Study quality – MINORS score
		Total	De novo	Upgrade					
Lipar et al., 2016	Single-centre, retrospective observational cohort	281	165	116	10 months	**All-cause mortality** **Heart failure events** **ΔEF** **ΔNYHA** **ΔQRS**	49% DDD PM, 22% DDD-ICD, 18% VVI, 12% VVI-ICD	<40% in 13% of pts 40-80% in 16% of pts >80% in 71% of pts	moderate
Vamos et al., 2017	Multicenter, prospective observational cohort	552	375	177	37 months	**All-cause mortality** **ΔEF** **ΔNYHA**	PMs / ICDs	NA	high

EDV= end-diastolic volume; EF= left ventricular ejection fraction; ICD= implantable cardiac defibrillator; PM= pacemaker; DDD-PM/ICD= dual chamber pacemaker or ICD; VVI-PM/ICD= single chamber ventricular pacemaker or ICD; Pts= patients; NYHA= New York Heart Association Class; MR= mitral regurgitation; RVAP= right ventricular apical pacing

Table 11b. Differences in the baseline patient characteristics of the included studies to the meta-analyses of CRT upgrade vs. de novo CRT implantation

(Parameters with significant difference in the original reports are highlighted with bold verbatim)

	Gender (male)		**Etiology (ischemic)**		**Atrial Fibrillation**		**Age (years)**		**QRS (ms)**		**NYHA**		**EF (%)**		**LV dimensions (EDV / EDD)**	
Study, Year	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade
Marai et al., 2006	64 (88%)	20 (80%)	65 (89%)	23 (92%)	**11 (15%)**	**8 (32%)**	69 ± 9	72 ± 9	**163 ± 30**	**203 ± 32**	3.1 ± 0.6	3.2 ± .5	22 ± 5	23 ± 9	67 ± 10 mm	64 ± 6 mm
Witte et al., 2006	NA	NA	21 (54%)	16 (50%)	**3 (8%)**	**17 (53%)**	67± 2	70 ± 4	**173 ± 4**	**207 ± 5**	3.2 ± 0.5	3.3 ± 0.5	20 ± 1	20 ± 2	70 ± 2 mm	70 ± 2 mm
Duray et al., 2008	50 (82%)	13 (72%)	30 (49%)	8 (44%)	NA	NA	63 ± 11	66 ± 10	NA	NA	NYHA II: 33% NYHA III-IV: 67%	NYHA II: 11% NYHA III-IV: 89%	22 ± 7	25 ± 9	NA	NA

Table 11b. Differences in the baseline patient characteristics of the included studies to the meta-analyses of CRT upgrade vs. de novo CRT implantation (continuation)

	Gender (male)		**Etiology (ischemic)**		**Atrial Fibrillation**		**Age (years)**		**QRS (ms)**		**NYHA**		**EF (%)**		**LV dimensions (EDV / EDD)**	
Study, Year	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade
Nagele et al., 2008	80%	92%	53%	49%	**14%**	**37%**	68.4 ± 11	68.7 ± 15	**168.3 ± 24**	**187.1 ± 28**	3.1	3.1	26.4 ± 9	28.1 ± 6	63 ± 9 mm	65 ± 13 mm
Foley et al., 2009	261 (78%)	48 (83%)	219 (65%)	42 (72%)	NA	14 (24%)	**68.7± 10.8**	**72.8 ± 11.4**	**150.9 ± 27.8**	**163.1 ± 32.3**	3.26 ± 0.54	3.36 ± 0.55	23.2 ± 10.2	23.1 ± 10.7	**253 ± 99 mL**	**212.5 ± 98.0 mL**
Wokhlu et al., 2009	**253 (75%)**	**146 (87%)**	204 (60%)	110 (66%)	**87 (26%)**	**69 (41%)**	**67.7 ± 11.8**	**70.1 ± 10.3**	**158 ± 31**	**184 ± 32**	3.0 ± 0.5	3.0 ± 0.5	23.1 ± 7.3	23.2 ± 7.2	235.6 ± 73.7 mL	225.0 ± 69.6 mL
Frohlich et al., 2010	82 (80.4%)	51 (72.9 %)	41 (40.2%)	36 (51.4%)	**32 (31.4%)**	**37 (52.9%)**	**61.0 (54–67)**	**66.5 (57.0–75.0)**	**154 (133–178)**	**184 (163–205)**	NYHA II: 20% NYHA III: 75% NYHA IV: 5%	NYHA II: 29% NYHA III: 69% NYHA IV:3%	20.0 (16.8–29.0)	24.0 (17.8–30.0)	244 (175–305) mL	219 (141–259 mL

Table 11b. Differences in the baseline patient characteristics of the included studies to the meta-analyses of CRT upgrade vs. de novo CRT implantation (continuation)

	Gender (male)		**Etiology (ischemic)**		**Atrial Fibrillation**		**Age (years)**		**QRS (ms)**		**NYHA**		**EF (%)**		**LV dimensions (EDV / EDD)**	
Study, Year	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade
Paparella et al., 2010	24 (56%)	23 (59%)	10 (23%)	16 (41%)	NA	8 (21%)	**71.5 ± 7.8**	**75.4 ± 5.8**	**172.1 ± 25.8**	**186.2 ± 22.1**	NYHA III: 55% NYHA IV: 18%	NYHA III: 51% NYHA IV: 30%	**26 ± 2**	**23 ± 7**	214.5 ± 54.8 mL	234.1 ± 48.4 mL
Ehara et al., 2010	**73%**	**61%**	**37%**	**18%**	**18%**	**32%**	**68**	**71**	**141**	**174**	NA	NA	NA	NA	NA	NA
Kabutoya et al., 2010	**79%**	**47%**	**33%**	**0%**	NA	NA	65.4 ±11.2	68.3 ± 11.5	**162 ± 25**	**189 ± 40**	NA	NA	**32 ± 12**	**30 ± 10**	NA	NA

Table 11b. Differences in the baseline patient characteristics of the included studies to the meta-analyses of CRT upgrade vs. de novo CRT implantation (continuation)

	Gender (male)		**Etiology (ischemic)**		**Atrial Fibrillation**		**Age (years)**		**QRS (ms)**		**NYHA**		**EF (%)**		**LV dimensions (EDV / EDD)**	
Study, Year	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade
Bogale et al., 2011	NA	NA	**778 (49.7%)**	**339 (54.6%)**	**336 (20.3%)**	**208 (30.4%)**	**69 (62–76)**	**71 (64–77)**	**152 + 28**	**171 + 35**	NYHA I: 1.6% NYHA II:20% NYHA III:70.1% NYHA IV:8.3%	NYHA I: 0.8% NYHA II:18.6% NYHAI II:71.1% NYHA IV:9.5%	**26 ± 8**	**28 ± 8**	NA	NA
Gage et al., 2014	68	75	58	58	**13**	**37**	**69 ±12**	**73 ± 11**	**171 ± 28**	**152 ± 24**	NYHA III: 66%	NYHA III: 67%	26.6 ± 6	26.7 ± 5	**62 ± 9mm**	**60 ± 9mm**

Table 11b. Differences in the baseline patient characteristics of the included studies to the meta-analyses of CRT upgrade vs. de novo CRT implantation (continuation)

	Gender (male)		**Etiology (ischemic)**		**Atrial Fibrillation**		**Age (years)**		**QRS (ms)**		**NYHA**		**EF (%)**		**LV dimensions (EDV / EDD)**	
Study, Year	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade
Tayal et al., 2016	60 (71%)	39 (80%)	44 (52%)	29 (58%)	NA	NA	**64 ± 12**	**69 ± 12**	174 ± 17	178 ± 20	NYHA III: 75% NYHA IV: 13%	NYHA III: 62% NYHA IV: 8%	**23 (19-29)**	**26 (23 - 32)**	**199 (157-250) mL**	**151 (133-191) mL**
Horst et al. 2016	**92 (69%)**	**110 (82%)**	**66 (49%)**	**82 (61%)**	21 (16%)	39 (29%)	**67 (60–72)**	**71 (63–75)**	NA	NA	NYHA I: 1% NYHA II:17% NYHA III: 77% NYHA IV: 5%	NYHA I: 1% NYHA II: 10% NYHAI II: 82% NYHA IV: 8%	23 ± 7	24 ± 7	NA	NA

Table 11b. Differences in the baseline patient characteristics of the included studies to the meta-analyses of CRT upgrade vs. de novo CRT implantation (continuation)

	Gender (male)		**Etiology (ischemic)**		**Atrial Fibrillation**		**Age (years)**		**QRS (ms)**		**NYHA**		**EF (%)**		**LV dimensions (EDV / EDD)**	
Study, Year	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade	De novo	Upgrade
Tondato et al., 2016	**77%**	**88%**	41%	44%	NA	NA	74.2 ± 10.5	76.2 ± 9.8	**154 ± 20**	**184 ± 29**	NYHA III-IV: 94%	NYHA III-IV: 91%	25.6 ± 8.4	27.2 ± 9.0	NA	NA
Lipar et al., 2016	35 (21%)	21 (18%)	94 (57%)	66 (57%)	NA	NA	74.3 (10.6)	75.5 (10.1)	**147 ± 26**	**178 ± 34**	2.3 ± 0.6	2.3 ± 0.6	26.1 ± 8.3	27.9 ± 9.7	120.2 ± 56.6 mL	111.0 ± 52.3 mL
Vamos et al., 2017	288 (77.4%)	139 (78.5%)	195 (51.7%)	103 (58.2%)	**124 (32.9%)**	**74 (41.8%)**	66.5 ± 11.3	68.3 ± 10.4	**155.3 ± 27.6**	**170.8 ± 29.8**	2.75 ± 0.66	2.81 ± 0.61	**25.3 ± 7.0**	**24.0 ± 7.9**	66.1 ± 9.9	65.5 ± 11.4

EDD: End-Diastolic Diameter, EDV: End-Diastolic Volume, EF: Ejection Fraction, NYHA: New York Heart Association, LV: Left Ventricle

5.2.1.2 All-cause mortality and heart failure events

Crude mortality rates were available in 6157 patients from 12 studies (87-89,91,93,94,96,98,100,102)(84, 88), while unadjusted or adjusted hazard ratios were available for 1734 and 1229 patients in three (91,102) (88) and four (91,98,102)(88) studies, respectively. All-cause mortality did not differ following an upgrade to CRT compared to de novo implantations (RR 1.10, 95% CI, 0.99 to 1.22, p=0.08, I^2=36.5%)(Figure 10a). Pooled analyses of the unadjusted or adjusted hazard ratios revealed similar findings (crude HR 1.07, 95% CI, 0.72 to 1.57, p=0.74, I^2=73.6%)(Figure 10b)(adjusted HR: 0.81, 95% CI, 0.36 to 1.81, p=0.61)(Figure 10c). In studies that provided relevant information, the unadjusted risk of heart failure events was significantly higher in patients with de novo implantations (RR 1.15, 95% CI, 1.04 to 1.27, p=0.01, I^2=46.5%)(Figure 10d).

5.2.1.3 Left ventricular reverse remodeling, clinical improvement

The extent of reverse remodeling in terms of improvement in left ventricular ejection fraction and end-diastolic volume was similar in the two patient groups (ΔEF de novo. 6.85% vs. upgrade 9.35%, p=0.235)(Figure 11a); (ΔEDV de novo -23.0 ml vs. upgrade -20.0 ml; p=0.730)(Figure 11b). Regarding symptoms, change in NYHA functional class was also comparable after de novo CRT implantation and upgrade procedures (ΔNYHA de novo - 0.74 vs. upgrade - 0.70 class; p=0.737)(Figure 11c). When QRS narrowing was compared, no significant difference was found between the two patient groups (ΔQRS de novo -9.6 ms vs. upgrade -29.5 ms; p=0.485)(Figure 11d).

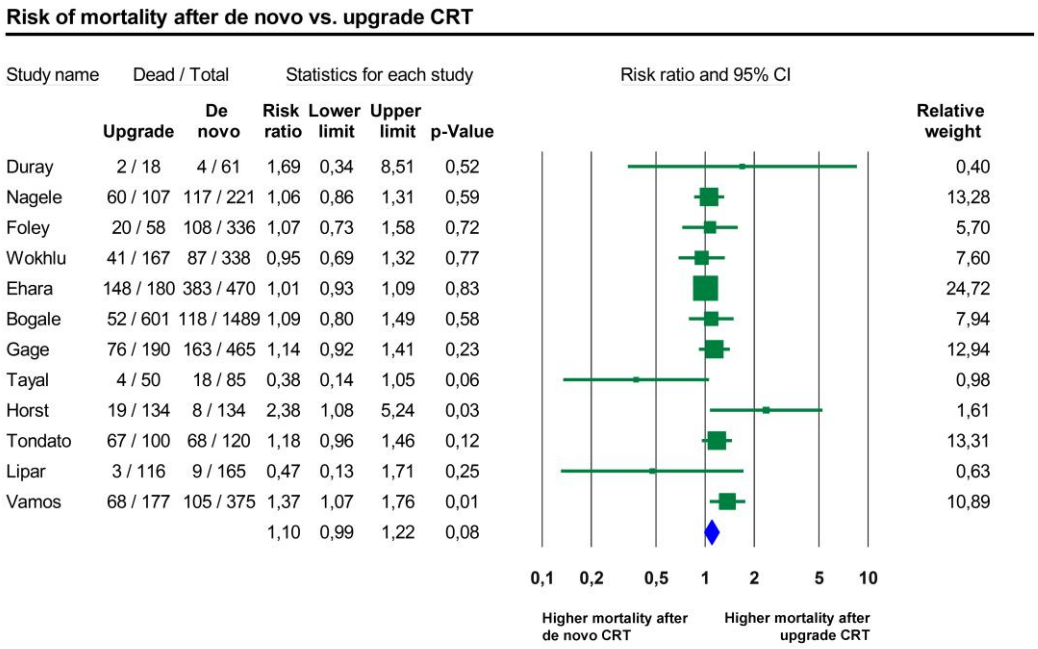

Figure 10a. Risk of all-cause mortality (Risk Ratio) after de novo vs. upgrade CRT

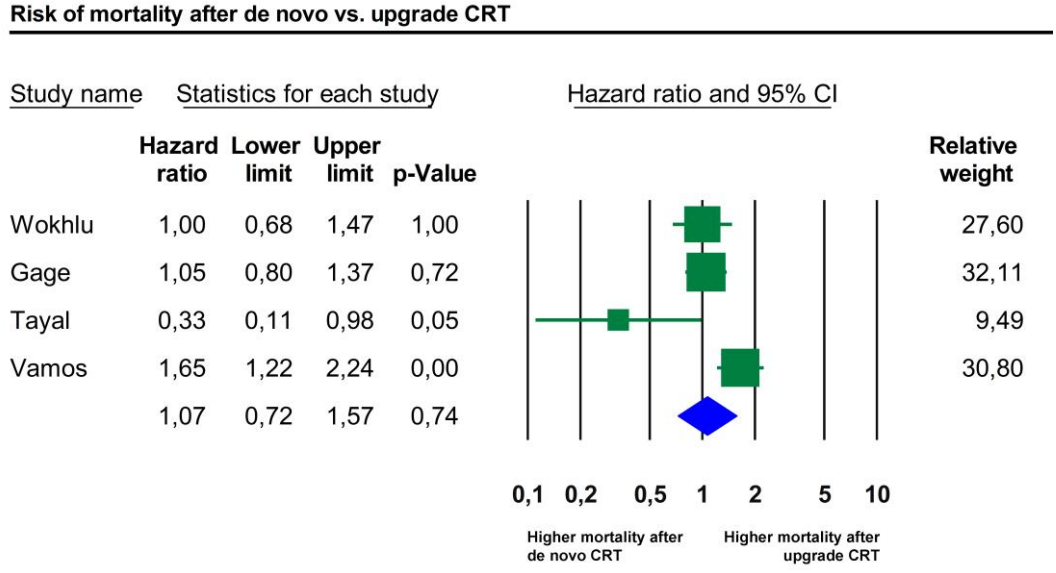

Figure 10b. Risk of all-cause mortality (Hazard Ratio, unadjusted) after de novo vs. upgrade CRT

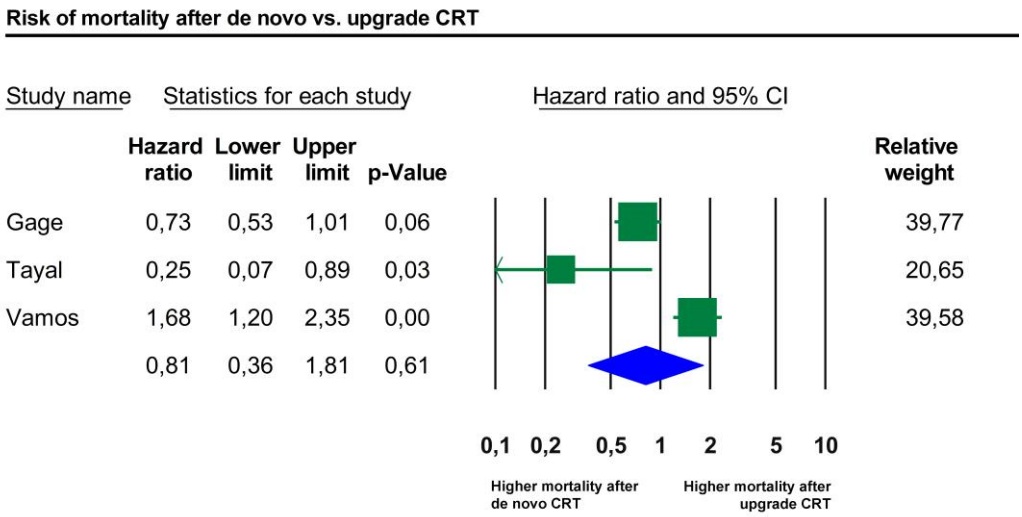

Figure 10c. Risk of all-cause mortality (Hazard Ratio, adjusted) after de novo vs. upgrade CRT

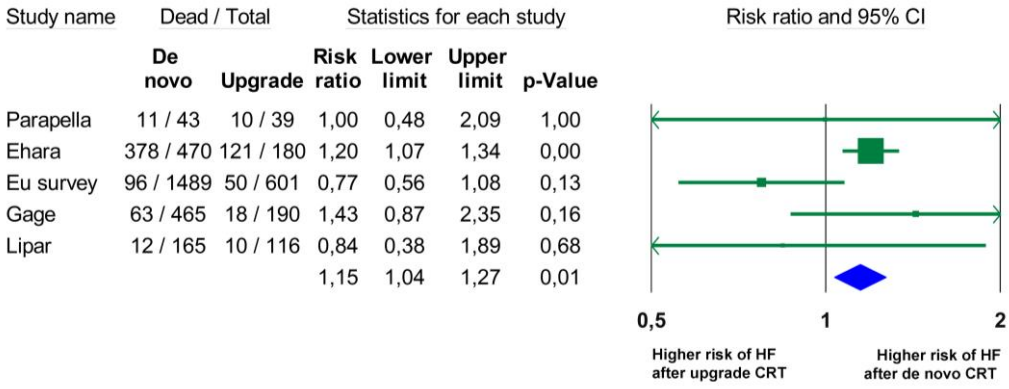

Figure 10d. Risk of heart failure events (Risk Ratio) after de novo vs. upgrade CRT

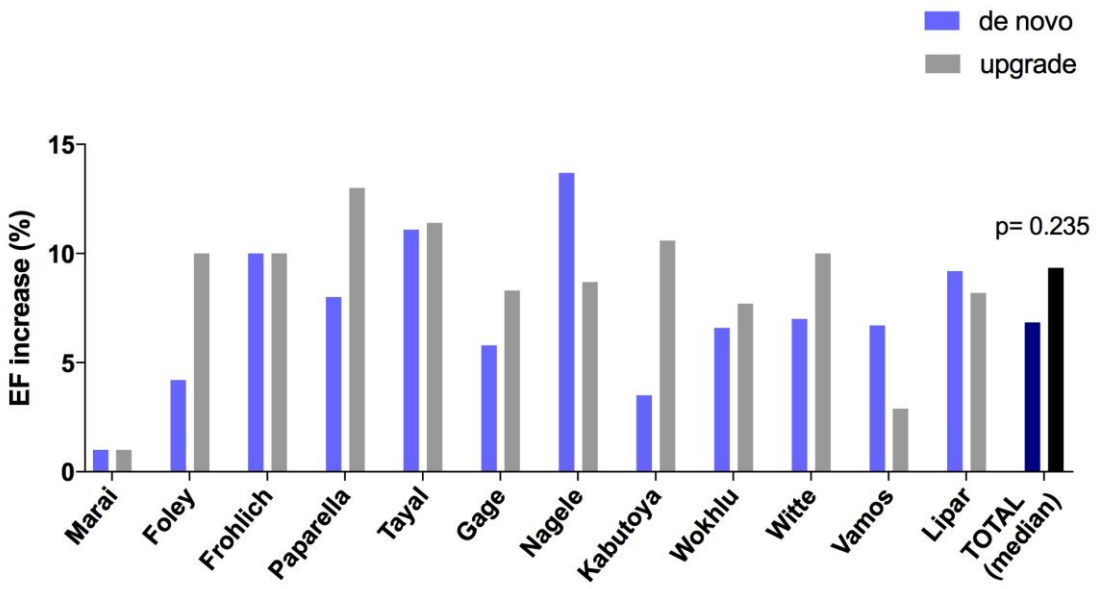

Figure 11a: Change in ejection fraction after de novo vs. upgrade CRT

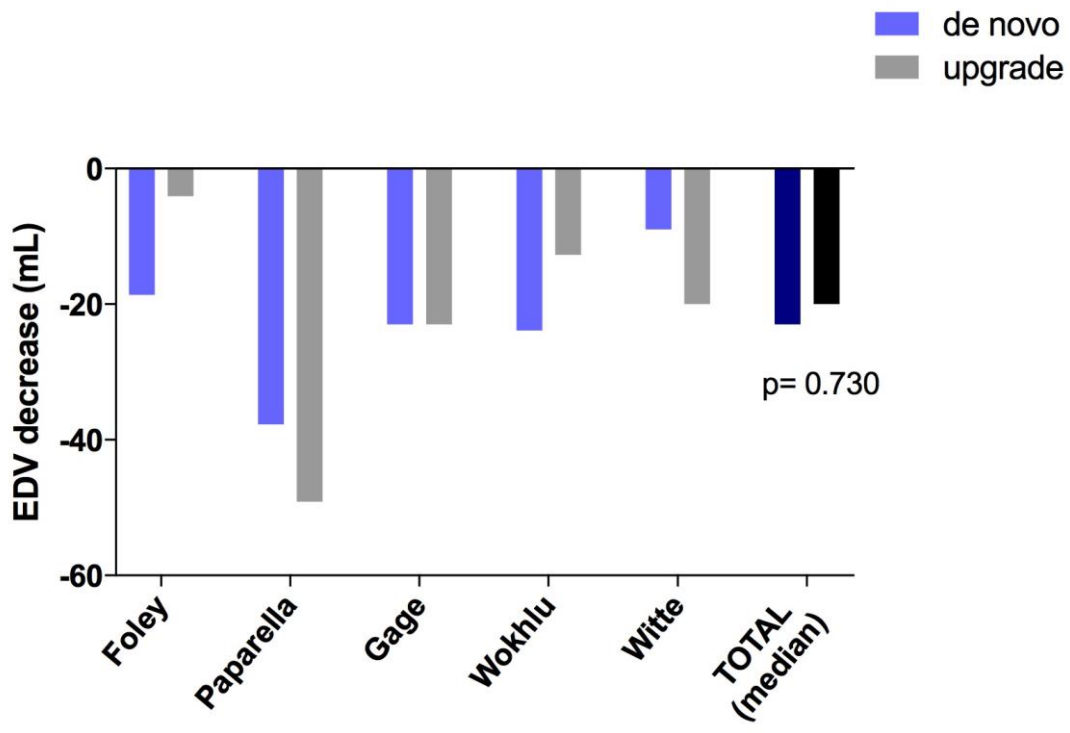

Figure 11b. Change in end-diastolic volume after de novo vs. upgrade CRT

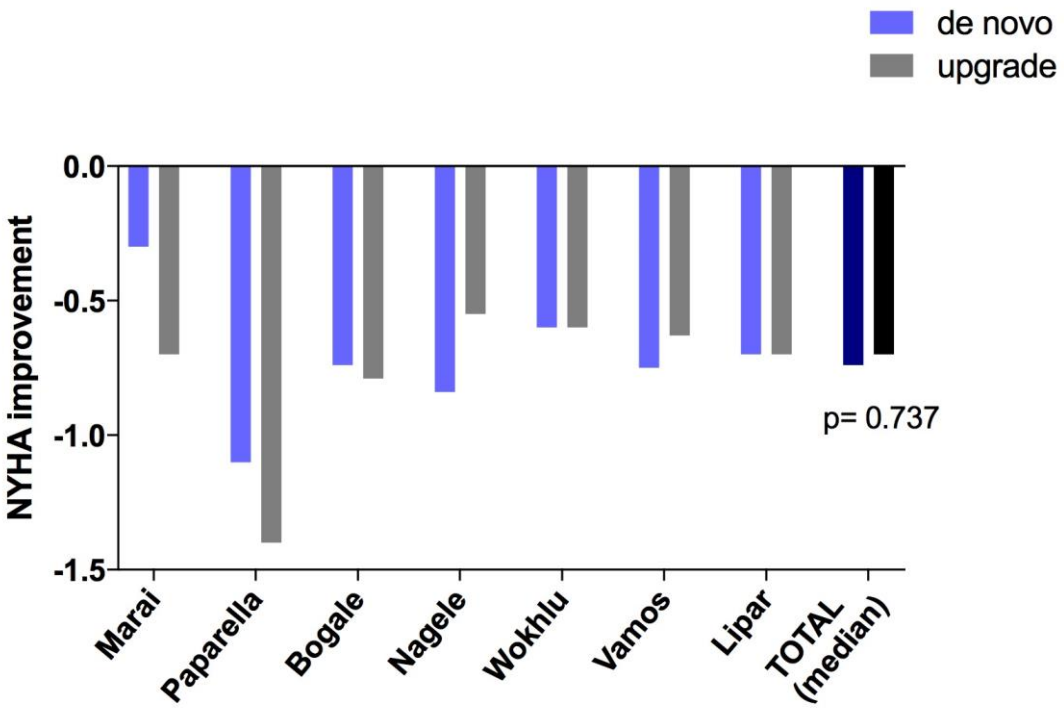

Figure 11c. Change in NYHA functional class after de novo vs. upgrade CRT

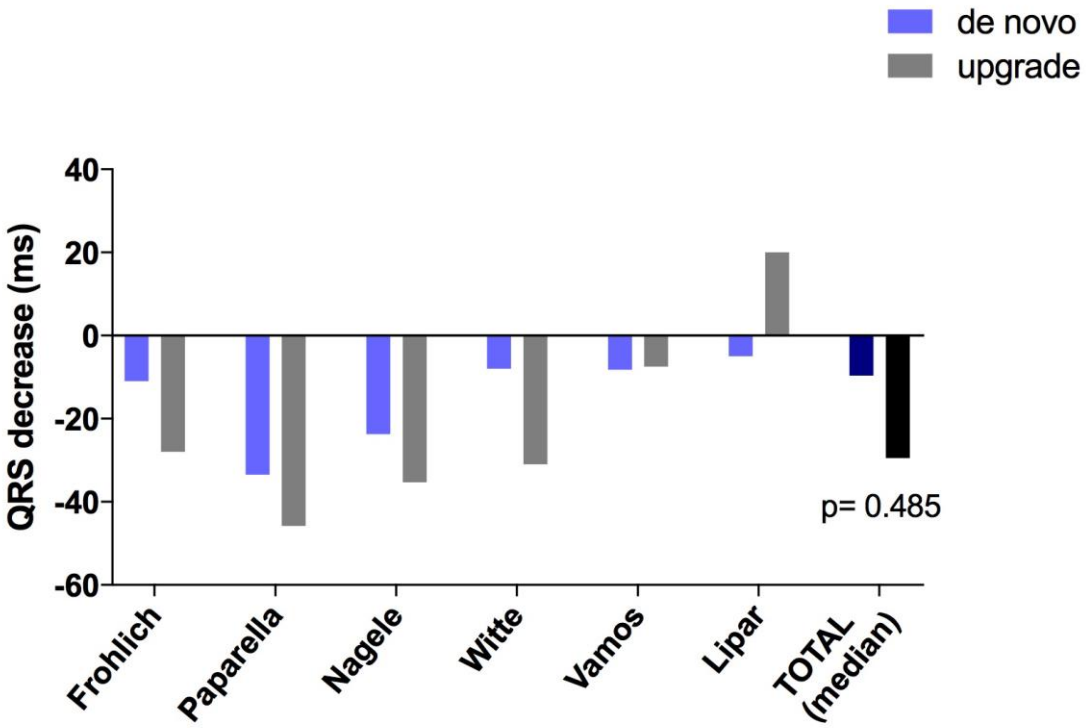

Figure 11d. Change in QRS duration after de novo vs. upgrade CRT

5.2.1.4 System-related complications

Based on three studies (87,96,100) of 2714 patients, where detailed analyses regarding system-related complications were published, only fluoroscopic time(87) and the rate of phrenic nerve(96) stimulation showed significant difference between the two patient groups, favoring upgrade implantations (Table 12).

Table 12. Complications during de novo CRT vs. upgrade CRT implantations (Parameters with significant difference in the original reports are highlithed with bold verbatim)

	Duray et al.		**Bogale et al.**		**Horst et al.**	
	upgrade	de novo	upgrade	de novo	upgrade	de novo
Total number of patients	18	61	692	1675	134	134
Procedure time	164 ±63	154 ±44	100 (60-140)	100 (70-140)	na	na
X-Ray time (min)	32 ± 22	25 ± 18	**15 (8-27)**	**18 (11-29)**	na	na
X-Ray dose (mGy)	52 ± 49	41 ± 31	na	na	na	na
Tamponade	0	0	3	4	0	2
Perforation	0	0	na	na	na	na
Vena cava superior dissection	1	0	na	na	0	1
Coronary Sinus Dissection	1	1	6	25	4	4
Pocket hematoma	0	1	26	46	na	na
Bleeding / Trasfusion due to bleeding	0	1	4	15	2	0
Allergic reaction	0	1	na	na	na	na
PTX	0	1	3	16	1	4
Infection	0	0	na	na	na	na
Lead revision / dislocation	0	2	11	48	2	5
Phrenicus nerve stimulation	na	na	11	35	**4**	**10**

PTX: Pneumothorax

5.2.2 Current status and preliminary results of the BUDAPEST CRT upgrade study

5.2.2.1 Enrolment and baseline clinical characteristics

Altogether 26 centers are participating in the study, 20 European (from Hungary, Czech Republic, Germany Poland, Russia, Serbia and Slovenia) and 6 Isreali sites. List of the European sites are shown in Table 13, from Isreali sites, only one center is active, therefor not included in the table.

From November 2014 one hundred and eleven patients were included and randomized (Figure 12), 67 (60%) to CRT-D and 44 (40%) to ICD arm.

In the Semmelweis University, Heart and Vascular Center 64 (58%) patients were enrolled. From these patients three became ineligible due to late inconsent to the study. From the remaining 61 patients, 36 (59%) were on CRT-D arm and 25 (41%) on ICD arm. From the latter group, four patients were also implanted an entire CRT-D system and programmed to *RV only* mode.

Regarding the baseline clinical characteristics of patients in the Semmelweis University, the preliminary results are shown in Table 14. In our total patient cohort, 48 had conventional pacemaker devices and 14 had ICDs. The mean ejection fraction was 28.6 ± 4.5%, 7 (12%) patients were female, the mean age was 72.0 ± 6.1 years in the total patients cohort, while these parameters did not show significant differences in CRT-D and ICD groups (Table 14). Data are not shown about further clinical parameters, which are under analyses yet.

5.2.2.2 Success rate and safety of upgrade procedures

On the CRT-D arm in two cases (6%) the first attempt of LV lead implantation was not successful due to gracile coronary sinus branch, thereafter one patient received a transseptal LV lead, the other procedure is awaiting for the second attempt.

During the procedures, in 7 (12%) cases prior implanted RV leads were extracted successfully. No hematoma, infections or pneumothorax occurred yet.

5.2.2.3 Follow up, heart failure events and all-cause mortality

During the 28 months from the time of our first enrolment, three (5%) patients were lost. Fourty-four (72%) patients completed the 12-months follow up.

One patient on ICD arm had heart failure event, however we switched to biventricular pacing, he died in a non-cardiovascular event. Except for this case no other death could be observed yet.

Altogether 7 heart failure events occured, each patients were on ICD arm. After the consideration of requiring intravenous diuretic administration with hospital admission and complete clinical evaluations, these patients became cross-overs and LV leads were switched on. Out of these patients four had no prior LV leads, thus an upgrade had to be performed. This preliminary event rate was significantly higher in patients with an ICD compared to those with a CRT-D device (Table 14).

Table 13. European sites of BUDAPEST CRT upgrade study

Site number	Name of Principal Investigators	Dates of site initiation	Enrolment status
HU-01	**Prof. Merkely**	18/11/14	active
HU-02	**Dr. Duray**	11/05/15	active
HU-03	**Prof. Édes**	04/05/15	active
HU-04	**Dr. Sághy**	18/04/16	active
HU-05	**Dr. Kónyi**	05/04/16	active
HU-06	**Dr. Földesi**	22/09/16	
RU-01	**Prof. Pokushalov**	19/07/16	
RU-02	**Prof. Popov**	13/07/16	
SL-01	**Prof. Zupan**	03/08/15	
DE-01	**Prof. Hindricks**	25/11/15	
DE-02	**Dr. Veltmann**	18/08/16	active
DE-03	**Prof. Kuck**	19/10/16	
PL-01	**Prof. Wranicz**	18/08/15	active
PL-02	**Prof. Grabowski**	01/04/16	
PL-03	**Prof. Lubinski**	30/03/16	
PL-04	**Dr. Goscinska-Bis**	29/03/16	active
PL-05	**Dr. Oreziak**	13/02/17	
PL-06	**Prof. Kasprzak**	14/02/17	
CZ-01	**Prof. Kautzner**	20/10/16	
RS-01	**Prof. Milasinovic**	18/02/16	active

Table 14. Baseline clinical variables of patients included in the Semmelweis University in the BUDAPEST CRT upgrade study

Baseline clinical variables	Total patient population (n= 61)	CRT-D (n= 36)	ICD (n=25)	p value
Age (yrs, mean±SD)	72.0 ± 6.1	71.5 ± 6.4	72.6 ± 5.6	0.50
Gender (female, n, %)	7 (12%)	6 (17%)	1 (4%)	0.22
LV Ejection fraction (%, mean±SD)	28.6 ± 4.5	29.0 ± 4.0	28.0 ± 5.0	0.42
DDD-PM	32 (52%)	20 (56%)	12 (48%)	0.61
VVI-PM	12 (20%)	8 (22%)	4 (16%)	0.75
VDD-PM	4 (7%)	2 (6%)	2 (8%)	1.00
VVI-ICD	9 (15%)	4 (11%)	5 (20%)	0.47
DDD-ICD	4 (7%)	2 (6%)	2 (8%)	1.00
Primary Endpoints				
All-cause mortality (n, %)	0 (0%)	0 (0%)	1 (4%)	0.41
Heart Failure Events (n, %)	7 (12%)	0 (0%)	7 (28%)	0.001
Completed 12-months follow up	44 (72%)	30 (83%)	14 (56%)	0.02

CRT-D= Cardiac Resynchronization Therapy with Defibrillator; ICD= Implantable Cardioverter Defibrillator; LV=Left Ventricular; PM= pacemaker - DDD-PM/ICD= dual chamber pacemaker or ICD; VVI-PM/ICD= single chamber ventricular pacemaker or ICD

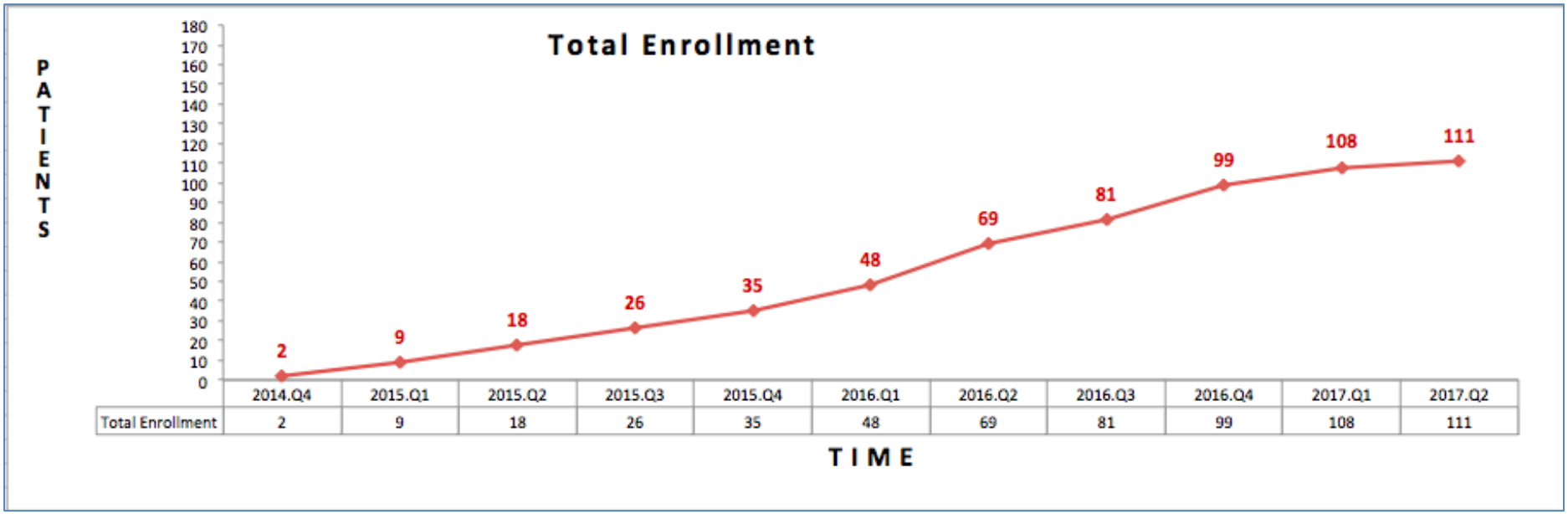

Figure 12. Total enrolment of BUDAPEST CRT upgrade study by quarters from November 2014

6 DISCUSSION

6.1 Optimization of patient selection and intraoperative techniques in order to achieve a beneficial clinical response after CRT implantation

There are conclusive data in the literature about the success of de novo CRT implantations, which improves exercise capacity, reduces the risk of heart failure events and improves event-free survival (13-15). However, approximately 20-40% of patients fail to develop reverse remodeling and prove to be non-responders (104).

While in average 2 to 5-fold higher hazard for all-cause mortality (34,105) and heart failure events can be observed in non-responder patients, it would be crucial on one hand to select an optimal patient population for the therapy, on the other hand to identify non-responders in an early phase of the resynchronization and extend the optimal heart failure therapy or tailor to further ventricular assist device implantation or transplantation as appropriate.

Regarding patient selection for CRT therapy, the assessment of QRS morphology and width, symptoms, ejection fraction, age, gender or co-morbidities are essential, measuring biomarkers might be also useful and reflect the overall status of the patient.

In this regard, NT-proBNP is a feasible marker to stratify patients into risk categories (106,107) at baseline, however data are controversial on its possible predictive role in evaluating the response (108).

Therefor first we aimed to assess the predictive role of baseline NT-proBNP and the diagnostic value of 6-month follow-up levels in identifying non-responder patients to CRT. In our patient cohort, baseline levels were similar in responders and non-responders, but 6-month NT-proBNP levels significantly decreased in responders to CRT. In line with the biomarker data, responders showed clear echocardiographic evidences of reverse remodeling (Table 2).

Similar results were found in CARE-HF trial (109), where Fruhwald et al. demonstrated that CRT significantly reduces NT-proBNP levels after 3 to 6 months compared to optimal pharmacological treatment. The MADIT-CRT trial also suggested that baseline serum levels of NT-proBNP were not related to non-response and to echocardiographic

improvements; however, follow-up levels of NT-proBNP were in significant association with the echocardiographic response to resynchronization (108).

In addition to NT-proBNP, a recently identified cardiac peptide, apelin has attracted considerable attention in chronic heart failure. Although changes in plasma apelin levels during the progression of heart failure, clinical trials are controversial. In one of the largest studies including 202 patients Chong et al. found that plasma apelin-12 (also cross-reactive with apelin-13, -36 fragments) was significantly lower in patients with advanced heart failure referred for heart transplantation (47). In another study Chen et al. examined 80 patients with moderate to severe chronic heart failure compared to healthy volunteers. According to their findings, circulating apelin increases in the early stage, while in advanced heart failure it decreases to a lower level, but remains over the normal plasma range (110).

However, the role of apelin in patients after CRT is not well elucidated. To date, the only small-sized study which described changes in levels of apelin after CRT was published by Francia et al. (111). In fourteen patients undergoing CRT implantation, significant increase in serum apelin levels was found after 9 months of resynchronization. Evidently, this low sample size did not allow the authors to compare apelin in responder and non-responder patients; the single patient considered non-responder had higher apelin level than the others.

In our prospective trial including 81 patients, responders and non-responders showed the same CT-apelin values at baseline. However, non-responders had significantly higher CT-apelin levels at six months compared to responders after CRT implantation. Likewise, patients with high CT-apelin levels had a 10-fold higher risk for non-response. Given the potential collinearity between NT-proBNP and apelin, multivariate models were developed to determine the independent estimate of non-response. Based on such statistical models, apelin proved to be the independent biomarker in identifying non-response.

These results suggest that a simple measurement of biomarkers at baseline has limited impact on identifying non-responder patients, while follow-up levels may help in identifying them, which might come from the fact that the efficacy of resynchronization is influenced by multiple parameters.

After the optimal patient selection, the implantation procedure is also essential. There can be a determinative anatomical limit, when there is no optimal coronary sinus branch or

difficult to reach the wedge position. Several multicenter, randomized trials investigated the role of LV lead location in CRT response(112,113). The mid-term follow up of MADIT-CRT with 29±11 months, the LV lead position was assessed in 799 patients, where 71% of the patient population had typical LBBB QRS morphology and approximately 50% had ischemic etiology(113). Positions were categorized by short (anterior, lateral, or posterior) and long axis (apical vs. non-apical) positions. The beneficial response to cardiac resynchronization therapy was similar with short axis positions (P=0.652), but it was significantly better in nonapical positions compared to leads located in the apical region regarding the risk of heart failure events and death (HR=1.72, 95% CI: 1.09 to 2.71; P=0.02) after adjustment for the clinical covariates. REVERSE(112) trial also found similar results, thus based on these conclusive data of the largest, randomized trials, LV lead positioning in the apical region is associated with an unfavorable outcome, suggesting that this lead location should be avoided in cardiac resynchronization therapy.

Extended beyond the localization, right to left ventricular activation delay, the parameter used in our prospective, single-center study is however a more comprehensive measurement providing information not only about the LV lead, but also about the RV lead position. Several studies have indicated that the location of the right ventricular lead plays a role in the clinical outcome of CRT patients (114). Furthermore, RV-LV activation delay may reflect slow conduction, as it is frequently seen in patients with ischemic heart disease and extensive scarring of the posterior or lateral wall.

At the same time it seems that RV-LV AD may point to significant electrical dyssynchrony that could be a better surrogate marker for CRT benefit than mechanical dyssynchrony. A recent editorial suggests LBBB as an electrical disease, and CRT as a potent therapy for this electrical disease (115). Therefore, it is sensible that patients with non-LBBB did not derive a significant benefit from CRT therapy in our study, independently of short or long RV-LV AD at implantation. The disease process may be more complex in patients with non-LBBB and needs further investigations.

Therefor we investigated the impact of RV-LV AD specified by typical LBBB morphology on clinical outcome in our patient cohort. Based on our results, LBBB patients with an RV-LV activation delay ≥86 ms have a significantly lower risk of HF or death and lower risk of all-cause mortality compared to those with non-LBBB ECG morphology combined with LBBB and RV-LV AD < 86 ms. In non-LBBB patients, RV-LV AD was not predictive of clinical outcome. Furthermore, we found that RV-LV AD

has an independent role in predicting improvement in left ventricular ejection fraction, NT-proBNP and functional outcome in LBBB patients undergoing CRT implantation. In our analyses we used 86 ms as a cut-off value for RV-LV AD, the lower quartile of RV-LV AD to predict the primary composite endpoint, which was pre-specified in our analysis.

D'onofrio et al. (55,56) published similar results in 301 patients who underwent CRT implantation and had LBBB morphology. In this article ROC curves showed 80 ms as the optimal cut-off value of RV-LV AD and 65% of its normalization to QRS. Those patients who had greater RV-LV AD than 80ms or RV-LV AD to QRS than 65% had significantly better outcome in echocardiographic reverse remodeling, which was defined as >15% ESV change. Their results are in line with our findings, the normalization of AD to QRS is also a feasible parameter in selecting patients who might benefit from CRT implantation. Those patients who have higher RV-LV AD to QRS and LBBB morphology have the lowest risk for heart failure events or death. The assessment of these parameters have higher importance in the subgroup of patients who have narrower QRS. In another study by Kristiansen et al. (54), they used an RV-LV interlead sensed electrical delay of ≥ 85ms and showed differences in echocardiographic response and in clinical outcome. However, none of these studies looked specifically at sub-groups of LBBB and non-LBBB patients.

Other studies used a different approach of evaluating successful resynchronization with CRT. Gold and colleagues (116) were focusing on the association of clinical outcome and ventricular electrical delay measured by Q-LV in 426 patients with advanced heart failure, measuring LV lead activation time from the beginning of the QRS. Similarly to our results they found significant differences in functional parameters such as end-systolic volume reduction and quality of life improvement 6 months after CRT implantation in those patients who had a greater Q-LV time than the median of 95 ms.

Our prospective trial is in line with several previous studies (69,117,118) suggesting that best response to cardiac resynchronisation therapy is achieved in patients with a "left bundle branch block cardiomyopathy" with optimal positioning of the left ventricular lead. However to our knowledge, this is one of the first studies evaluating the effect of RV-LV activation delay in patients undergoing CRT by their baseline LBBB ECG pattern. Some of the previous studies adjusted the multivariate models for LBBB, but there were no pre-specified sub-group analysis performed in patients with a baseline LBBB or non-LBBB.

Moreover, in our prospective, single-center study the beneficial clinical outcome was reflected in the decrease of prerenal dysfunction, independently of the baseline renal function values. In patients with longer RV-LV AD and LBBB morphology, serum creatinine and BUN values were significantly lower than in those with shorter RV-LV AD or non-LBBB ECG morphology at six month follow up.

Several trials assessed impaired renal function as a potential independent risk factor of mortality and morbidity in chronic heart failure (119,120). The markers of prerenal dysfunction were also discussed in mildly symptomatic patients (121) and in advanced heart failure (122) after resynchronization.

In an early study of MIRACLE(122), 453 severe heart failure patients (228 CRT vs. 225 control) with symptoms (NYHA III-IV), low ejection fraction (LVEF≤ 35%) and wide QRS (≥130ms) were investigated. They were categorized according to their baseline eGFR (≥ 90; 60-89; 30-59) and changes of 6-months levels were assessed. Patient group with GFR<30 was excluded from analyses due to the low number of investigated patients. However no data was shown about the amount of LBBB patients in this study, their results showed, CRT improved LV function in all categories, but the most prominent improvement of GFR was observed in patients with GFR<60 compared to control group (−2.4±1.2 vs. +2.7±1.2 mL/ min per 1.73 m2; p=0.003). These early results underscored the importance of cardiorenal interaction and the beneficial effects of CRT which indirectly improve renal function. The association of RV-LV AD and the changes of renal function have not been directly investigated before, our results show first, that the improvement in renal function might be more pronounced when the most eligible patients are selected: those with LBBB and a longer RV-LV AD.

6.2 Part 2 - The question of CRT upgrade

As discussed above, several high volume, multicenter, randomized trials investigated extensively the effect of de novo CRT implantation, provided comprehensive data and clear evidences for patients with chronic heart failure.

Besides recommendations on CRT upgrades are still ambiguous, although biventricular upgrade affects roughly 5-10% of patients who undergo prior ICD or pacemaker implantation (123,124). The evidences are partly extended over time, however still not cover the entire population who are referred for CRT upgrade.

The 2013 ESC/EHRA guidelines recommend CRT upgrade in patients with LVEF < 35%, NYHA III-IVa and high percentage of ventricular pacing – although the cited evidence stands for de novo CRT implantations and crossover trials as opposed to upgrades from existing devices, with level of evidence "B" and class I indication (125). The 2012 ACCF/AHA/HRS guidelines are listing CRT upgrade with IIa indication, level of evidence "C" for patients with LVEF ≤ 35%, and a need for at least 40% ventricular pacing, for both new implants and device replacements (126). The 2012 ESC/HFA guidelines (127), the 2013 Appropriate Use Criteria (AUC) document, endorsed by the ACCF/HRS/AHA,(128) and the most recent 2015 ESC/EHRA Guideline on ventricular arrhythmias and sudden cardiac death do not provide any recommendations on CRT upgrade (129). (Table 15)

Table 15. Indication for upgrade to cardiac resynchronization therapy in patients with existing pacemaker or ICD

ESC/EHRA 2013 (125)	CRT is indicated in HF patients with LVEF <35% and high percentage of ventricular pacing who remain in NYHA class III and ambulatory IV despite adequate medical treatment. Remark: Patients should generally not be implanted during admission for acute decompensated HF. In such patients, guideline-indicated medical treatment should be optimized and the patient reviewed as an out-patient after stabilization. It is recognized that this may not always be possible.	Class I LOE B
ACCF/AHA/HRS 2012 (126)	CRT can be useful for patients on GDMT who have LVEF less than or equal to 35% and are undergoing new or replacement device placement with anticipated requirement for significant (>40%) ventricular pacing	Class IIa LOE C
ESC/HFA 2012 (127)	CRT is recommended as an alternative to conventional right ventricular pacing in patients with HF-REF who have a standard indication for pacing or who require a generator change or revision of a conventional pacemaker	No specific recommendations for CRT upgrade

AHA= American Heart Association; ACCF= American College of Cardiology Foundation; CRT= Cardiac Resynchronization Therapy; EHRA= European Heart Rhythm Association; ESC= European Society of Cardiology; GDMT= Guideline Determined Medical Therapy; HFA= Heart Failure Association; HF-REF= Heart Failure with Reduced Ejection Fraction; HRS: Heart Rhythm Society; LOE= Level Of Evidence; LVEF= Left Ventricular Ejection Fraction; NYHA= New York Heart Association

These recommendations are based on trials with design of RV pacing vs. CRT upgrade and non-randomized, observational prospective "upgrade vs. de novo" studies, which are included in the our meta-analysis (87,89,90,95,101) and which will be discussed in details. In addition, there are small observational retrospective (130-136) and cross-over (137-140) trials with a low number of patients.

The harmful effect of chronic RV pacing and inferiority to biventricular pacing revealed from early large randomized studies.

Regarding the association of frequent RV pacing and adverse clinical outcomes, several trials confirmed an increased risk of heart failure events, atrial fibrillation and all-cause mortality (125,141).

The Dual-Chamber and VVI Implantable Defibrillator (DAVID) trial demonstrated worse outcomes in patients with reduced LVEF and dual chamber ICD programming to DDDR 70 bpm when compared to patients with VVI 40 bpm pacing. Every 10% increase in RV pacing increased the risk of death or HF hospitalization by 16%. The most significant separation was observed with 40% RV pacing, strongly predicting death or HF hospitalization (HR=5.2, P=0.008) (142).

Another multicenter, randomized clinical trial, the Mode Selection Trial (MOST) confirmed the correlation of RV pacing and impaired clinical outcome in patients with preserved LVEF and sinus node dysfunction. The risk of HF hospitalization linearly increased with RV pacing up to 40% (141).

In contrast, Olshansky et al. suggested that reducing RV pacing does not necessarily eliminate the risk of an adverse outcome. In the INTRINSIC RV Study patients were categorized into six groups based on increasing RV pacing rates. A significant difference was found between rates concerning patients' age, history of ventricular tachycardia, atrial fibrillation, atrial flutter, and amiodarone therapy. Adjusting for these parameters, the best outcome was seen in patients with RV pacing between 10-19% (2.8% event rate over a median follow up of 11.6 months). Increasing RV pacing has been found predictive of death or HF hospitalization (p=0.003). Other than expected, patients with rare RV pacing (0–9%) experienced worse outcome (8.1% event rate, p=0.016), although a lower RV pacing rate may be advantageous to improve AV dyssynchrony (143).

In addition, echocardiographic and functional parameters (6-minute walk test, symptoms) may also worsen even in patients with previously preserved ejection fraction(144,145) or mild heart faliure(146) after frequent RV pacing.

Thus due to the RV pacing-induced dyssynchrony, patients with a high percentage of RV pacing are at high risk of adverse clinical outcomes (71,72) and can become candidates for CRT upgrade. Based on these findings, several trials focused on patients with RV vs. biventricular pacing and confirmed the superiority of CRT upgrade in this patient population.

First small crossover trials have compared RV pacing only to CRT in patients with symptomatic bradycardia and reduced LVEF. They showed that CRT reduced mortality, heart failure hospitalization and lead to reverse ventricular remodeling (125,147).

Then for the first time, the Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block Trial (BLOCK HF) showed that CRT is superior to RV pacing in patients with AV block, LVEF ≤ 50% and heart failure class NYHA I-III. After a median follow-up of 37 months, primary endpoints (death from any cause, heart failure visit that required intravenous therapy, or ≥15% increase in LVESV index) occurred in 190 of 342 patients (55.6%) in the RV pacing group, compared with 160 of 349 (45.8%) in the CRT group. The LV lead related complications occurred in 6.4% of the patients in the CRT treated group.(146)

The Homburg Biventricular Pacing Evaluation (HOBIPACE) trial compared CRT to RV pacing in patients with bradycardia and LV dysfunction (LV end-diastolic diameter ≥ 60 mm and LVEF ≤40%). Three months of RV pacing vs. biventricular pacing were studied in 30 patients. Improved echocardiographic parameters- laboratory values and quality of life scores, as well as improved peak exercise capacity were found only with biventricular pacing. (148)

The Conventional versus Multisite Pacing for BradyArrhythmia Therapy crossover Study (COMBAT) compared biventricular versus right ventricular pacing in 60 patients with AV block, LVEF <40 % and heart failure with NYHA class II-IV. After a follow-up of 17.5 months the quality of life, NYHA class and echocardiographic parameters improved in patients with CRT. Overall mortality was significantly higher in patients with RV pacing alone (86.7% vs. 13.3%, p=0.012)(147). Studies performed in patients with preserved LVEF also demonstrated benefit with CRT, showing increased reverse LV remodeling.

The Long term from the Pacing to Avoid Cardiac Enlargement (PACE) trial investigated the clinical outcomes of 149 patients with CRT with the mean EF of approximately 62% (RV group 62.0 ± 6.4% vs. BIV group 62.4 ± 6.7%; p= 0.72), randomized to one year of

RV or biventricular pacing after an extended follow-up of five years (mean 4.8 ± 1.5 years). In the RV pacing group, LVEF and LVESV worsened progressively during 1-year, 2-year, and long-term follow-up, whereas both parameters remained unchanged in the CRT group (LVEF difference respectively $p<0.001$). However, patients with RV pacing needed significantly more HF hospitalization (23.9%) than CRT patients (14.6%)(149). In summary, chronic biventricular pacing seems to be superior to RV only pacing, but the results cannot be extrapolated to patients with intermittent or chronic pacing who developed worsening of heart failure only recently.

The RD-CHF study upgraded 56 patients from VVI pacing (NYHA III-IV, and LV dyssynchrony) to CRT at the time of generator replacement. The study had a three month cross-over design with RV pacing only or CRT. CRT pacing significantly improved NYHA class, 6MWT and quality of life (125).

Regarding the study design of trials referred in the current ESC recommendations, the last and at the same time, the largest group came from the non-randomized, observational prospective "upgrade vs. de novo" studies (87,89,90,95,101).

The only trial, in which patient groups were analysed retrospectively came from the Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) study. In RAFT 644 of 1346 enrolled patients (48%) underwent de novo CRT implantation, 80 patients were upgraded to CRT from a previously implanted ICD device, and 60 patients underwent CRT upgrade 6 months after the end of the initial study.

The success rate was 95.2% for de novo, 96.3% for upgrade and 90.0% for post-trial CRT upgrade sub-study ($p=0.402$). The acute complication rate was 26.2% for de novo, 18.8% for upgrade and 3.4% for the sub-study CRT upgrade ($p <0.001$), most commonly due to LV lead dislodgement. The main reasons for not attempting upgrade in the sub-study group were patient preference (31.9%), NYHA class I (17.0%), and QRS<150 ms (13.1%).

The authors conclude that the success of CRT upgrade is high and that the complication rates are similar to de novo CRT implantation (150). However, in the prospective REPLACE Registry with 1750 patients undergoing device replacement, those who required upgrade experienced a high rate of major complications during a 6-month follow-up time (18% vs. only 4%).

While there are no randomized trials with such design, we decided to perform a systematic review including 17 studies with more than 6600 patients undergoing de novo

or upgrade CRT implantations. Our meta-analyses revealed no significant difference in all-cause mortality between the two patient groups. Also, no significant differences were found in changes of echocardiographic parameters of reverse remodeling (EF, EDV). Functional changes (i.e. improvement of NYHA functional class) and narrowing of QRS were also similar, suggesting that adding left ventricular pacing in patients with prior cardiac devices may be a safe and feasible procedure that may result in similar clinical benefits as de novo implantations.

In most of these trials, only soft endpoints, such as NYHA functional class, 6-minute walk test, quality of life or echocardiographic parameters were analyzed. Summarizing the most frequently investigated clinical parameters, such as change in NYHA functional class, decrease in QRS duration, changes of left ventricular ejection fraction and end-diastolic volume, no significant differences were observed between the de novo and upgrade groups in our analysis.

The only outcome that showed a significant difference is the risk of heart failure events that was more common in the de novo group as compared to patients with upgrade therapy. However, this difference should be interpreted cautiously due to the non-randomized, non-adjusted design and limited number of reporting studies.

Data regarding long-term mortality were reported only in a few prior trials(87,89,91,93,94,98,100,102). The largest report from these was the European Cardiac Resynchronization Survey(87) comprising 1489 de novo and 601 upgrade CRT patients from 2011. Total mortality at 1 year was low and similar in both groups (8.6% vs. 7.9%, p=0.57). Although this registry showed representative data about mortality rates with high number of enrolled patients, there are a huge number of potential confounders that may have biased the overall results.

Therefore, trials with adjusted analyses are essential to control baseline differences to better assess the effects of CRT upgrade on long-term survival. In the current meta-analysis, three observational studies with adjusted all-cause mortality endpoints were included.

Tayal et al (102) compared 85 patients who underwent de novo CRT implantation and 50 patients with CRT upgrade. During the 4 years of follow-up time, patients with prior right ventricular pacing had a significantly lower risk of fatal events than patients with de novo CRT implantation (adjusted HR 0.25, 95% CI 0.07-0.88, P= 0.03).

Gage et al. (91) compared 190 patients with prior high percentage of right ventricular pacing (>40%) to 465 non-paced patients who underwent CRT implantation. During the

median follow up of 4.2 years, upgrade patients tended to have better outcomes in terms of all-cause mortality (adjusted HR 0.73; 95% CI 0.53-1.01; p=0.055).

In contrast, Vamos et al. (103) recently reported a higher risk for mortality in the upgrade group when compared to de novo implantation in 552 patients. In this multicenter study with a mean follow up of 37 months, patients who underwent CRT upgrade had a significantly higher risk of all-cause mortality compared to patients with de novo implantations even after adjusting for potential confounders with multivariate Cox regression analysis (adjusted HR 1.68, 95% CI 1.20-2.34, p=0.002) and after applying propensity score matching (PS-adjusted HR 1.79, 95% CI 1.08-2.95, p=0.023).

Summarizing all these results in our meta-analysis, a similar long-term survival was found between the two patient groups. However, heterogeneities in the results of adjusted studies largely emphasize that randomized controlled trials are needed to objectively clarify this clinical dilemma.

Despite the current detailed review and meta-analysis of the available clinical evidence, several questions remain unanswered. Most striking from these include which populations may derive the largest benefits from upgrading and what is the optimal timing for such procedures.

According to these lines of evidences and considerations it seems reasonable upgrading to CRT in HF patients with previously implanted cardiac devices and a high percentage of right ventricular pacing. On the other hand, upgrade procedures may be associated with higher surgical risk, such as venous access issues, the risk of damage or extraction of previously implanted leads, higher infection rates, and longer procedure times (123,151), that all together may significantly compromise the success of LV pacing.

It should be also noted, that etiology or the cause of decreased ejection fraction might be different in upgrade vs. de novo CRT groups. Regarding the etiology, similar percentage of ischemic and non-ischemic heart disease were reported in most of the included studies, however the baseline QRS was wider (paced QRS) and patients were older and had atrial fibrillation more often in the upgrade group.

To conclude there was a clear need for a large, randomized trial on this field, thus we initialized the BUDAPEST CRT upgrade study, the first, multicenter, randomized, investigator-initiated trial, which clarifies the question of CRT upgrade.

In the BUDAPEST CRT upgrade study patients with previously implanted PM or ICD devices, symptomatic heart failure (NYHA II-IVa), reduced ejection fraction ($\leq$ 35%) and intermittent (>20%) or permanent right ventricular pacing are investigated and

randomized to CRT-D or ICD in a 3:2 manner.

When the design of the trial was prepared by the PI's and members of the Steering Committee, the inclusion and exclusion criteria were discussed in details. We would include patients regardless of heart failure etiology with no prior acute events in the last three months prior to enrolment and as required in clinical studies we would like to exclude those factors that could influence the final results and patient's response such as e.g. genetic disorders, those parameters lead to high numbers of lost-to follow up or severe diseases that are waiting for procedures or co-morbidities with a specific regard to renal insufficiency or dilated right ventricle (Table 1).

In the inclusion criteria, the cut off value for left ventricular ejection fraction was defined as 35% or less, while most of the previously discussed trials and evidences for CRT showed a clear benefit in this patient population. However the BLOCK-HF which included patients with preserved ejection fraction (total mean EF 40 ± 8%), also showed superiority of biventricular pacing compared to right ventricular pacing in a large, randomized study, but patients had less severe symptoms (NYHA I-III) and III. degree AV-block, which is not exactly the same patient population, that we would like to investigate.

In exclusion criteria intrinsic LBBB morphology was crucial, while evidences are also comprehensive in this regard, such patients are need to be upgraded.

To define the cut off value of the rate of right ventricular pacing for inclusion citeria was also essential during the preparation. While the previously described MOST(71) trial provided the highest risk for adverse events at 40% of DDD pacing, and at the same time in DAVID trial (72) each 10% higher pacing related to 16% increase in the risk of heart failure events and death, we decided to have a 20% pacing or higher for inclusion criteria in order to cover also the grey zone of 20-40%, which is actually missing from the American and European guidelines.

The primary endpoints are the composite of heart failure events, all-cause mortality and echocardiographic increase of ESV>15% after 12 months. As this criteria also occurred at the BLOCK-HF trial, we would investigate together the tough endpoints (heart failure and all-cause mortality) and echocardioghraphic response as well.

It was also a special point of view during design preparation to encourage sites to follow their every-day clinical practice, therefor physicians are allowed to perform lead extraction during the procedures or use any techniques, that help them in successful implantation.

Regarding the current status of the BUDAPEST CRT upgrade study, 31% of the planned total patient number have been already enrolled from 26 centers (20 European: Hungary, Czech Republic, Germany Poland, Russia, Serbia and Slovenia and 6 Israeli sites). Where the Semmelweis University included approximately 60% of patients as the top enroller.
Our preliminary data about baseline clinical characteristics show similar results as the patient cohorts in the literature in regards of mean age, mean left ventricular ejection fraction or gender. However it is early to discuss the question of endpoints or adverse events, at this time we have more heart failure events on ICD arm, while no significant number of complications can be occurred.
In summary the BUDAPEST CRT upgrade study would be a milestone on the field of CRT upgrade and might further clarify and confirm the current recommendations.

6.3 LIMITATIONS

Our prospective single-center study has some certain limitations. First, this was a relatively small registry-based patient cohort with low rate of endpoint events that may result in overestimating our results.
Notably, this is still the largest dataset among patients after CRT implantation with apelin level assessments at a relatively long (3-year) follow-up.
Second, the observed plasma levels of CT-apelin in our study were considerably higher than found in other prior studies.(46,48) This may be due to the various sensitivities of the assays for different apelin fragments, making it difficult to directly compare results. By using RayBiotech C-Terminus-apelin ELISA kit we have detected apelin -36, -13, -28 and -31 fragments, that might be responsible for the differences compared to other authors that usually detected only the apelin -12, -13, -36 fragments by another commercially available ELISA kit.(48,110,111)
Finally, the 3-year rate of cardiovascular mortality may sound quite low in the present study compared to other experiences. (13,14) However, we only included patients with successful device implantation and having 6-months biomarker laboratory results available. Therefore, our results may reflect a lower-risk cohort with successful device implantation and without mortality within the first 6 months of CRT operation.
Regarding RV-LV AD measuring, it may have been influenced by baseline QRS duration and by the suitable coronary sinus side branches. However, as a sensitivity analysis, we

adjusted our models for QRS duration and our results were similar. Furthermore, suitable vein distribution for LV lead implantation is a known bias for all CRT studies and therefore needs to be acknowledged. Alternatively, minimal invasive techniques eg. mini-thoracotomy LV lead implantation (152) or transseptal LV endocardial pacing could have been used to further maximize RV-LV AD and optimize CRT outcome. However such methods have not become widely used in the past due to the relative invasive nature of the procedure.

Regarding our meta-analysis patients in the two groups were not randomly allocated, all included studies were either retrospective studies with historical controls or prospective observational data collections. Furthermore we did not have access to individual patient-level data precluding us from calculating adjusted hazard ratios for all the included studies. Finally, the length of follow-up was also heterogeneous in the included reports. However, so far, this is the largest available comprehensive evidence in this respect and sensitivity analysis from adjusted results corroborated our initial findings.

7 CONCLUSIONS

Cardiac resynchronization is an effective device therapy, while improve cardiac function, symptoms and reduce the risk of hospitalization and all-cause mortality in patients with mild to severe heart failure and a prolonged QRS (13-15). However there have been still a large amount of patients who could not show a beneficial response after CRT implantation.

Thus in our prospective, single-center study which was implemented from Semmelweis University, Heart and Vascular Center - our high-volume experienced clinic, those parameters which could influence or predict the response to CRT were investigated in regard of optimal patient selection and intraoperative parameters.

In our cohort less than 20% of heart failure patients failed to develop reverse remodeling and became non-responders to resynchronization, showing an elevated risk for all-cause mortality compared to responders.

However resynchronization therapy proved to be the most beneficial non-pharmacological treatment, selection of these vulnerable patients is essential in order to extend the heart failure therapy or tailoring forward to definitive therapy as heart transplantation or ventricular assist device.

Our results showed, baseline levels of biomarkers: CT-apelin and NT-proBNP were not associated with non-response. Therefore, these biomarkers are ineligible as *predictors* of success before device implantation. However when six-month levels of both CT-apelin and NT-proBNP were investigated, a significant association with non-response was found, suggesting the possible role of such biomarkers in *identifying* high risk patients, where CT-apelin showed the superiority over NT-proBNP.

These findings are rational, while the response to CRT is multifactorial, but these biomarkers may give additional information to define non-responders assigning the most vulnerable patients.

In those patients having typical LBBB morphology, where the largest benefit is expected, there are further factors, that might help optimizing the effect of CRT.

The intraoperative right to left ventricular activation delay, which reflects not only the the distance of right and left ventricular leads but also shows the electrical dyssynchrony

and prolonged activation pattern derived from the slow conduction, had a predictive value for the outcome.

Our results showed, in LBBB patients with a longer or equal to 86 ms right to left ventricular activation delay, a significantly lower risk of composite of heart failure events and death occured and lower risk of all-cause mortality alone compared to those with non-LBBB or those with LBBB and shorter than 86ms right to left ventricular activation delay. Moreover our results show that right to left ventricular activation delay predicts the improvement in left ventricular ejection fraction, NT-proBNP and functional outcome in LBBB patients. Thus simple assessment of intraventricular right to left ventricular activation delay could tailor the procedure to achieve the optimal position with a longer activation delay.

Despite having conclusive data about those patients who are eligible for de novo CRT implantation, there is still a lack of evidences and recommendations for CRT upgrade in the current ESC guidelines, however approximately 10% of patients who are referred for the procedure underwent conventional pacemaker or ICD implantation before.

We summarized the currently available data from the literature with 17 studies and more than 6600 patients, who underwent de novo or upgrade CRT implantations. Concluding our results, patients after CRT upgrade from conventional pacemakers or ICDs show similarly beneficial response compared to de novo CRT implantation regarding all-cause mortality or clinical outcome such as echocardiographic reverse remodeling or functional outcome. Despite the more complex upgrading procedure, the risk of adverse events also seems comparable. Our results suggest that CRT upgrade may be safely and effectively offered to patients in routine clinical practice. These are the first results which will be released from a prospective multicenter randomized clinical trial, the BUDAPEST-CRT upgrade study, which will provide conclusive data on the effects of upgrade procedures in patients with previously implanted pacemaker or ICD devices, reduced LVEF $\leq$ 35%, symptomatic heart failure (NYHA-II-IVa), and intermittent or permanent right ventricular pacing with wide paced QRS $\geq$150ms.

Our results can be summarized in a point by point manner as follows:

- In our patient cohort 20% of heart failure patients failed to develop reverse remodeling
- A simple cross-sectional value of gold-standard NT-proBNP or CT-apelin could not predict the outcome, but serum levels after 6 months were significant indicators of non-response
- In this regard 6-months apelin level was superior compared to NT-proBNP
- From intraoperative parameters, assessment of RV-LV AD could predict the outcome in patients with typical LBBB morphology
- Patients with longer than 86ms LV-RV AD was associated with a better improvement of ejection fraction, NT-proBNP, and with better HF-free survival and overall survival
- But not in those with a shorter RV-LV activation delay, or in those with a non-LBBB morphology
- Concluding the currently available data, our meta-analysis suggests that patients undergoing CRT upgrade show similarly beneficial response compared to de novo CRT implantation regarding all-cause mortality or clinical outcome such as echocardiographic reverse remodeling or functional outcome.
- The BUDAPEST CRT upgrade study is the first investigator-initiated, multicenter, randmized trial from Semmelweis University, which will clarify the question and indications of CRT upgrade.

8 SUMMARY

Cardiac resynchronization is an effective device therapy of chronic heart failure**,** however there have been still a large amount of non-responder patients and those for whom the current guidelines do not provide clear recommendations such as patients with an already implanted device.

Thus first we aimed to evaluate those parameters which could predict or influence the response to de novo CRT implantation in regard of optimal patients selection - with assessment of serum biomarkers such as CT-apelin and NT-proBNP - and an intraoperative parameter, the right to left ventricular ativation delay specified by QRS morphology. Second we described the clinical response of patients with an already implanted pacemaker or implantable cardioverter defibrillator who underwent CRT upgrade.

In our single center, prospective study, 125 patients were registered who underwent CRT implantation as per current guidelines and followed for two years. Baseline and 6-month clinical parameters, laboratory tests, serum biomarkers, echocardiographic parameters were assessed, while right to left ventricular delay was measured at implantation. Regarding CRT upgrade, a meta-analysis was performed from all available data in the literature with de novo vs. upgrade CRT implantation.

Based on our results 20% of patients proved to be non-responders. Serum biomarkers at baseline could not predict and select such patients, but serum levels after 6 months were feasible in identifying non-responders, where 6-months apelin level was superior compared to NT-proBNP.

When right to left ventricular delay was assessed, it was an independent predictor of heart failure events and all-cause mortality in patients with LBBB and longer activation delay but not in those with nonLBBB or short activation delay. Patients with LBBB and long activation delay had also the greatest clinical improvement in ejection fraction, NT-proBNP, renal function and 6-minute walk test.

Our meta-analyses of upgrade vs. de novo CRT implantation revealed no significant differences can be observed between the two groups in all-cause mortality, changes of echocardiographic or functional parameters and QRS narrowing suggesting this is a safe and effective therapy of patients with a previously implanted device.

However this question will be clarified by the BUDAPEST CRT upgrade study, a multicenter, randmomized, investigator initiated trial.

9 ÖSSZEFOGLALÁS

A kardiális reszinkronizációs terápia hatékony eszközös kezelés szisztolés szívelégtelenségben, azonban a terápiára kevéssé reagáló non-responder betegek aránya még mindig igen magas, illetve az aktuális ajánlások hiányosak azon betegek reszinkronizációs kezelése, *CRT upgrade-je* tekintetében, akik már rendelkeznek konvencionális pacemakerrel vagy beültethetõ cardioverter defibrillátorral.

Kutatásunk célja olyan paraméterek vizsgálata volt, amelyek befolyásolják vagy elõre jelzik a CRT-re adott válaszkészséget. Az optimális betegszelekció tekintetében vizsgáltuk a serum biomarker-szintek, mint az NT-proBNP és CT-apelin változását és prediktív szerepét, illetve az intraoperativan mérhetõ kettősjeltávolság hatását QRS morfológia szerint. Emellett összefoglaltuk az irodalomban elérhetõ összes, a CRT upgrade-re vonatkozó eredményeket.

Egy-centrumos, prospektív vizsgálatunkban 125 beteg esett át CRT implantáción az aktuális ajánlásoknak megfelelõen. A beválasztáskori és 6 hónappal az implantáció után végzett klinikai értékeket regisztráltuk, így a laboratóriumi, funkcionális, serum biomarker és echocardiographiás paramétereket, valamint implantáció során a kettősjel távolságot. A betegeket 2 évig követtük. Emellett CRT upgrade témájában végzett meta-analízisünkben az upgrade-en átesett betegeket a de novo implantáción átesett betegek klinikai kimeneteléhez hasonlítottuk.

Az általunk vizsgált betegcsoportban 20% bizonyult non-respondernek. A beválasztáskor mért serum biomarker szintek nem voltak alkalmasak ezen betegek kiválasztására, azonban a hat hónappal késõbb mért szintek kijelölték a non-reponder betegcsoportot, amelyben a CT-apelin hatékonyabbnak bizonyult az NT-proBNP-hez képest. A kettősjel távolság vizsgálata során, az a mortalitás és a szívelégtelenség esemény független prediktív faktorának bizonyult bal-szárblokkos és hosszabb jeltávolsággal rendelkező betegekben. Ugyancsak ezen betegek mutatták a legnagyobb klinikai javulást az echocardiographiás válasz, az NT-proBNP, a vesefunkció és a 6-perces járásteszt tekintetében.

Meta-analízisünk alapján nincs különbség az össz-mortalitás, echocardiográphiás vagy funkcionális válasz illetve a QRS szélesség változásának tekintetében, amely eredmények szerint az upgrade biztonságos és hatékony eljárás. Mindezt azonban a multicentrikus, randomizált, BUDAPEST CRT upgrade vizsgálat fogja részletesebben megvizsgálni.

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11 PUBLICATIONS

Publications related to the current thesis

1. **Kosztin A**; Kutyifa V; Nagy KV; Gellér L; Zima E; Molnár L; Szilágyi Sz; Özcan EE; Széplaki G; Merkely B:
   Longer right to left ventricular activation delay at cardiac resynchropnization therapy implantation is associated with improved clinical outcome in left bundle branch block patients.
   Europace 2016; 18(4): 550-559. **IF: 4.021**

2. **Kosztin A**, Széplaki G, Kovács A, Földes G, Szokodi I, Nagy KV, Kutyifa V, Fórizs É, Végh EM, Gellér L, Becker D, Aradi D, Merkely B**:**
   Impact of CT-apelin and NT-proBNP on identifying non-responders to cardiac resynchronization therapy.
   Biomarkers 2016 [Epub ahead of print 2016 Jul 29] **IF: 2.016**

3. Merkely B; **Kosztin A**; Róka A; Gellér L; Zima E; Kovács A; Boros AM; Klein H; Wranicz JK; Hindricks G; Clemens M; Duray G; Moass AJ; Goldenberg I*; Kutyifa V*:
   Rationale and design of the BUDAPEST-CRT Upgrade Study: a prospective, randomized, multicenter clinical trial.
   Europace [Epub ahead of print 2016 Oct 6] **IF: 4.021**

Amount of impact factors related to the current thesis: 10.058

Publications not related to the current thesis

1. **Kosztin A**; Soós P; Polgár L; Kutyifa V; Becker D; Kovács A; Merkely B:
   EORP Szívelgtelenség Regiszter a Városmajori Szív-és Érgyógyászati Klinikán.
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   Inflamm Res 2016; 65(12): 933-940. **IF: 2.557**

6. **Kosztin A**, Costa J, Moss AJ, Biton Y, Nagy VK, Solomon S, Gellér L, McNitt S, Polonsky B, Merkely B, Kutyifa V:
Clinical presentation at first heart failurehospitalization does not predict recurrent heart failure admission
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7. Lakatos B, Tősér Z, Tokodi M, Doronina A, **Kosztin A**, Muraru D, Badano LP, Kovács A, Merkely B:
Quantification of the relative contribution of the different right ventricular wall motion components to right ventricular ejection fraction: the ReVISION method Cardiovasc Ultrasound [Epub ahead of print 2017 Mar] **IF: 1.463**

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