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# Cardiac Resynchronization Therapy: Current Practice, Refining Implantation Methods, Effects on Ventricular Arrhythmias and New Indications

Ph.D. Thesis

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# Preface

*Invictus*

*Out of the night that covers me,*
*Black as the Pit from pole to pole,*
*I thank whatever gods may be*
*For my unconquerable soul.*

*In the fell clutch of circumstance*
*I have not winced nor cried aloud.*
*Under the bludgeonings of chance*
*My head is bloody, but unbowed.*

*Beyond this place of wrath and tears*
*Looms but the Horror of the shade,*
*And yet the menace of the years*
*Finds, and shall find, me unafraid.*

*It matters not how strait the gate,*
*How charged with punishments the scroll.*
*I am the master of my fate:*
*I am the captain of my soul.*

*William Ernest Henley*

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# Abbreviations

| | |
|---|---|
| CI | Confidence Interval |
| CRT | Cardiac Resynchronization Therapy |
| CRT-P | Cardiac Resynchronization Therapy with Pacemaker Capabilities |
| CRT-D | Cardiac Resynchronization Therapy with Defibrillator |
| HF | Heart Failure |
| ICD | Implantable Cardioverter Defibrillator |
| IVD | Interventricular Delay |
| JTc | JT Interval Corrected for Heart Rate |
| LV | Left Ventricle |
| LAV | Left Atrial Volume |
| LBBB | Left Bundle Branch Block |
| LVEF | Left Ventricular Ejection Fraction |
| LVEDD | Left Ventricular End-Diastolic Diameter |
| LVEDV | Left Ventricular End-Diastolic Volume |
| LVESD | Left Ventricular End-Systolic Diameter |
| LVESV | Left Ventricular End-Systolic Volume |
| NYHA | New York Heart Association |
| PM | Pacemaker |
| RV | Right Ventricular |
| TDR | Transmural Dispersion of Repolarization |
| VT | Ventricular Tachycardia |
| VF | Ventricular Fibrillation |

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# 1 Introduction

## 1.1 Current Practice of Cardiac Resynchronization Therapy

Heart Failure (HF) is a growing public health problem worldwide with rising prevalence due to aging, improved medical treatment and successful prevention of cardiac events. The prevalence of heart failure is 2-3% in developed European countries, while it might reach 10-20% in the elderly.[1]

Cardiac resynchronization therapy (CRT) provides synchronization of the dyssynchronous left ventricular activation in patients with conduction abnormalities and severely reduced left ventricular function, resulting in an immediate decrease of left ventricular intra- and interventricular dyssynchrony, mitral regurgitation and an acute increase of LV dP/dt.[2] During long-term follow-up, patients develop reduction in left ventricular end-diastolic (LVEDV) and left ventricular end-systolic volume (LVESV), and improvement in left ventricular ejection fraction (LVEF), this process is described as left ventricular reverse remodeling.[3-12]

Cardiac resynchronization therapy or a combination of CRT with an Implantable Cardioverter Defibrillator (CRT-D) was proven to reduce heart failure symptoms, hospitalizations and mortality in patients with severe heart failure (NYHA class III-IV), reduced left ventricular ejection fraction (LVEF≤35%) and a prolonged QRS (QRS width≥120 ms).[10, 13]

The Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy (MADIT-CRT), the Resynchronization-Defibrillation in Ambulatory Heart Failure Trial (RAFT) and Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trials have further broadened CRT indication to patients with mild HF and NYHA class I and II.[6, 7, 12] Table 1 is summarizing the main randomized clinical trials on CRT.[3-12]

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**Table 1.** Randomized clinical trials on CRT

| Trials | Patients (n) | Female (%) | Primary endpoints | Secondary endpoints | Etiology (isch. %) | LVEF (%) | QRS (ms) |
|---|---|---|---|---|---|---|---|
| PATH-CHF | 41 | 50% | 6MWT, peak VO2 | NHYA class, QOL, Hospitalizations | 29% | 21±7 | 175 |
| MUSTIC-SR | 58 | 26% | 6MWT | NYHA, QOL, Peak VO2, MR, LV, Hosp, Mortality | 37% | 23±7 | 174 |
| MIRACLE | 453 | 32% | 6MWT, NHYA, QOL | Peak VO2, LVEF, LVEDD, MR, Clin Response | 54% | 22±6 | 166 |
| MIRACLE ICD | 555 | 23% | 6MWT, NYHA, QOL | Peak VO2, LVEF, LV volumes, MR, Clinical Response | 70% | 24±6 | 164 |
| COMPANION | 1520 | 22% | All-cause mortality or hospitalization | All-cause mortality and cardiac mortality | 56% | 21 | 159 |
| CARE-HF | 814 | 26% | All-cause mortality | NYHA, QOL, LVEF, LVESV, Hospitalization for heart failure | 38% | 25 | 160 |
| REVERSE | 610 | 21% | HF clinical composite score | LVESVi | 54% | 27±7 | 153 |
| MADIT-CRT | 1820 | 25% | HF or death | LVESV, LVEDV change, multiple HF events | 57% | 24±5 | 162 |
| RAFT | 1798 | 17% | All-cause mortality or HF hospitalization | All-cause mortality, cardiac mortality, HF hospitalization | 67% | 23±5 | 158 |

6MWT, 6-min walk test; CARE-HF, Cardiac Resynchronization-Heart Failure; COMPANION, Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; HF, heart failure; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MADITCRT, Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy; MIRACLE, Multicenter InSync Randomized Clinical Evaluation; MIRACLE ICD, Multicenter InSync Implantable Cardioverter Defibrillator trial; MR, mitral regurgitation; MUSTIC, Multisite Simulation in Cardiomyopathies; NYHA, New York Heart Association; PATH-CHF, Pacing Therapies in Congestive Heart Failure trial; QOL, quality-of-life score; RAFT, Resynchronization-Defibrillation for Ambulatory Heart Failure; REVERSE, Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction; VO2, volume of oxygen.

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Besides multicenter randomized clinical trials, multi- and single-center registries are also important sources for providing real-world information on CRT. It is well-known, that patients with NYHA class IV and inotropes, those with severe renal dysfunction, or on dialysis, those who are having coexisting malignant diseases, or previously implanted pacemakers are excluded from randomized clinical studies. However, evaluating the effects of CRT in registry patients might refine treatment delivery, and potentially expand the use of CRT in patients who may not have been included in clinical trials.[14]

## 1.2 MADIT-CRT

Patients with heart failure and reduced left ventricular function are at increased risk for arrhythmia-related sudden cardiac death. Implantation of an implantable cardioverter–defibrillator (ICD) reduces mortality and the risk of sudden death in selected patients with cardiac disease.[15] However, life-prolonging defibrillator therapy might be associated with an increased risk of first and recurrent heart-failure events.[16]

The MADIT-CRT trial was designed to investigate whether CRT–D therapy would prevent death or nonfatal heart-failure events (whichever came first) in mild heart failure patients as compared with ICD-only treatment.[17]

From December 22, 2004, through April 23, 2008, a total of 1820 patients who had ischemic or non-ischemic cardiomyopathy, an ejection fraction (LVEF) less than 30%, prolonged intraventricular conduction with a QRS > 130 ms were randomized to receive CRT-D or ICD therapy in a 3:2 ratio in 110 hospital centers: 1271 patients at 88 centers in the United States, 22 patients at 2 centers in Canada, and 527 patients at 20 centers in Europe.

Patients were excluded if they had an existing indication for CRT, if they received a

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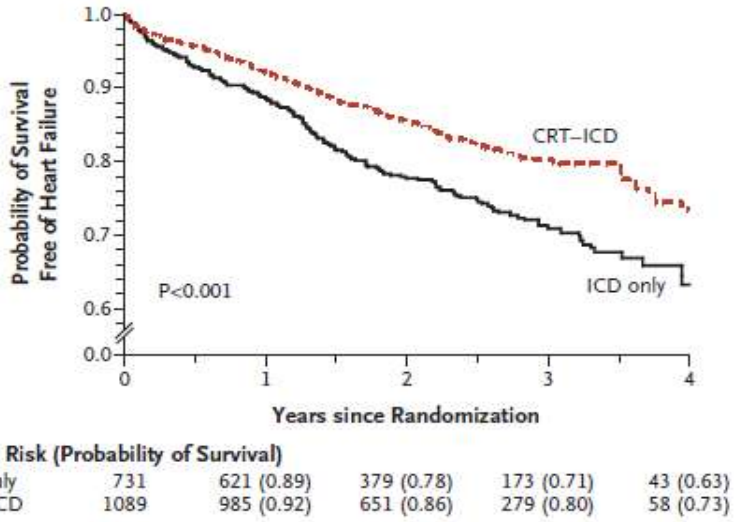
pacemaker, had NYHA class III/IV less than 90 days before enrolment, underwent coronary artery bypass graft surgery or percutaneous coronary intervention, or had myocardial infarction within the past 90 days prior to enrolment.

**Figure 1**. MADIT-CRT trial. Kaplan-Meier Cumulative Probability of Survival Free of Heart Failure Stratified by Treatment Arm




| No. at Risk (Probability of Survival) | | | | | |
|---|---|---|---|---|---|
| ICD only | 731 | 621 (0.89) | 379 (0.78) | 173 (0.71) | 43 (0.63) |
| CRT–ICD | 1089 | 985 (0.92) | 651 (0.86) | 279 (0.80) | 58 (0.73) |

During the average follow-up of 29 months, the primary end point occurred in 187 of 1089 patients in the CRT–D group (17.2%) and 185 of 731 patients in the ICD-only group (25.3%). This indicates a 34% reduction in the risk of death or heart failure events (whichever came first) in the CRT–D group, as compared to the ICD-only treated patients. This effect was driven by a 41% reduction in the risk of heart failure in CRT-D patients as compared to those who received ICD-only (Figure 1). During the study, 127 deaths occurred of any cause representing a low 3% annual mortality rate. CRT-D treatment was associated with significant reduction in left ventricular (LV) volumes and improvement in left ventricular ejection fraction.[18]

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## 1.3 Refining Implantation Methods

### 1.3.1 *Prognostic Significance of Right Ventricular to Left Ventricular Interlead Sensed Electrical Delay in CRT Patients*

Cardiac resynchronization therapy is most commonly achieved using a standard approach to implant the LV lead in a lateral or postero-lateral coronary sinus branch.[19, 20] However, recent studies suggested that implanting the LV lead at the latest LV mechanical activation segment might provide a better resynchronization effect with CRT.[21, 22]

Right ventricular to left ventricular interlead sensed electrical delay, interventricular delay (IVD) is the time delay on the sensed electrogram between RV and LV sensing signals. This parameter is measured during CRT implantation, after positioning the right and left ventricular leads. Essentially, this measure is representing the electrical time delay between the right and left ventricle at the right and left ventricular lead position.

Previous studies failed to predict left ventricular reverse remodeling using the right to left ventricular interlead electrical delay.[23-25] However, it was shown to be correlated with intraventricular dyssynchrony,[24, 25] a well-known powerful predictor of response to CRT.[26-28]

### 1.3.2 *Electroanatomical Mapping Guided Transseptal Endocardial LV Lead Implantation*

The left ventricular lead is usually implanted using a transvenous approach. However, even with innovative lead technology, LV lead placement fails in 4-8%.[29, 30] The most frequent reasons are coronary sinus occlusion or dissection, abnormal ostium of the coronary sinus, coronary vein stenosis, lead instability, high threshold or phrenic nerve stimulation.[29, 31, 32] Epicardial lead placement is an alternative method, which includes minimal-invasive thoracoscopy or lateral thoracotomy and usually requires general anaesthesia.[33] When epicardial LV lead implantation is

contraindicated or at higher risk, LV endocardial lead implantation might be considered.[34]

CRT is typically delivered aiming a lateral or posterolateral LV lead position,[19, 29, 35] and the LV lead is usually placed in the middle or distal portion of the side-branch to ensure stable position. In contrast, when using endocardial transseptal approach, the LV lead position is independent of the coronary vein anatomy. The major difficulty of this method is to relocate the transfemoral transseptal puncture site performed from the subclavian access and to find the optimal LV lead position within the LV cavity.

Electroanatomical mapping is visualizing cardiac structures and gathering data of electrical activation of the heart. It is widely used to guide ablation procedures in the left atrium, in the right ventricle and in the left ventricle.[36] Electroanatomical mapping might be a useful tool to guide endocardial LV lead implantation for CRT.

## 1.4 Effects of CRT on Ventricular Arrhythmias

### 1.4.1 *Left Ventricular Lead Location and the Risk of Ventricular Tachyarrhythmias*

Heart failure patients are at higher risk of ventricular tachycardia (VT) or ventricular fibrillation (VF),[37] even after receiving CRT.

The Cardiac Resynchronization in Heart Failure (CARE-HF) extension trial reported 7.8% of sudden cardiac death during the mean follow-up of 29.4 months in patients receiving CRT.[38] In the Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Heart Failure (COMPANION) study, 19.3% of the CRT-D patients experienced appropriate ICD therapy by the second year after device implantation. ICD shock therapy is associated with worse outcome.[29, 39]

There are several risk factors contributing to the occurrence of ventricular

tachyarrhythmias, ischemic events, depressed left ventricular function, increased ventricular wall stress, renal dysfunction and atrial fibrillation.[29, 40] Some data also indicate that there is a potential pro-arrhythmic risk of biventricular pacing itself.[41-45] However, other studies demonstrated anti-arrhythmic effects of CRT, explained by the improved hemodynamic status and left ventricular reverse remodeling.[22, 46-48]

It is currently unknown, whether left ventricular lead location might play a role in the development of VT/VF, possibly by enhancing electrical heterogeneity.

### 1.4.2 *Left Ventricular Dyssynchrony and the Risk of Ventricular Tachyarrhythmias*

Intraventricular mechanical dyssynchrony might also play an important role in the development of VT/VF by abnormal mechanical and subsequent electrical activation inducing electrical heterogeneity.

The effects of LV lead location and LV dyssynchrony on ventricular arrhythmias have not yet been investigated in mild heart failure patients with implanted CRT-D or ICD.

## 1.5 New Indications of CRT

### 1.5.1 *Chronic Right Ventricular Apical Pacing*

Large randomized trials have demonstrated the adverse effects of chronic right ventricular (RV) apical pacing associated with increased risk of atrial fibrillation and heart failure.[49, 50] Up to 40% of patients with chronic RV apical pacing develop heart failure during long-term follow-up.[49, 50] These detrimental effects might be attributed to the altered electrical and mechanical activation

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of the ventricles resulting in left ventricular (LV) dyssynchrony, impaired LV filling, perfusion defects and myofibrillar disarrays.[51]

Randomized clinical trials showing beneficial effects of CRT were performed only in patients with de novo implantations[4, 8, 10, 11] however, according to registry data more than one quarter of CRT implantations are upgrades of implanted pacemaker devices.[52]

Previous smaller studies demonstrated the efficacy, feasibility and safety of CRT upgrade in patients with RV apical pacing compared to de novo CRT implantation.[53-57] However, we have no data on the outcome of patients with implantable cardioverter-defibrillator (ICD) upgraded to CRT. Additionally, predictors of long-term outcome have not yet been investigated in this patient cohort.

### 1.5.2 *Cardiac Resynchronization Therapy in Patients with Less Severe Ventricular Dysfunction*

Using pre-selected cut-off point for left ventricular ejection fraction as an inclusion criterion for CRT is considered an arbitrary method, as patients develop heart failure across the spectrum of left ventricular ejection fraction. Depressed LVEF was shown to be a surrogate marker of heart failure status and is associated with increased risk of adverse events, all-cause mortality and sudden cardiac death.[58-60] However, the risk associated with LVEF was shown to be a continuum until the range of 45%.[59] Therefore, there is a rationale for CRT in patients with less depressed LVEF.

In MADIT-CRT, the inclusion criteria comprised patients with LVEF below or equal to 30%, as evaluated by the enrolling centers prior to enrollment. All patients additionally underwent central echocardiographic analysis of LVEF in the study core laboratory of Brigham

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and Women's Hospital, Harvard Medical School in Boston, Massachusetts, where a substantial proportion of patients were identified to have an LVEF of greater than 30%, beyond the eligibility criteria. This provides unique opportunity to evaluate the efficacy of CRT-D in patients with less decreased cardiac function.

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# 2 Aims

## 2.1 Current Practice of Cardiac Resynchronization Therapy

### 2.1.1 *Evaluating the Effects of CRT-P versus CRT-D in a CRT Registry*

In this analysis, we sought to evaluate the long-term echocardiographic and clinical outcome of CRT patients in a single-center high-volume registry, and to assess the all-cause mortality of patients with an implanted CRT-P or CRT-D device.

## 2.2 Refining Implantation Methods

### 2.2.1 *Prognostic significance of right ventricular to left ventricular interlead sensed electrical delay in CRT patients*

We aimed to determine the prognostic significance of right to left ventricular interlead sensed electrical delay on the end point of all-cause mortality in CRT patients of the single-center, high-volume registry.

### 2.2.2 *Electroanatomical Mapping-Guided Transseptal Endocardial LV Lead Implantation*

We sought to evaluate the feasibility and safety of transseptal endocardial left ventricular lead implantation in a small patient cohort of the single-center, high volume CRT registry. Furthermore, we aimed to determine whether electroanatomic mapping guided left ventricular lead targeting might be associated with better clinical and echocardiographic improvement after CRT implantation.

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## 2.3 Effects of CRT on Ventricular Arrhythmias

### 2.3.1 *Left Ventricular Lead Location and the Risk of Ventricular Tachyarrhythmias*

We aimed to analyze the association between LV lead position and the risk of VT/VF/Death or VT/VF in patients enrolled in the MADIT-CRT trial.

### 2.3.2 *Left Ventricular Dyssynchrony and the Risk of Ventricular Tachyarrhythmias*

We sought to investigate the association between left ventricular dyssynchrony, CRT-induced change in LV dyssynchrony and the risk of VT/VF/Death or VT/VF events in LBBB and non-LBBB patients enrolled in MADIT-CRT.

## 2.4 New indications of CRT

### 2.4.1 *Chronic Right Ventricular Apical Pacing*

The aim of this analysis was to evaluate the effects of CRT upgrade in ICD patients with chronic RV pacing compared to PM patients with chronic RV pacing, and to identify predictors of long-term outcome in this patient population.

### 2.4.2 *Cardiac Resynchronization Therapy in Patients with Less Severe Ventricular Dysfunction*

We aimed to evaluate the relationship between LVEF and the clinical outcome of mild heart failure patients enrolled in MADIT-CRT; the echocardiographic response to CRT-D in the trial; and the clinical benefit of CRT-D, with a specific focus on the subset of patients with more preserved LVEF enrolled in the trial.

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# 3 Methods

## 3.1 Current Practice of Cardiac Resynchronization Therapy

### 3.1.1 *Evaluating the Effects of CRT-P versus CRT-D in a CRT Registry*

#### 3.1.1.1 Patient Population

From June 2000 to April 2011, 1122 consecutive patients had undergone CRT device implantation at the Semmelweis University Heart Center, Budapest, Hungary. Patients met the guideline criteria for CRT, including New York Heart Association (NYHA) class II, III or IV, QRS $\geq$ 120 ms, LVEF $\leq$ 35% and optimal medical treatment including beta-blocker, ACE-inhibitor or ARB therapy, diuretics and aldosterone antagonist, unless contraindicated or not tolerated by the patient. Optimization of the medical therapy was performed according to current guidelines.[61] All patients gave written informed consent before the procedure.

#### 3.1.1.2 Pre-implant Assessment

Diagnostic coronary angiography and revascularization was performed if indicated. Baseline clinical characteristics were recorded prior CRT implantation. Two-dimensional transthoracal echocardiography was performed before CRT implantation and during follow-up using commercially available systems (Toshiba Aplio, Toshiba Medical Systems Co, Ltd, Tokyo, Japan, and Philips iE33, Andover, Massachusetts, USA). Left ventricular end-diastolic and end-systolic diameters (LVEDD, LVESD) and left ventricular ejection fraction were measured according to standard methods.[62]

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#### 3.1.1.3 Device implantation

CRT device implantation was performed using transvenous, epicardial or transseptal approach. Patients in sinus rhythm or those with paroxysmal atrial fibrillation were implanted a right atrial lead and right ventricular lead, while patients in permanent atrial fibrillation received right and left ventricular leads only. During the implantation procedure after cannulating the coronary sinus, balloon catheter was used to perform coronary sinus venogram and to identify the target vein for CRT therapy, preferably the lateral or postero-lateral vein. Left ventricular pacing, sensing and impedance were measured. Phrenic nerve stimulation was tested in supine body position using 10 V at 0.5 ms pacing of the LV lead at the end of CRT implantation. Commercially available LV leads and CRT devices were used. If the patient received a CRT device with ICD capabilities, ventricular fibrillation (VF) testing was performed at implantation according to current standards to achieve a safety margin of at least 10 J.

#### 3.1.1.4 Post-implant Assessment

All patients were scheduled for outpatient visit one month after the implantation and every 6-month thereafter. Clinical status assessment and device follow-up was performed at each follow-up visit or at any meaningful clinical event. Two-dimensional echocardiography was performed 6 months after CRT upgrade and every 12-month thereafter or in case of heart failure progression. Echocardiographic data available at last follow up (median 20 months, IQR: 10-38 months) were analyzed.

#### 3.1.1.5 Study End Points

The primary end point of this analysis was all-cause mortality. Secondary end points included

improvement in NYHA functional class, increase in left ventricular ejection fraction and decrease in left ventricular end-diastolic and end-systolic volumes. Mortality data were collected from medical records, phone follow-up, and using the mortality database of the Hungarian National Health Fund.

## 3.2 Refining Implantation Methods

### 3.2.1 *Prognostic Significance of Right Ventricular to Left Ventricular Interlead Sensed Electrical Delay in CRT Patients*

#### 3.2.1.1 Patient Population

From June 2000 to April 2011, 494 of 1122 patients (44%) undergoing CRT implantation at the Semmelweis University Heart Center, Budapest, Hungary and had measurements of right to left ventricular interlead sensed electrical delay. Patients met the guideline criteria for CRT, including New York Heart Association (NYHA) class II, III or IV, QRS $\geq$ 120 ms, LVEF $\leq$ 35% and optimal medical treatment including beta-blocker, ACE-inhibitor or ARB therapy, diuretics and aldosterone antagonist, unless contraindicated or not tolerated by the patient. Optimization of the medical therapy was performed according to current guidelines.[61] All patients gave written informed consent before the procedure.

#### 3.2.1.2 Pre-, Post-implant Assessment

Pre- and post-implant assessment was performed as explained in section 3.1.1.2. and 3.1.1.4.

#### 3.2.1.3 Device Implantation

CRT device implantation was performed according to standard methods as described in section

3.1.1.3. (Current practice of cardiac resynchronization therapy-methods).

During implantation, after positioning the right and left ventricular leads we connected the right and left ventricular leads to an electrophysiology system (Biotronik, Berlin, Germany) and measured the right to left interventricular sensed delay by the time delay of the peak activation in the right and left ventricular sensed signals (ms).

#### 3.2.1.4 Study End Points

The end point of this analysis was death of any cause. Mortality data were collected from hospital records, using follow-up of the patients and the mortality database of the Hungarian National Health Fund.

### 3.2.2 *Electroanatomical Mapping-Guided Transseptal Endocardial LV Lead Implantation*

#### 3.2.2.1 Study Population

Four patients had undergone endocardial LV lead implantation at the Semmelweis University Heart Center, Budapest, Hungary between November 2007 and May 2010, guided by electroanatomical mapping. Patients met the indication criteria for CRT according to current guidelines.[63] All patients had left bundle branch block (LBBB) or paced rhythm with LBBB-morphology.

CRT was attempted or performed either via a transvenous or an epicardial approach. Patient 1 had epicardial LV lead dysfunction, a repeated surgery was contraindicated therefore the patient was referred for endocardial LV lead implantation. Patient 2 and 4 had unsuccessful transvenous LV lead implantation. Patient 3 had LV lead dysfunction after successful transvenous LV lead implantation. In Patient 2 and 3, mini-thoracotomy was contraindicated

because of multiple comorbidities and higher risk of surgical intervention. Patient 1 and 4 did not give the consent for epicardial surgical LV lead implantation. All patients had given informed consent prior to procedure.

#### 3.2.2.2 LV Lead Implantation Procedure

Left ventricular endocardial lead implantation was performed using a combined femoral and subclavian approach guided by electroanatomical mapping. The first step of the procedure was to introduce the CARTO Quick Star catheter (Biosense Webster, Diamond Bar, CA) through the right femoral vein to capture the anatomical map of the right atrium and the right ventricle. The transseptal puncture was performed with the guidance of both fluoroscopy and intracardiac echocardiography, including continuous monitoring of the arterial pressure. Intravenous heparin was given after the transseptal puncture (5000 IU), in case of long-lasting procedures it was administered repeatedly to maintain an ACT level of 250 msec.

The puncture point of the septum was marked on the CARTO map (Biosense Webster, Diamond Bar, CA) (Figure 2). A guide wire (0.035 inch*260 cm) was inserted into the left atrium (LA) and advanced into the left upper pulmonary vein. The dilator of the transseptal sheath was removed and an angioplasty balloon (6mm*20mm Maverick, Boston Scientific, Natick, MA, USA) was inserted into the LA. The transseptal sheath was withdrawn into the right atrium and the balloon was positioned across the septal puncture site. It was inflated 3 times with 12 atm for 5 seconds before its removal. The transseptal sheath was then positioned into the LA cavity.

**Figure 2.** Patient 1. CARTO image, AP projection. The location of the transseptal puncture is indicated with a single white arrow on the CARTO map.

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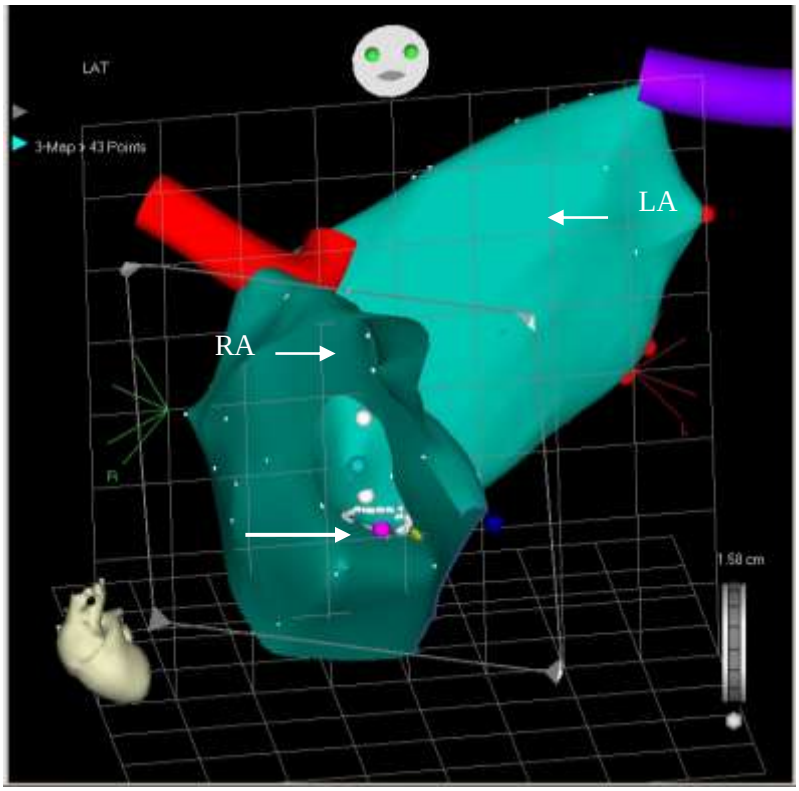


The Quick Star deflectable catheter was inserted into the LA and advanced in the LV cavity via the right femoral vein. LV activation map was recorded (Figure 3).

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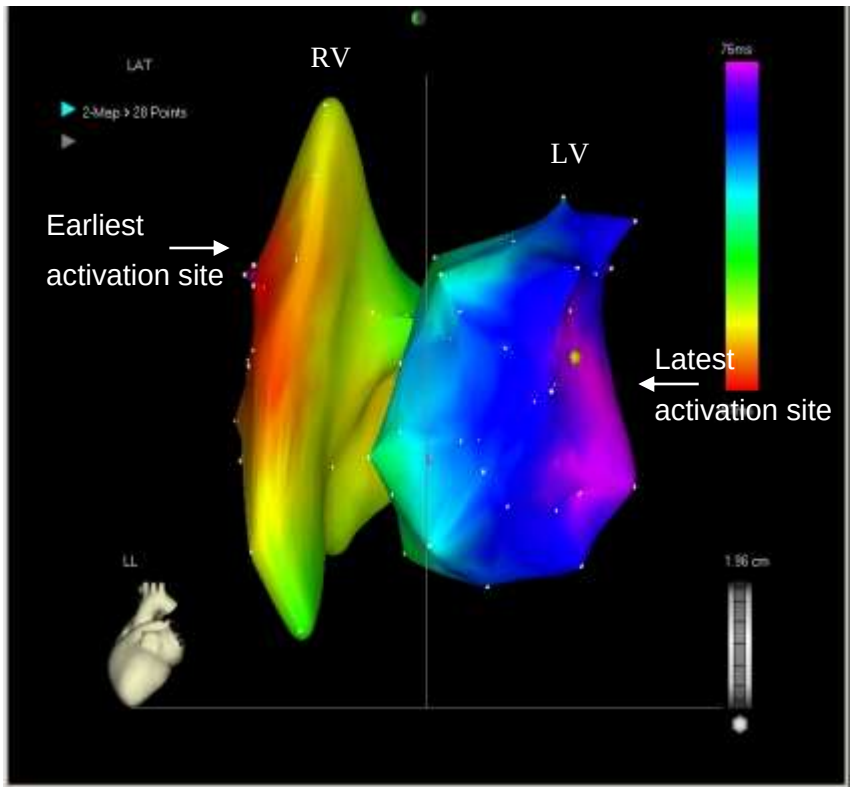
**Figure 3.** Patient 1. CARTO image, left lateral projection. Right and the left ventricular activation map: the earliest activation site is the right ventricular anteroseptal region, the latest one is the mid-basal part of the posterolateral wall.




An 11 F long sheath (SCOUT Pro 8 Fr, Biotronik GmbH&Co, Berlin, Germany) was introduced via the left subclavian vein. The Quick Star catheter was advanced into the sheath and guided to the location of the transseptal puncture by CARTO location guidance. At this time, a second angioplasty balloon (6mm*20mm Maverick, Boston Scientific, Natick, MA, USA) was positioned to the puncture site through the previously applied guide-wire from the femoral access to facilitate the manipulation of the Quick Star catheter across the septum. The long sheath was pushed over the deflectable catheter through the interatrial septum into the LA and further into

the LV. The Quick Star catheter was used to relocate the LV segment with the latest activation. At this step, the Quick Star catheter was withdrawn into the sheath and the sheath was pushed against the left ventricular wall to ensure stable position. Active fixation LV leads were implanted at the most delayed area of the LV via the sheath. The leads were fixed at the basal or mid-basal portion of the left ventricle in all patients where the latest activation was detected on the activation map. The sheath was pushed against the LV wall to have a stable support and facilitate to position the LV lead close to the mitral valve. Standard unipolar srew-in leads were used in all patients (Medtronic- 5076-52cm, Medtronic, Minneapolis, MN, n=1; Medtronic 5076-65cm, Medtronic, Minneapolis, MN, n=2 and Vitatron, ICQ09B-58 cm, Medtronic, Minneapolis, MN, n=1). The LV lead was connected to the CRT device placed in the left pectoral area.

## 3.3 Effects of CRT on Ventricular Arrhythmias

### 3.3.1 *Left Ventricular Lead Location and the Risk of Ventricular Tachyarrhythmias*

#### 3.3.1.1 Evaluation of LV Lead Locations

LV lead position was evaluated by biplane coronary venograms and anterior/posterior, lateral chest X-rays in patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial - Cardiac Resynchronization Therapy. At the time of CRT implantation, coronary venous angiograms were obtained in at least 2 orthogonal views (Right Anterior Oblique- RAO and Left Anterior Oblique- LAO) as well as fluoroscopic images in the same views after definitive LV lead placement. Anterior-posterior and lateral chest X-rays were performed after the procedure or prior to discharge. The stored images were copied onto a CD-ROM and sent to the core laboratory at the University of Rochester Medical Center for central reading. The study protocol recommended positioning the LV lead in the lateral or postero-lateral side-branch of the

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coronary sinus if possible.

The final LV lead position was assessed in the longitudinal axis view (RAO 20°-40°) and the short axis view (LAO 20°-40°) together with the anterior/posterior and lateral chest-X ray. In case the LV lead images were not available in both angle views, stored at completely different angles or showed poor quality making lead assessment impossible, the lateral chest-X rays were used to define the final lead position.

The LAO view, representing the short-axis view of the heart was used to classify the left ventricular wall into 3 equal parts; anterior, lateral (antero-lateral, lateral, postero-lateral) and posterior. The RAO view, representing the long axis of the heart, was used to distinct the lead position to be basal, mid-ventricular or apical.[36, 64] We defined an anterior, lateral and posterior LV lead location along the short axis, including all basal and mid-ventricular lead locations. We also grouped patients with apical versus non-apical (basal and mid-ventricular) LV lead location along the short axis (Figure 4).

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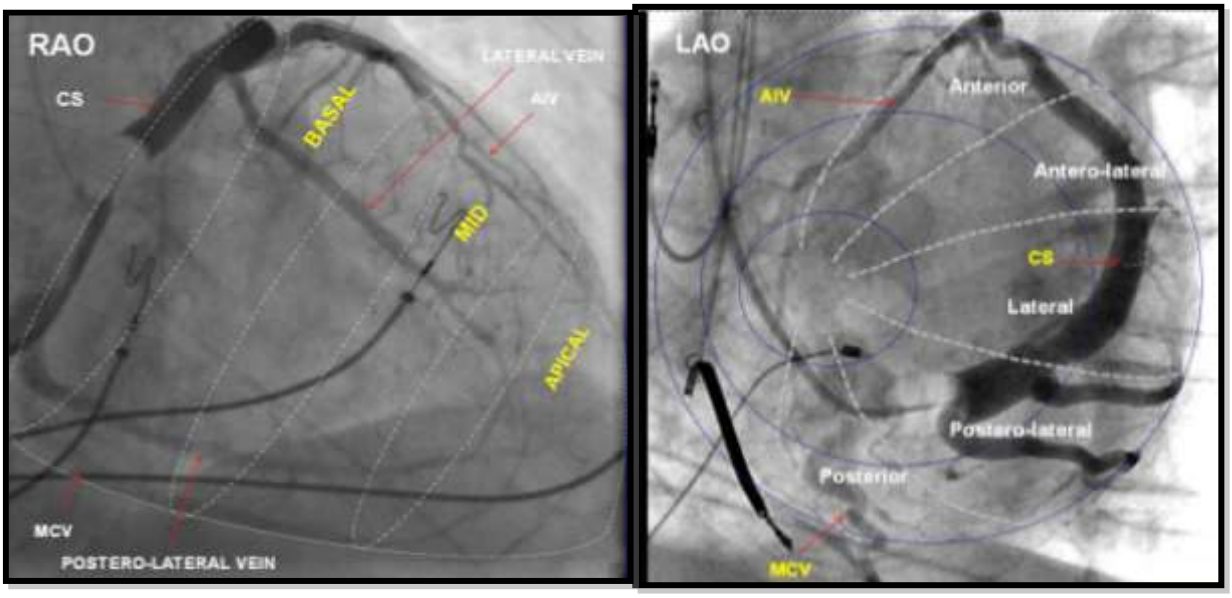
**Figure 4.** Classification of LV lead location. Sinus venograms in RAO (left panel) and LAO view (right panel) representing the segments of the left ventricle along the long- and the short axis of the heart. In this analysis, the antero-lateral, lateral and postero-lateral segments were grouped as lateral lead location. Lateral and posterior locations were grouped together as lateral-posterior. Reproduced with permission (license number: 2884921460326, Circulation).




We compared anterior, lateral, posterior and apical LV-lead locations; anterior versus lateral-posterior and apical lead location along short axis as well as the apical versus non-apical lead positions along the long-axis of the heart.

#### 3.3.1.2 Study Population

We were able to analyze LV lead location in 797 of 1089 (73%) patients who received CRT-D devices and were followed over a mean of 30.6 (±10.9) months. The following patients were not included in the analysis: those who needed a cross-over to ICD only (n=66, 6.1%) or to CRT-D (n=2, 0.2%), who were withdrawn prior to device implantation (n=56, 5.1%), who underwent LV

lead repositioning more than one week after initial CRT device implantation because of lead dislodgement (n=54, 5%), those, who had epicardial LV lead placement (n=36, 3.3%) or cases with incomplete data-sets of device implantation venograms and X-rays (n=78, 7.2%).

#### 3.3.1.3 Device Programming and Interrogation

Commercially available transvenous ICD and CRT-D devices (Boston Scientific) were used in the trial. Standard techniques were used to implant the devices. Device testing and programming were performed as reported in the study protocol.[65] Devices were programmed to monitor + therapy, with protocol recommendation to a setting of ventricular tachycardia (VT) zone at 180 bpm, and ventricular fibrillation (VF) zone at 250 bpm. Sensitivity was programmed according to physician discretion. Detection was 1.0 second for the VF zone and 2.5 seconds for the VT zone. The protocol recommended to program VT zone first therapy to burst-type antitachycardia pacing (ATP), then shock therapy; second therapy should be shock at defibrillation threshold plus at least 10 J. The remaining therapies should be maximal energy shocks. All device interrogation disks were sent to an independent core laboratory for categorization and final evaluation of detected arrhythmias.

#### 3.3.1.4 Patient Follow-Up

Patients had outpatient follow-up 1-month after CRT-D or ICD implantation and every 3 months thereafter until the termination of the trial. The mean follow-up of the enrolled patients was 29.4 months. All patients had clinical evaluation and ICD interrogation with retrieval of stored electrograms at each follow up visit or at any meaningful clinical events.

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#### 3.3.1.5 End Points

The primary end point of the current study was the first occurrence of appropriate therapy for ventricular tachycardia (VT) or ventricular fibrillation (VF) or death assessed as the cumulative probability of first events or risk of events. All ICD interrogations were adjudicated by an independent, blinded core laboratory reviewing the electrograms of the episodes for categorization and final evaluation of the detected arrhythmias. Definition of VT was set to a rate from 180 bpm (recommended programming) up to 250 bpm, V rate ≥ A rate if 1:1 A:V, V-V changes drive AA changes. VF was defined as ventricular rate faster, than 250 beats/min with disorganized ventricular electrograms. Only appropriate therapy, antitachycardia pacing (ATP) or shock delivery for VT or VF was considered in the present analysis.

We analyzed VT/VF and rapid VT/VF episodes (rate ≥ 200 bpm) as separate end points. We evaluated VT/VF events requiring ICD shock or death, as well as recurrent VT/VF events (≥2 VT/VF episodes in one patient). We also analyzed all-cause mortality of the subgroups.

### 3.3.2 *Left Ventricular Dyssynchrony and the Risk of Ventricular Tachyarrhythmias*

#### 3.3.2.1 Echocardiographic Methods

Echocardiography investigators and sonographers from each enrolling sites were qualified to perform echocardiography according to the approved echocardiography protocol. Recordings were analyzed off-line at the Brigham and Women's Hospital, Boston, Massachusetts as an independent echocardiography core laboratory.

LV mechanical dyssynchrony was measured using B-mode speckle tracking software (TomTec Imaging Systems, Unterschleissheim, Germany) as reported previously.[66] Briefly, endocardial borders were traced in the end-systolic frame of the 2D images from the apical four-

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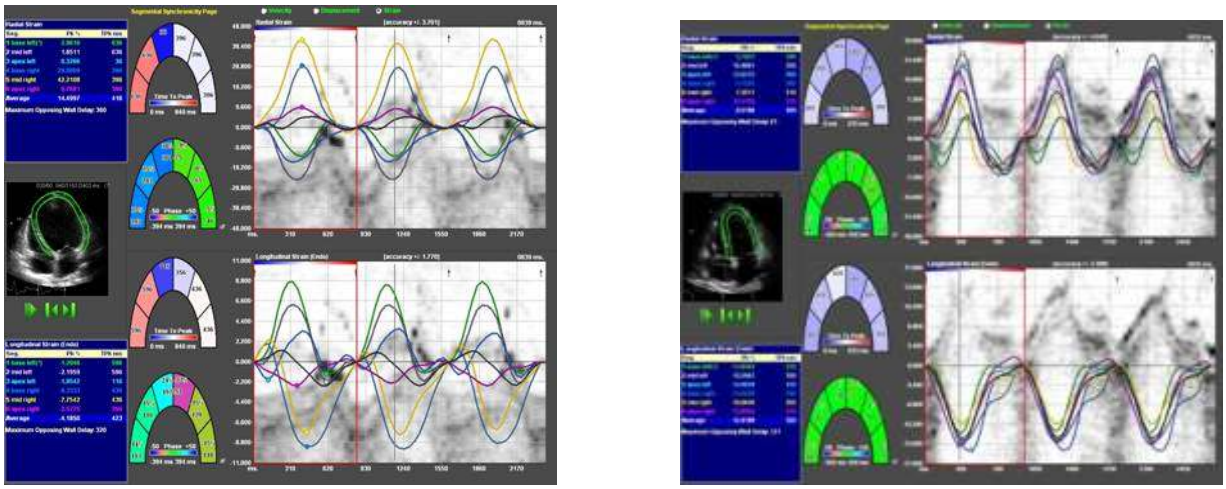
and two-chamber views. Speckles were tracked frame-by-frame using two or more cardiac cycles. Segments if needed were manually adjusted. If we had at least two segments which could not be tracked, the study was excluded from the analysis. Transverse strain is a measure of myocardial thickening (like radial strain from parasternal view) but the nomenclature is different as in this case the apical view is utilized for data analysis (Figure 5 a, b).

**Figure 5.** Assessment of LV dyssynchrony before and after CRT implantation. This Figure is showing two-dimensional speckle-tracking imaging from the apical four-chamber view before (A) and after CRT-D implantation (B). Upper curves represent transverse strain and left ventricular dyssynchrony was measured by assessing the standard deviation of time-to-peak transverse strain. Panel A represents heterogeneous LV activation and significant LV dyssynchrony before CRT implantation, while Panel B shows synchronized LV activation after CRT implantation in the same patient.

A. B.



Tracings in each view were performed by a single investigator blinded to treatment assignment, clinical/demographical data and clinical outcomes. LV mechanical dyssynchrony

was determined as the standard deviation of regional time-to-peak transverse strain, measured during systole in the 12 anatomic wall segments of the ventricle from the apical 4- and 2-chamber views (septum, lateral, anterior and inferior walls; all of them subdivided into basal, mid and apical segments). The intra- and inter-observer variability for LV dyssynchrony was 13.8% and 15.4% for time-to-peak transverse strain, respectively as reported elsewhere.[66, 67]

#### 3.3.2.2 Study Population

One-thousand seventy-seven patients had digital echocardiograms of sufficient image quality to allow for 2D speckle tracking analysis,[66] after excluding 607 patients with non-DICOM images and 136 patients with poor image quality. Therefore, we analyzed 764 patients (42%) with LBBB and 312 (17%) patients with non-LBBB at baseline. One patient whose ECG pattern was unknown was excluded from the analysis.

Paired echocardiograms from baseline and at 12 months eligible for 2D speckle-tracking were available in 761 of 1077 patients. 361 patients had either poor image quality or their CRT device OFF at the time of the echocardiographic analysis. Out of the 761 patients with paired echocardiograms, 288 patients received ICD device, 473 patients received CRT-D. Patients who needed a cross-over to ICD therapy (n=45) were excluded from this analysis. Those patients with CRT-D had either LBBB ECG pattern (n=303) or non-LBBB ECG pattern (n=125).

#### 3.3.2.3 Device Programming, Patient Follow-up, Device interrogation

Device programming, patient follow-up, device interrogation was identical as reported in the section of Left Ventricular Dyssynchrony and the Risk of Ventricular Tachyarrhythmias, Device Programming (3.3.1.3. and 3.3.1.4.).

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#### 3.3.2.4 Definitions and Study End Points

The relationship between baseline LV dyssynchrony and study end points was analyzed in the total patient population with LV dyssynchrony data regardless of treatment assignment, split up by LBBB and non-LBBB ECG pattern, as significant differences were demonstrated earlier in clinical outcome and ventricular arrhythmia rate in these patient subgroups.[68] Patients were divided into quartiles of baseline LV dyssynchrony as suggested earlier.[67]

The change in LV dyssynchrony was analyzed in CRT-D patients only, since ICD patients did not show improvement in LV dyssynchrony.[66] Again, LBBB and non-LBBB patients were analyzed separately. The change of dyssynchrony was calculated as the difference between LV dyssynchrony from baseline to the 12-month recording. CRT-D patients were categorized into 2 groups based on the change, improving or unchanged/worsening LV dyssynchrony. Improving LV dyssynchrony was defined as negative change, decrease in LV dyssynchrony, while unchanged/worsening dyssynchrony included no change (difference=0) and any positive change indicating more LV dyssynchrony. We also evaluated the effects of LV dyssynchrony improvement at one-year using 5% or 15% LV dyssynchrony percent change cut-offs.

Arrhythmia episodes were defined as descrived in the Left Ventricular Lead Location analysis, in the section of End points.

The end point of the baseline analysis was the first episode of VT/VF or death and first VT/VF events. When analyzing the effects of LV dyssynchrony change at the 12-month follow-up, first VT/VF events after one-year assessment or death and first VT/VF after one-year were considered as end points, excluding 25 LBBB patients who had VT/VF or death in the first year.

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## 3.4 New indications of CRT

### 3.4.1 *Chronic Right Ventricular Apical Pacing*

#### 3.4.1.1 Patient Population

From December 2001 to September 2011, 198 consecutive patients had undergone CRT upgrade procedure at the Semmelweis University Heart Center, Budapest. Patients met the guideline criteria for CRT, New York Heart Association (NYHA) class II, III or IV, QRS ≥ 120 ms, LVEF ≤ 35% and optimal medical treatment including beta-blocker, ACE-inhibitor or ARB therapy, diuretics and aldosterone antagonist, unless contraindicated or not tolerated by the patient. Optimization of the medical therapy was performed according to current guidelines.[61] All patients gave written informed consent before the procedure.

#### 3.4.1.2 Pre-, Post-implant Assessment

Pre- and post-implant assessment was performed as explained in section 3.1.1.2. and 3.1.1.4.

#### 3.4.1.3 Device Implantation

Implantation of CRT devices was performed using transvenous, epicardial or transseptal approach. Patients with single chamber devices (PM or ICD) were implanted right atrial lead and LV lead, while patients with dual-chamber devices received LV lead only. Patients with chronic atrial fibrillation have not received right atrial lead. During the implantation procedure, after cannulation of the coronary sinus, balloon catheter was used to perform coronary sinus venogram and to identify the target vein, preferably lateral or postero-lateral vein for CRT therapy. Left ventricular pacing, LV sensing, LV impedance were measured and phrenic nerve stimulation was

tested during the implantation procedure. Commercially available LV leads and CRT devices were used. If the patient received CRT device with ICD capabilities, VF testing was performed at implantation to provide a safety margin of at least 10 J.

#### 3.4.1.4 Study End Points

The primary end point of the present analysis was all-cause mortality. Secondary endpoints included improvement in NYHA functional class, in left ventricular ejection fraction (LVEF) and in quality of life assessed by EQ-5D questionnaires. Mortality data were collected from medical records, patient follow-ups, and using the mortality database of the Hungarian National Health Fund.

### 3.4.2 *Cardiac Resynchronization Therapy in Patients with Less Severe Ventricular Dysfunction*

#### 3.4.2.1 Study Population

The design, protocol and results of the MADIT-CRT study have been described previously.[11, 65]

This analysis included all patients enrolled in MADIT-CRT. Patients were excluded if baseline LVEF measurement was not available due to missing images or poor quality of echocardiographic images. Accordingly, the present study sample comprised 1809 of the 1820 patients enrolled in MADIT-CRT (99%) patients; of whom 1074 (60%) were randomized to CRT-D therapy. The baseline analysis was performed on an intention-to-treat basis.

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#### 3.4.2.2 Data Acquisition and Patient Follow-Up

The MADIT-CRT trial was carried out from December 22, 2004 through June 22, 2009. After the device implantation, patients had an ambulatory follow-up at one-month and every three months thereafter until the termination of the trial. The mean follow-up of the enrolled patients was 29.4 months. All patients had clinical evaluation at each follow up visit or at any meaningful clinical event.

#### 3.4.2.3 Echocardiographic Methods

Left ventricular (LV) volumes were measured by Simpson's disk method in the apical 4- and 2-chamber views and LVEF was calculated according to the established American Society of Echocardiography protocols.[62] The coefficients of variation for end-diastolic volume, end-systolic volume and LVEF were 5.2%, 6.2%, and 5.5%, respectively, as reported previously.[18]

#### 3.4.2.4 Definitions and End Points

Patients with baseline LVEF measurements were divided into three pre-specified groups based on the echocardiography core laboratory assessment, LVEF $\leq$ 25%, LVEF 26-30% (classical criterion) and LVEF > 30% (beyond the eligibility criteria).

The primary endpoint of the current study was the first occurrence of a heart failure episode or death from any cause. The diagnosis of heart failure was made by physicians un-blinded to treatment assignment, if patients were exhibiting signs and symptoms consistent with congestive HF that resulted in intravenous decongestive treatment in an outpatient setting or augmented decongestive therapy with oral or parenteral medications during an in-hospital stay. Adjudication of the end points was carried out by an independent mortality committee and by a

heart-failure committee unaware of treatment assignments, according to pre-specified criteria, as described previously.[65]

When analyzing the echocardiographic response to CRT, we evaluated the left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and left atrial volume (LAV) percent changes at the 12-month follow-up in all three LVEF groups.

The left ventricular remodeling effect of CRT-D was defined as percent reduction in LVEDV between enrollment and 1-year echocardiogram, calculated as the difference between 1-year and baseline LVEDV, divided by baseline LVEDV. The left atrial remodeling effect of CRT-D was defined as percent reduction in left atrial volume between enrollment and 1-year echocardiogram, calculated as the difference between 1-year volume and baseline volume, divided by baseline volume.

## 3.5 Statistical Considerations

### 3.5.1 *Current Practice of Cardiac Resynchronization Therapy, Evaluating the effects of CRT-P versus CRT-D in the total patient population: Statistical considerations*

Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Baseline clinical characteristics were compared between the subgroups, stratified by implanted CRT-D or CRT-P and using nonparametric Wilcoxon or Kruskal-Wallis tests for continuous variables and the $\chi^2$ - test for dichotomous variables, as appropriate.

Cumulative probability of survival was determined according to the Kaplan-Meier method in subgroups of CRT-D and CRT-P patients, with comparisons of cumulative event rates by the log-rank test. Multivariate Cox proportional hazards regression analysis was used to

evaluate the effect of implanted CRT-D or CRT-P device on the risk of mortality after adjustment for all relevant clinical covariates showing potential imbalance at baseline.

Adjusted hazards ratios (HR) with their 95% confidence intervals (CI) are reported. A p-value < 0.05 was considered statistically significant. Analyses were carried out with SAS software (version 9.3, SAS institute, Cary, North Carolina).

### 3.5.2 *Refining Implantation Methods: Statistical considerations*

#### 3.5.2.1 Prognostic Significance of Right Ventricular to Left Ventricular Interlead Sensed Electrical Delay in CRT Patients

Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Baseline clinical characteristics were compared between the subgroups, stratified by median interlead sensed electrical delay (106.5 ms) and using nonparametric Wilcoxon or Kruskal-Wallis tests for continuous variables and the $\chi^2$ - test for dichotomous variables, as appropriate.

Cumulative probability of survival was determined according to the Kaplan-Meier method in subgroups of low vs. high interlead sensed electrical delay, with comparisons of cumulative event rates by the log-rank test. Multivariate Cox proportional hazards regression analysis was used to evaluate the effect of interlead sensed electrical delay on mortality after adjustment for relevant clinical covariates at baseline.

Adjusted hazards ratio (HR) with 95% confidence intervals (CI) is reported. A p-value < 0.05 was considered statistically significant. Analyses were carried out with SAS software (version 9.3, SAS institute, Cary, North Carolina).

#### 3.5.2.2 Electroanatomical Mapping-Guided Transseptal Endocardial Left Ventricular Lead Implantation

Data are presented as mean ± standard deviation. Changes in the LV pacing threshold, LV pacing impedance at implantation and at last patient visit were analyzed using paired t-test. NYHA functional class and mitral regurgitation were analyzed using the Wilcoxon's signed rank test, as appropriate. Statistical significance was considered at $p<0.05$. Statistical analyses were performed using GraphPad Prism software (GraphPad Software Inc., La Jolla, CA, USA).

### 3.5.3 *Left Ventricular Lead Location and the Risk of Ventricular Tachyarrhythmias: Statistical considerations*

Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Baseline clinical characteristics were compared between the pre-specified subgroups, stratified by implanted device and LV lead position, using nonparametric Wilcoxon or Kruskal-Wallis tests for continuous variables and $\chi^2$ - test for dichotomous variables, as appropriate. Baseline, 12-month and change in LV dyssynchrony were evaluated among the subgroups using the Kruskal-Wallis test.

Cumulative probability of first VT/VF or death episodes was displayed according to the Kaplan-Meier method, with comparisons of cumulative event rates by the log-rank test. Multivariate Cox proportional hazards regression analysis was used to identify and evaluate the impact of LV lead location on the end point of first VT/VF or death, whichever occurred first. The Cox model was adjusted for the following covariates: female gender, etiology of cardiomyopathy, left ventricular ejection fraction, apical LV lead location, QRS duration and morphology (left bundle branch block - LBBB and right bundle branch block - RBBB). Crude event rates were reported as counts of events. As these are composite descriptive measures of

risk, ignoring risk variation across patients, no statistical analyses were done.

Propensity analysis was additionally performed to evaluate the robustness of our findings. The propensity score was developed using logistic regression, which showed RBBB, LVEF and BUN to be statistically significant predictors of lead position.

Adjusted hazards ratios (HR) with their 95% confidence intervals (CI) are reported. A p-value of <0.05 was considered statistically significant and all statistical tests were two-sided. Analyses were conducted with SAS software (version 9.2, SAS institute, Cary, North Carolina).

### 3.5.4 *Left Ventricular Dyssynchrony and the Risk of Ventricular Tachyarrhythmias: Statistical considerations*

Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Baseline clinical characteristics were compared between pre-specified non-LBBB and LBBB subgroups, stratified by baseline LV dyssynchrony quartiles or by changes over one-year in LV dyssynchrony, using nonparametric Wilcoxon or Kruskal-Wallis tests for continuous variables and Chi squarred test or Fisher test for dichotomous variables, as appropriate. When analyzing the effects of LV dyssynchrony change, only first VT/VF events after the 12-month visit were considered as end points.

The correlation of baseline LV dyssynchrony and baseline QRS duration was analyzed using Pearson's correlation method. Paired comparisons of baseline LV dyssynchrony and change in LV dyssynchrony at 12-months in LBBB and non-LBBB patients were analyzed using nonparametric Wilcoxon test.

Cumulative probability of first VT/VF/Death and VT/VF episodes was determined according to the Kaplan-Meier method with comparisons of cumulative event rates by the log-rank test in non-LBBB and LBBB patients separate. Multivariate Cox proportional hazards

regression analysis was used to identify and evaluate the impact of LV dyssynchrony on the end point of first VT/VF or death and on VT/VF events. The Cox model was adjusted for the variables showing potential imbalances in clinical characteristics in non-LBBB and LBBB patients. Interaction p-values for LBBB, non-LBBB are reported. Adjusted hazards ratios (HR) with their 95% confidence intervals (CI) are reported. All statistical tests were two-sided, a p-value of <0.05 was considered statistically significant.

### 3.5.5 *Chronic Right Ventricular Apical Pacing: Statistical considerations*

Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Baseline clinical characteristics were compared between the subgroups, stratified by first implanted device of either PM or ICD and using nonparametric Wilcoxon or Kruskal-Wallis tests for continuous variables and the $\chi^2$ - test for dichotomous variables, as appropriate.

Cumulative probability of survival was determined according to the Kaplan-Meier method in subgroups of ICD and PM patients, with comparisons of cumulative event rates by the log-rank test. Multivariate Cox proportional hazards regression analysis was used to evaluate the effect of first implanted device on risk of mortality after adjustment for all relevant clinical covariates showing potential imbalance at baseline.

Multivariate regression analysis was performed to identify predictors of mortality in the total patient population and in patients stratified by the first implanted device of PM or ICD.

Adjusted hazards ratios (HR) with their 95% confidence intervals (CI) are reported. A p-value < 0.05 was considered statistically significant. Analyses were carried out with SAS software (version 9.3, SAS institute, Cary, North Carolina).

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### 3.5.6 *Cardiac Resynchronization Therapy in Patients with Less Severe Ventricular Dysfunction: Statistical considerations*

Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Baseline clinical characteristics were compared between the pre-specified subgroups stratified by baseline LVEF, using Kruskal-Wallis test for continuous variables and $\chi^2$ - test or Fisher exact test for dichotomous variables, as appropriate. The correlation of LVEF identified by the centers and measured by the echocardiography core laboratory was analyzed using the Spearman's rank correlation method.

Cumulative probability of first HF or death episodes by baseline LVEF and by treatment arm within each LVEF group was displayed according to the Kaplan-Meier method, with comparisons of cumulative event rates by the log-rank test. Multivariate Cox proportional hazards regression analysis was used to identify and evaluate the impact of LVEF groups on the endpoint of HF or death. The Cox model was adjusted for relevant clinical covariates using best subset regression modeling.

All statistical tests were two-sided, a p-value of $<0.05$ was considered statistically significant. Analyses were carried out with SAS software (version 9.2, SAS institute, Cary, North Carolina).

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# 4 Results

## 4.1 Current Practice of Cardiac Resynchronization Therapy

### 4.1.1 *Evaluating the Effects of CRT-P versus CRT-D in a CRT Registry*

#### 4.1.1.1 Baseline Clinical Characteristics

The most relevant baseline clinical characteristics, stratified by the implanted device are listed in Table 2. During 10 years, 693 CRT-P (62%) and 429 CRT-D (38%) devices were implanted. The mean age of the patients was 65±10.7 years (262 female).

**Table 2.** Baseline clinical characteristics of CRT-D and CRT-P patients

| **Clinical parameters** | **CRT-D Patients** | **CRT-P Patients** |
|---|---|---|
| | **n= 429** | **n= 693** |
| Age at enrollment (years) | 63.9±10.9 | 66.3±10.5* |
| Female | 68 (16) | 194 (29)* |
| Ischemic etiology | 220 (51) | 235 (34)* |
| QRS (ms) | 158.2±27.1 | 165.5±27.8* |
| Diabetes Mellitus | 134 (31) | 241 (35) |
| Hypertension | 277 (65) | 427 (62) |
| Prior MI | 230 (54) | 227 (33)* |
| Prior PCI | 124 (29) | 132 (19)* |
| Prior CABG | 88 (21) | 66 (10)* |
| Paroxysmal atrial fibrillation | 69 (16) | 94 (14) |
| Permanent atrial fibrillation | 96 (22) | 192 (28)* |
| Ventricular arrhythmia in the past | 212 (23) | 41 (6)* |
| Creatinine (μmol/L) | 114.2 ± 43.6 | 117.1 ± 53.3 |
| Urea (mM/L) | 9.8 ± 5.1 | 10.3 ± 6.4 |

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| **Medications** | | |
|---|---|---|
| Beta-blockers | 376 (88) | 582 (84) |
| ACEI/ ARB | 367 (86) | 583 (84) |
| Diuretics | 328 (77) | 522 (75) |
| Aldosterone antagonist | 259 (61) | 368 (53)* |
| Amiodarone | 180 (42) | 139 (20)* |
| **Echocardiography** | | |
| LVEF, % | 27.6 ± 6.4 | 28.2 ± 7.4 |
| LVEDD, mm | 65.5 ± 9.8 | 64.2 ± 9.8 |
| LVESD, mm | 55.0 ± 10.1 | 53.6 ± 10.5 |

$p < 0.05$ for comparison between CRT-D and CRT-P patients. Values are given as percent of patients or mean ± SD. CABG = Coronary Artery Bypass Graft; MI = myocardial infarction; PCI = Percutaneous Coronary Intervention; ACEI= ACE-inhibitor; ARB = Angiotensin receptor blocker; LVEF = Left Ventricular Ejection Fraction; LVESD = Left Ventricular End-Systolic Diameter; LVEDD = Left Ventricular End-Diastolic Diameter.

Patients with an implanted CRT-P were significantly older, more often females and had less frequently ischemic cardiomyopathy as compared to CRT-D patients. Accordingly, prior MI, prior PCI and prior CABG were less prevalent in CRT-P patients. Patients with CRT-P had more often permanent atrial fibrillation and significantly wider QRS complexes as compared to CRT-D patients (165.5 ± 27.8 ms vs. 158.2 ± 27.1 ms, $p<0.001$). Renal function at baseline was similar in both groups. CRT-D patients were more often prescribed aldosterone antagonist drugs. Baseline LVEF, LV end-diastolic and end-systolic diameters were similar at baseline, with trend towards greater end-diastolic diameter in CRT-D patients ($p= 0.06$).

#### 4.1.1.2 Device Implantation

CRT implantation procedure was performed using transvenous (n= 1094, 97.5%), epicardial (n= 17, 1.5%) or transseptal (n=11, 1%) approach. LV leads were implanted in the lateral or postero-

lateral side-branch of the coronary sinus in 630 CRT-P patients (91%) and in 395 CRT-D patients (91%), and in the anterior position in 48 CRT-P patients (7%) and 21 CRT-D patients (5%). Epicardial LV lead placement was performed in 10 CRT-P and 7 CRT-D patients, and transseptal approach was used in 5 CRT-P and 6 CRT-D patients after unsuccessful transvenous LV lead implantation.

During the implantation, LV pacing, sensing parameters and LV impedance were within normal range. Patients did not manifest phrenic nerve stimulation. Device defibrillation threshold testing was successful in all patients.

Implantation of a CRT-D or CRT-P device resulted in immediate reduction in QRS duration in both patient groups, with more pronounced decrease in the CRT-P group (CRT-D -26.6 ± 25.3 ms vs. CRT-P -36.0 ± 26.9 ms, $p<0.001$).

#### 4.1.1.3 Response to CRT

*Clinical response*

Implantation of a CRT device was associated with significant, similar improvement of NYHA functional class in both patient groups (CRT-D -0.86 ± 0.82 vs. CRT-P -0.74 ± 0.81, $p = 0.168$).

Echocardiographic response

After CRT implantation, significant, similar improvement of left ventricular ejection fraction was observed in both patient groups (CRT-P 6.9 ± 10.3 vs. CRT-D 6.3 ± 19.3 %; $p=0.49$). Left ventricular end-diastolic and end-systolic diameters significantly decreased in CRT-P and CRT-D patients (EDD mean decrease CRT-P -2.0 ± 9.8 mm vs. -0.4 mm ± 10.2 mm, $p=0.08$; ESD CRT-P -2.5 ± 10.2 vs. CRT-D -0.8 ± 11.7 mm, $p=0.08$), as evidence of left ventricular reverse

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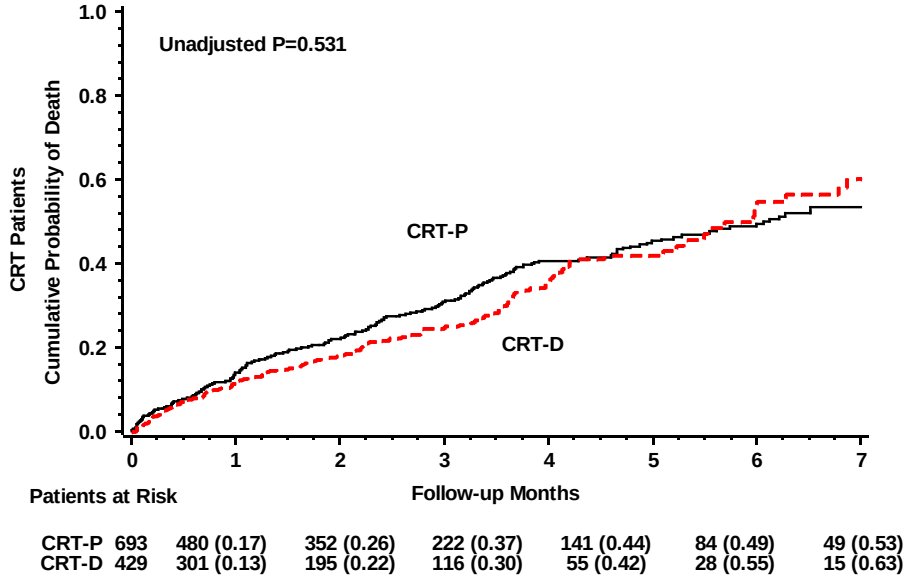
remodeling. There was a trend towards greater decrease in left ventricular end-diastolic and end-systolic diameters in patients with implanted CRT-P (p = 0.08).

*Survival response*

During the median follow-up of 28 months (IQR: 12-47), 378 (34%) patients died of any cause, 249 patients (36%) in the CRT-P arm and 129 patients (30%) in the CRT-D arm. The 5-year cumulative survival was 56% in the total patient population (data not shown). Kaplan-Meier cumulative probability of death from any cause stratified by the implanted device is shown in Figure 6. There was no significant difference in the outcome among CRT-P or CRT-D patients (Kaplan-Meier 7-year cumulative event rate of CRT-P 63% vs. CRT-D 53%, p log-rank = 0.531).

**Figure 6.** Cumulative probability of all-cause mortality in patients with implanted CRT-P or CRT-D.



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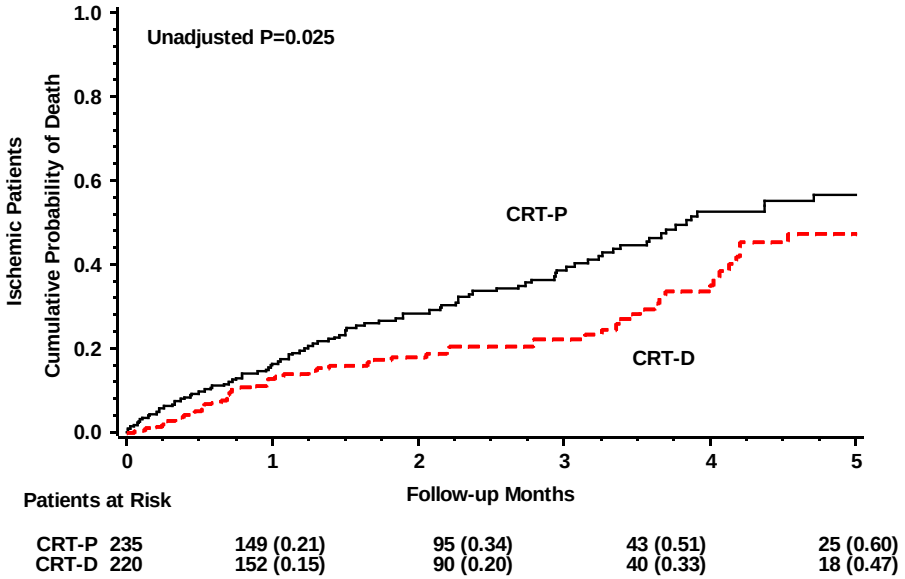
Multivariate analysis after adjustment for ischemic etiology of cardiomyopathy, baseline LVEF and baseline urea showed consistent result to the univariate Kaplan-Meier model (CRT-D HR=0.78, 95 % CI: 0.57 - 1.06, p = 0.11). Patients with implanted CRT-D and CRT-P gained similar mortality benefit in this patient cohort.

In patients with ischemic cardiomyopathy, CRT-D treatment was associated with significant, 35% risk reduction in all-cause mortality as compared to patients with implanted CRT-P (HR=0.65, 95 % CI: 0.44 - 0.95, p = 0.03, interaction p-value= 0.11) (Figure 7). In a second model forcing known predictors of mortality, age and gender in the model, the results were consistent (HR=0.61, 95 % CI: 0.41 - 0.91, p = 0.02, interaction p-value= 0.14).

**Figure 7.** Cumulative probability of all-cause mortality in ischemic cardiomyopathy patients with implanted CRT-P or CRT-D.



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## 4.2 Refining Implantation Methods

### 4.2.1 *Prognostic Significance of Right Ventricular to Left Ventricular Interlead Sensed Electrical Delay in CRT Patients*

#### 4.2.1.1 Baseline Clinical Characteristics

From the total patient cohort of the CRT registry, 494 patients (44%) had right to left ventricular interlead sensed electrical delay measurements during the device implantation. The most important baseline clinical characteristics, stratified by the median right to left ventricular interlead sensed electrical delay (106.5 ms) are listed in Table 3.

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**Table 3.** Baseline clinical characteristics of CRT patients stratified by right to left ventricular interlead sensed electrical delay.

| **Clinical parameters** | **IVD ≤ 106.5 ms** | **IVD > 106.5 ms** |
|---|---|---|
| | **n= 247** | **n= 247** |
| Age at enrollment (years) | 66.9±10.0 | 65.2±10.9* |
| Female | 52 (21) | 62 (25) |
| Ischemic etiology | 108 (44) | 105 (43) |
| QRS (ms) | 154.4±23.9 | 166.2±25.5* |
| Diabetes Mellitus | 91 (37) | 79 (32) |
| Hypertension | 165 (67) | 159 (64) |
| Prior MI | 110 (45) | 97 (39) |
| Prior CABG | 37 (15) | 39 (16) |
| Paroxysmal atrial fibrillation | 36 (15) | 39 (16) |
| Permanent atrial fibrillation | 73 (30) | 60 (25)* |
| Ventricular arrhythmia in the past | 56 (23) | 56 (23) |
| **Medications** | | |
| Beta-blockers | 217 (88) | 220 (89) |
| ACEI/ ARB | 219 (89) | 223 (90) |
| Diuretics | 197 (80) | 197 (80) |
| Aldosterone antagonist | 144 (58) | 160 (65) |
| **Echocardiography** | | |
| LVEF, % | 28.1 ± 7.5 | 27.7 ± 6.8 |
| LVEDD, mm | 64.3 ± 10.0 | 65.8 ± 10.3 |
| LVESD, mm | 53.6 ± 10.6 | 55.5 ± 10.6* |

$p < 0.05$ for comparison between CRT-D and CRT-P patients

Values are given as percent of patients or mean ± SD. CABG = Coronary Artery Bypass Graft; MI = myocardial infarction; PCI = Percutaneous Coronary Intervention; ACEI= ACE-inhibitor; ARB = Angiotensin receptor blocker; LVEF = Left Ventricular Ejection Fraction; LVESD = Left Ventricular End-Systolic Diameter; LVEDD = Left Ventricular End-Diastolic Diameter.

Patients with right to left ventricular interlead sensed electrical delay greater than 106.5

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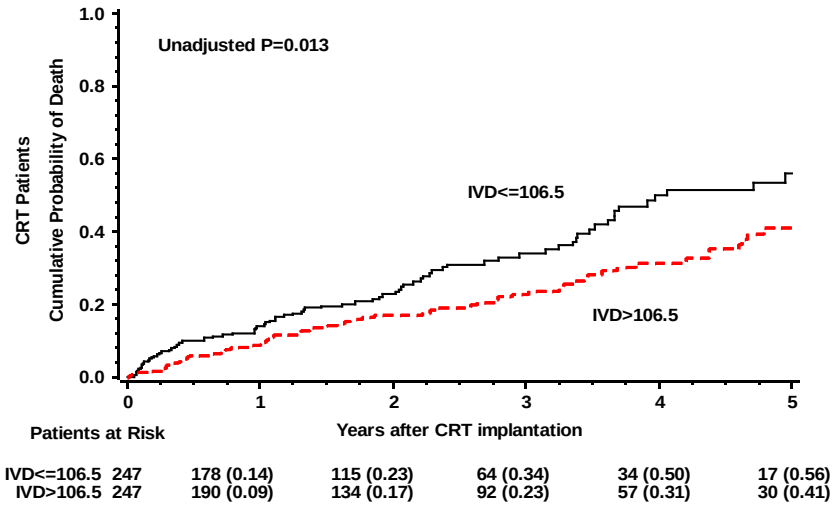
ms were younger, had longer QRS duration at baseline, less often atrial fibrillation and significantly larger left ventricular end-systolic diameter.

#### 4.2.1.2 Survival Response to CRT

During the median follow-up of 24 months (IQR: 12-42), 145 (29%) patients died of any cause, 80 patients (16%) with right to left ventricular interlead sensed electrical delay lower than 106.5 ms and 65 patients (13%) with right to left ventricular interlead sensed electrical delay greater than 106.5 ms. Kaplan-Meier cumulative probability of all-cause mortality stratified by right to left ventricular interlead sensed electrical delay is shown in Figure 8. CRT patients with right to left ventricular interlead sensed electrical delay lower than 106.5 ms had a 5-year cumulative mortality of 56% as compared to patients with right to left ventricular interlead sensed electrical delay greater than 106.5 ms who had a 41% 5-year cumulative mortality rate (p log-rank = 0.013).

**Figure 8.** Cumulative probability of all-cause mortality in CRT patients stratified by right to left ventricular interlead sensed electrical delay.



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In the multivariate model, after adjustment for age, female gender, left ventricular ejection fraction at baseline, ischemic etiology of cardiomyopathy, QRS duration at baseline, left ventricular end-systolic diameter at baseline, and permanent atrial fibrillation, right to left ventricular interlead sensed delay of greater than 106.5 ms was associated with significant, 48% risk reduction in all-cause mortality (95% CI: 0.31-0.88, p= 0.01).

### 4.2.2 *Electroanatomical Mapping-Guided Transseptal Endocardial LV Lead Implantation*

Pre-implant echocardiography and tissue Doppler imaging showed severely depressed left ventricular function and dyssynchronous activation pattern with a significant delay of the lateral (n=3) and the posterolateral wall (n=1). Mitral regurgitation was evaluated by color Doppler imaging using a semi-quantitative method (grade I-IV).

LV endocardial leads were successfully implanted in all patients. CRT pacemaker was implanted in one patient (Stratos LV-T, Biotronik GmbH&Co, Berlin, Germany), while three patients received CRT-D devices (Cognis, Boston Scientific, Miami, FL, USA, n=1; Concerto, Medtronic, Minneapolis, MN, USA n=1; Atlas HF, St Jude, Sylmar, CA, USA, n=1). The atrial lead was implanted in the right atrial appendage in all patients, the right ventricular lead was positioned in the right ventricular septum (Figure 9 a, b).

**Figure 9 a, b.** Patient 4. Typical final lead positions in a. RAO projection and b. LAO projection. RA- right atrial lead is positioned in the right atrial appendage, RV- right ventricular lead is positioned in the right ventricular apical septum, LV- left ventricular lead is positioned in the mid-basal portion of the lateral wall.

Figure 9 a.

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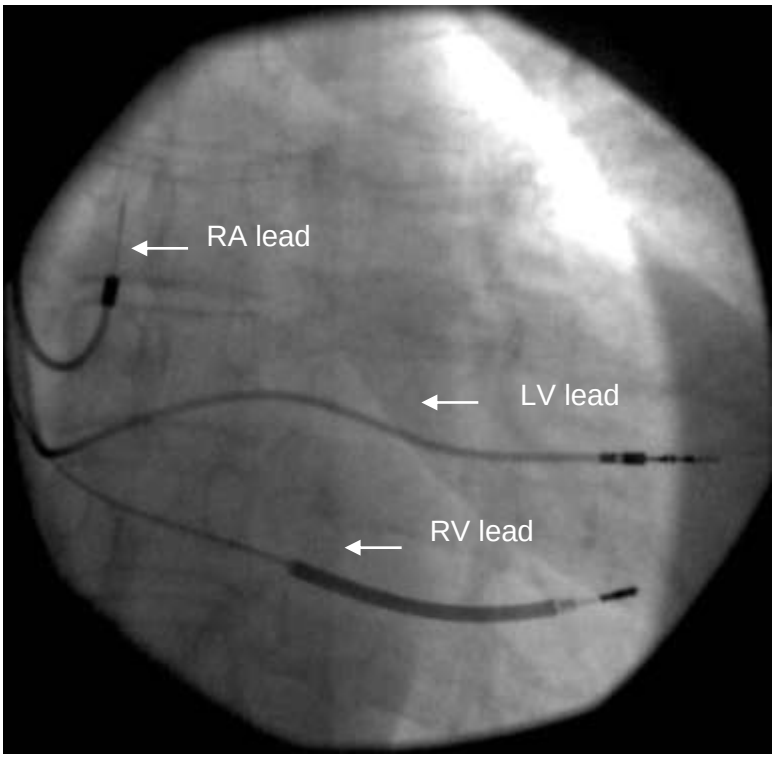
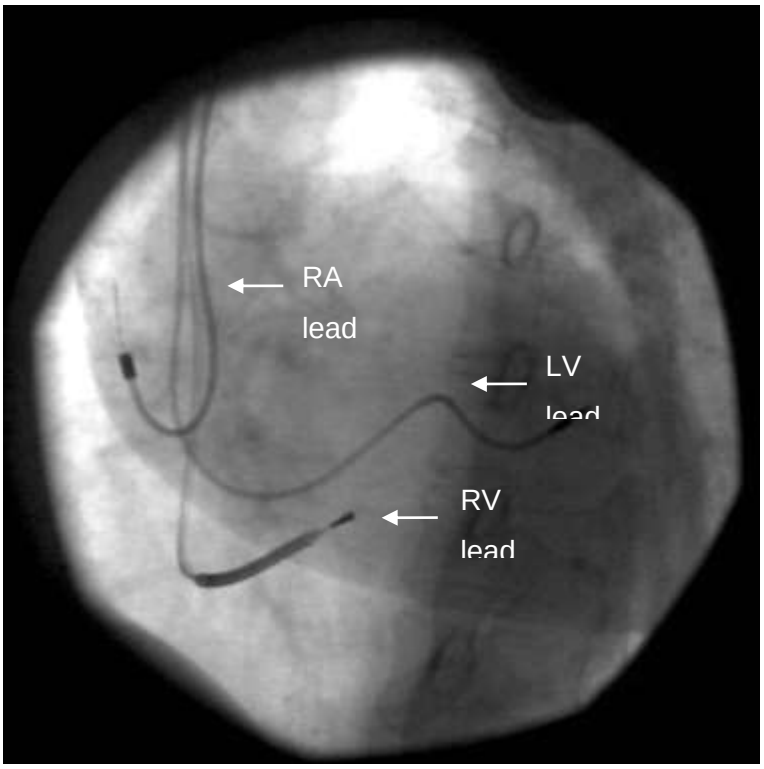



Figure 9 b.



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Electrical parameters during device implantation were as follows: LV signal amplitude 8.5±3.0 mV, LV pacing threshold 0.78±0.18 V, impulse width of 0.5 ms and LV lead impedance 520±177 Ohms. No phrenic nerve stimulation occurred at 10 V; 0.5 ms with rapid LV pacing (100 bpm). The procedure time was 92.5±22.2 minutes. Fluoroscopy time was 16.25±3.8 minutes.

In all patients, the international normalized ratio (INR) was maintained between 3.5-4.5 as for those with mechanical valve prostheses and high thrombotic risk. Neither pericardial fluid nor intracardiac thrombi were observed during echocardiography in the early postoperative period or during follow-up. Neither major hematoma nor post-procedural bleeding occurred. During the mean follow-up of 18.3 months stable sensing and pacing parameters were found. The mean LV pacing threshold was 0.6±0.1 V at impulse width of 0.5 ms ($p=0.44$), LV lead impedance was 439±119 Ohms ($p=0.12$).

We did not observe lead dysfunction, insulation failure or dislocation of the LV lead. There were no signs of lead infection during the follow-up period. Heart failure symptoms improved at least one NYHA class in all patients, left ventricular systolic function improved significantly from a mean LV ejection fraction (LVEF) of 28±5.2% to 41±6.6% ($p=0.015$). The grade of mitral regurgitation did not change significantly during the follow-up period ($p=0.28$) (Table 4). We did not observe residual left-right shunts. No thromboembolic or hemorrhagic events occurred.

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**Table 4.** Patient characteristics and follow-up.

| Pt. No. | Gender | Age (years) | Etiology of cardio-myopathy | QRS (ms) | NYHA functional class | LVEF (%) | Follow-up (months) | NYHA at FU | LV EF (%) FU | MR grade before CRT | MR grade after CRT |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pt 1 | Female | 56 | Non-ischemic | 160 | III | 24 | 27 | II | 38 | IV | IV |
| Pt 2 | Male | 71 | Ischemic | 165 | III | 35 | 21 | I | 44 | III-IV | II-III |
| Pt 3 | Male | 45 | Ischemic | 200 | III-IV | 24 | 12 | II | 33 | II | II-III |
| Pt 4 | Female | 58 | Non-ischemic | 190 | III-IV | 28 | 6 | II | 48 | III-IV | II |

Pt = patient, NYHA = New York Heart functional class, CRT-D = CRT device with an ICD backup, LV = left ventricular, CS = coronary sinus, DDD = dual chamber pacemaker, VVI = single chamber pacemaker, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, FU = follow-up.

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## 4.3 Effects of CRT on Ventricular Arrhythmias

### 4.3.1 *Left Ventricular Lead Location and the Risk of Ventricular Tachyarrhythmias*

LV lead location was evaluated in 797 of 1089 patients (73%). The LV lead was placed in the lateral position in 448 (56%), in the posterior position in 93 (12%), in the anterior position in 146 (18%), and in the apical position in 110 (14%) patients.

Of the 797 CRT-D patients with LV lead assessment, 166 (20.8%) reached the combined end point of VT/VF or death, 133 patients (16.7%) reached the arrhythmia end point of ventricular tachycardia or ventricular fibrillation (VT/VF) episode. Forty-seven patients (5.9%) died during the follow-up: 15 with cardiac pump failure, 7 from sudden death, 2 from acute coronary ischemic event, 19 with non-cardiac death and in 4 patients, the cause of death was indeterminable. Of the seven patients who had sudden death, three had an anterior, three a lateral and one patient a posterior lead position.

#### 4.3.1.1 Relation of Left Ventricular Lead Location and Risk of Ventricular Tachyarrhythmias

During the follow-up, VT/VF episode occurred in 62 patients (13.7%) with the LV lead located in the lateral, in 15 patients (16.1%) in the posterior, in 36 patients (24.6%) in the anterior and in 20 patients (18.2%) in the apical LV lead position (Figure 10).

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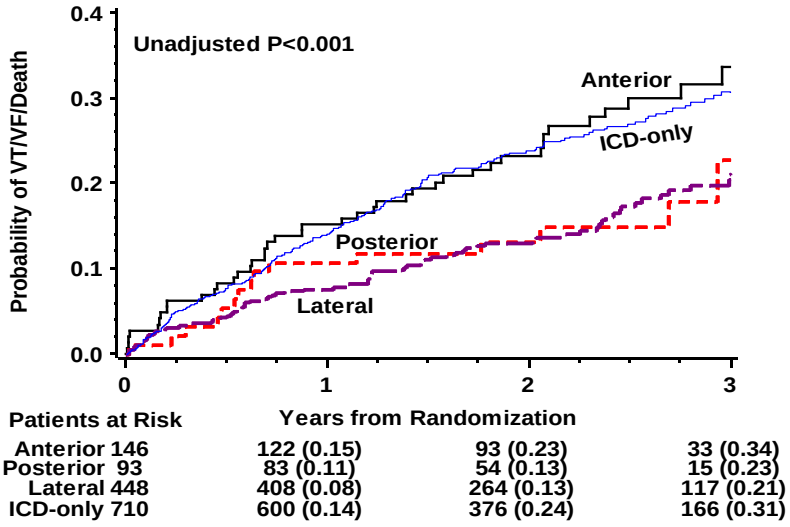
**Figure 10.** Kaplan–Meier Estimates of the Cumulative Probability of VT/VF/Death Episodes by device type and LV lead location




Patients with apical LV lead location had similar incidence of VT/VF as patients with non-apical LV lead position. Therefore, this analysis is mainly focusing on patients with lateral-posterior vs. anterior LV lead location, comparing them to ICD patients as a control group. Patients with anterior LV lead locations had similar frequency of VT/VF/Death (Figure 10) and VT/VF episodes (not shown) as ICD-only treated patients.

Lateral or posterior LV lead location was associated with significantly lower incidence of VT/VF or death (Figure 11a) (p=0.002) or VT/VF alone compared to the anterior lead location (Figure 11b) (p=0.006).

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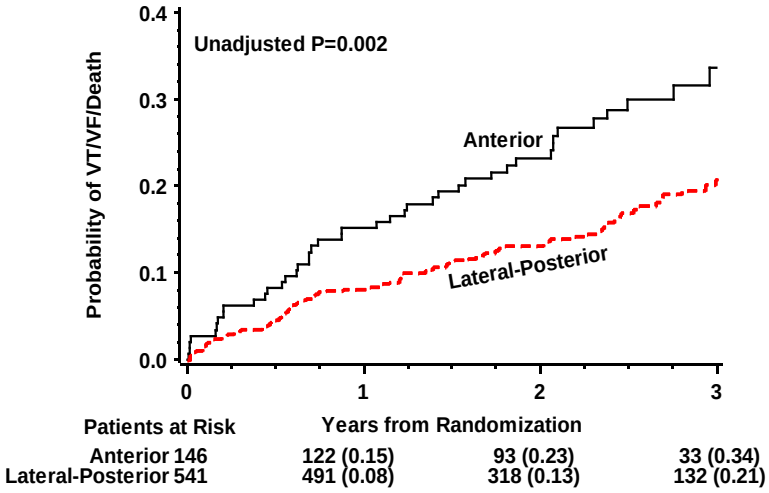
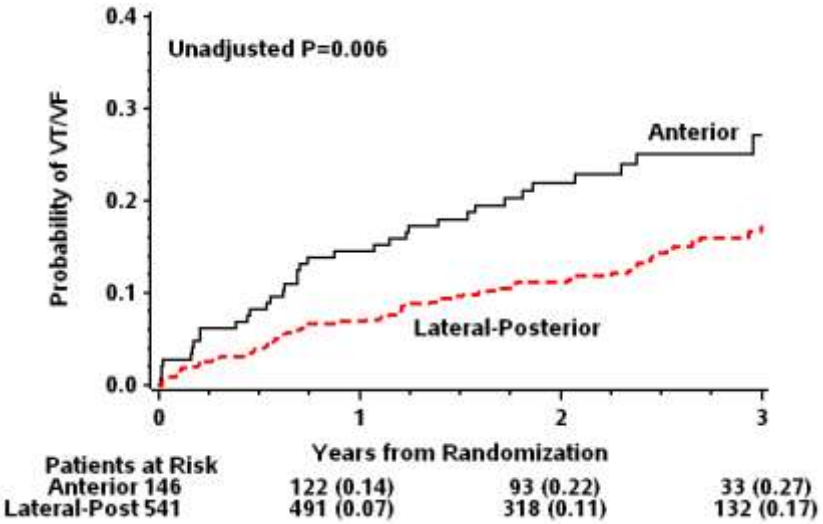
**Figure 11.** Kaplan–Meier Estimates of the Cumulative Probability of a. VT/VF/Death Episodes

b. VT/VF episodes by LV lead location

a.




b.



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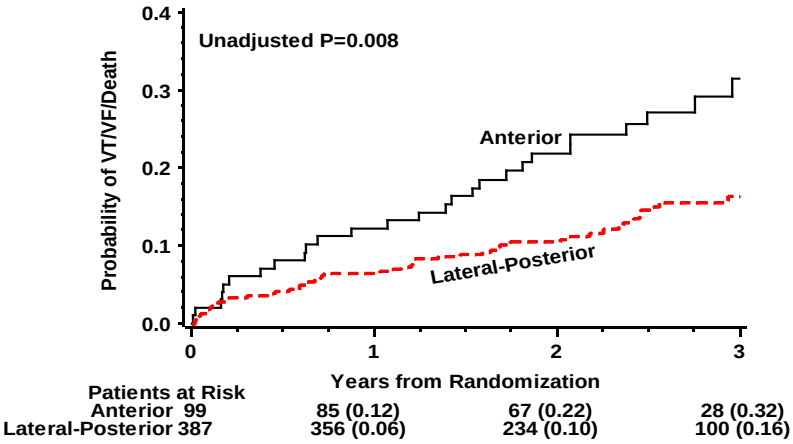
These findings were similar in both ischemic- and non-ischemic cardiomyopathy (data not shown) and also in patients with LBBB ECG pattern (Figure 12).

**Figure 12.** Kaplan–Meier Estimates of the Cumulative Probability of VT/VF/Death Episodes in LBBB patients by LV lead location.




In patients with non-LBBB ECG pattern, the effect was similar, but did not reach statistical significance when analyzing cumulative probability of VT/VF/Death (Figure 13) and VT/VF episodes (p=0.101, not shown) with anterior or lateral-posterior LV lead locations.

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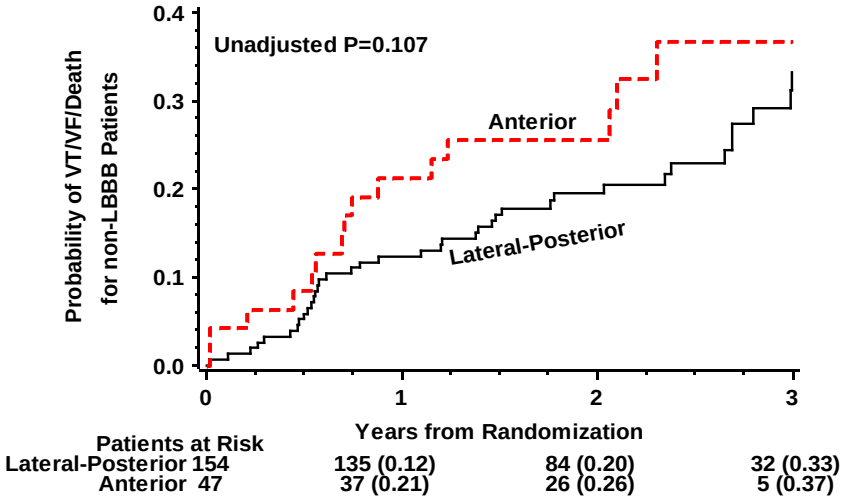
**Figure 13.** Kaplan–Meier Estimates of the Cumulative Probability of VT/VF/Death Episodes in non-LBBB patients by LV lead location.




Rapid ventricular tachyarrhythmic episodes with VT ≥ 200 bpm or VF (rapid VT-VF) or death occurred less often in patients with lateral-posterior LV lead locations (3-year event rate 16%) compared with anterior LV lead locations (3-year event rate 24%, p=0.014) (data not shown). Consistent findings were revealed when analyzing VT/VF episodes requiring shock therapy or death (data not shown).

#### 4.3.1.2 Clinical Characteristics by Device Type and LV Lead Location

The clinical characteristics of patients with anterior (n=146) and lateral-posterior (n=541) lead positions, as well as the cohort with ICD-only therapy (n=710) are shown in Table 5. Patients with a lateral-posterior lead location were less likely to have RBBB-QRS morphology than patients with anterior leads (11% vs. 19%, p=0.006). The frequency of moderate or severe heart

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failure more than three months prior to enrolment, LVEF at enrolment and baseline antiarrhythmic drug treatment were similar in the three groups.

Reverse remodeling with a decrease of left ventricular volumes after one year was similar in patients with lateral-posterior and anterior LV leads. Left ventricular transverse dyssynchrony, measured as the standard deviation of the 12-myocardial segments using speckle tracking imaging in patients with anterior and lateral-posterior LV lead location was similar at baseline (186±68 ms versus 189±61 ms, p=0.589), after 12 months (135±60 ms versus 148±57 ms, p=0.064) or when measuring the change of dyssynchrony after 12 months (-51±86 ms versus -41±75 ms, p=0.481).

**Table 5.** Clinical characteristics of patients with Anterior and Lateral-Posterior LV lead

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locations and ICD only patients

| Clinical Characteristics | Anterior | Lateral-Posterior | ICD |
|---|---|---|---|
| Number of patients | **146** | **541** | **710** |
| Age (years) | 64.8±10.2 | 64.3±10.6 | 64.3±10.6 |
| Females | 36 (25%) | 136 (25%) | 172 (24%) |
| Ischemic NYHA I | 27 (18%) | 72(13%) | 109 (15%) |
| Ischemic NYHA II | 62(42%) | 212(39%) | 281(40%) |
| Non-Ischemic | 57(39%) | 257(48%) | 320(45%) |
| MI prior to enrolment | 73(51%) | 222(41%) * | 302(44%) |
| QRS complex (ms) | 158.8±20.1 | 157.3±19.7 | 158.8±20.2 |
| LBBB | 99 (68%) | 387(72%) | 505(71%) |
| RBBB | 28(19%) | 58(11%) * | 91(13%) † |
| IVCD | 19(13%) | 96(18%) | 113(16%) |
| LVEF prior to enrolment | 24.5±4.9 | 24.0±5.2 | 23.6±5.2 |
| ACE-inhibitors/ ARB | 144(99) | 532(98) | 689(97) |
| Beta blocker | 133(91%) | 508(94%) | 661(93%) |
| Diuretics | 111(76%) | 369(68%) | 478(67%) † |
| Anti-arrhythmic drugs | 12(8) | 47(9) | 55(8) |
| LVESV % change after 1 year | - 31.1±14.3 | - 33.0±15.4 | - 10.1±8.9† |
| LVEDV % change after 1 year | - 19.5±11.1 | - 21.2±11.7 | - 5.9±5.7 † |

Values are given as percent of patients or mean ± SD. * $p<0.05$ for comparison between anterior vs. lateral-posterior LV lead position. † $p<0.05$ for comparison between anterior LV lead location and ICD-only patients. NYHA stands for New York Heart Association class, MI= myocardial infarction, LBBB= left bundle branch block, RBBB= right bundle branch block, IVCD= intraventricular conduction delay, LVEF= left ventricular ejection fraction, LVESV= left ventricular end-systolic volume, LVEDV= left ventricular end-diastolic volume, ACE-inhibitors= Angiotensin converting enzyme inhibitors, ARB= Angiotensin receptor blocker.

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#### 4.3.1.3 Left Ventricular Lead Location and the Risk of VT/VF Events

We assessed the risk of VT/VF/Death, VT/VF events, rapid VT/VF events and death in Cox analysis after adjustment for relevant clinical covariates and compared the combined lateral and posterior LV lead positions with anterior lead locations and with ICD only treatment.

Lateral or posterior lead location was associated with a significantly lower risk of first VT/VF/Death episode only (HR=0.58, p=0.004) and VT/VF (HR=0.57, p=0.006) compared with anterior LV lead location, as well as when compared with ICD-only patients (Table 6). Patients with anterior lead position had a risk of first VT/VF similar to patients with ICD-only (HR=1.04; 95% CI: 0.72 - 1.50; p=0.837). Lateral or posterior LV lead locations were associated with decreased risk of rapid VT/VF (HR=0.53, p=0.018) when compared with anterior LV lead location. Again, no difference of first VT/VF was found in the Cox-model when comparing apical LV lead locations with non-apical locations (HR=1.12, 95% CI: 0.70-1.81; p=0.638).

CRT-D patients with lateral or posterior LV lead location had similar risk of all-cause mortality as patients with an anterior LV lead location. LV lead location did not modify the effects of CRT-D on all-cause mortality. However, patients with lateral or posterior LV lead placement had significantly lower risk of death as compared to patients with ICD-only. When using propensity score analysis, the results regarding the lateral-posterior vs. anterior hazard ratio (HR=0.56, 0.39-0.82, p=0.003) were similar to the original results.

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**Table 6.** Multivariate analysis. Left Ventricular Lead Location and the Risk of Ventricular Arrhythmic Events

| Parameter | Hazard Ratio | 95% CI | p- value |
|---|---|---|---|
| **VT/VF/Death** | | | |
| Lateral-Posterior: Anterior | 0.58 | 0.40 – 0.84 | **0.004** |
| Lateral-Posterior: ICD | 0.60 | 0.47 – 0.76 | **<0.001** |
| Anterior: ICD | 1.02 | 0.73 – 1.43 | 0.889 |
| **VT/VF** | | | |
| Lateral-Posterior: Anterior | 0.57 | 0.38-0.85 | **0.006** |
| Lateral-Posterior: ICD | 0.59 | 0.45-0.77 | **<0.001** |
| Anterior: ICD | 1.04 | 0.72-1.50 | 0.837 |
| **Rapid VT/VF** | | | |
| Lateral-Posterior: Anterior | 0.53 | 0.31 – 0.90 | **0.018** |
| Lateral-Posterior: ICD | 0.53 | 0.37 – 0.76 | **0.001** |
| Anterior: ICD | 1.00 | 0.62 – 1.60 | 0.993 |
| **Death** | | | |
| Lateral-Posterior: Anterior | 0.77 | 0.35 -1.66 | 0.500 |
| Lateral-Posterior: ICD | 0.60 | 0.37 – 0.99 | 0.044 |
| Anterior: ICD | 0.79 | 0.39 – 1.60 | 0.507 |

Model is adjusted for: female, ischemic, QRS≥150ms, LBBB, RBBB, apical LV lead location and LVEF.

#### 4.3.1.4 Recurrent VT/VF Episodes by LV Lead Location

From 133 patients who had previous VT/VF events, 21 (58.3%) patients with anterior, 36 (46.8%) patients with lateral-posterior LV lead location experienced recurrent VT/VF events (defined as ≥ 2 episodes in one patient) during the follow-up.

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### 4.3.2 *Left Ventricular Dyssynchrony and the Risk of Ventricular Tachyarrhythmias*

Of the 1077 patients with sufficient echocardiographic images, in the non-LBBB subgroup (n=312), 32 patients with ICD (27.1%) and 56 patients (28.9%) with CRT-D reached the end point of VT/VF/Death (p=0.74); while in the LBBB subgroup (n=764), 87 patients with ICD (29.3%) and 89 patients (19.1%) with CRT-D had VT/VF or death (p=0.001). During the mean follow-up of 2.3 ± 0.9 years, 188 patients (17.7%) developed VT, 55 (5.2%) experienced VF, 75 patients died (7%), 22 of them (2%) after VT/VF.

#### 4.3.2.1 Baseline Left Ventricular Dyssynchrony

Patients with non-LBBB (n=312) and LBBB (n=764) ECG pattern showed marked heterogeneity of LV dyssynchrony before device implantation irrespective of the QRS duration ($r^2$=0.025, p<0.001). LBBB patients exhibited more significant LV dyssynchrony than non-LBBB patients (186.5 ± 62.1 ms vs. 167.5 ± 74.5 ms, p=0.001).

The most relevant baseline clinical characteristics in LBBB and non-LBBB patients are listed in Table 7.

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**Table 7.** Baseline Characteristics of Patients with LBBB According to Baseline LV Dyssynchrony and in Patients with non-LBBB and LV dyssynchrony data available

| **Quartiles of Baseline LV Dyssynchrony (ms) in LBBB patients** | | | | | | |
|---|---|---|---|---|---|---|
| | ***Less Dyssynchrony*** → | | | ***More Dyssynchrony*** | | |
| | **117 ± 23 (Q1)** | **167 ± 10 (Q2)** | **208 ± 12 (Q3)** | **274 ± 41 (Q4)** | **p-value** | Non-LBBB patients (n=312) |
| | **(n=193)** | **(n=189)** | **(n=195)** | **(n=187)** | | |
| **Age, yrs** | 65.4 ± 11.1 | 63.1 ± 11.6 | 62.8 ± 10.8 | 64.6 ± 11.2 | 0.064 | 65.0 ± 10.6 |
| **Female, n (%)** | 45 (23) | 62 (33) | 60 (31) | 65 (35) | 0.079 | 36 (12) |
| **VT/VF/Death** | 35 (4.6%) | 45 (6%) | 49 (6.5%) | 47 (6.2%) | 0.970 | 88 (29%) |
| **VT/VF** | 24 (3.1%) | 34 (4.5%) | 40 (5.2%) | 39 (5.1%) | 0.659 | 74 (24%) |
| **Death** | 16 (2.1%) | 12 (1.6%) | 12 (1.6%) | 13 (1.7%) | 0.356 | 22 (7%) |
| **Non-ischemic NYHA II, n (%)** | 96 (50) | 103 (54) | 118 (61) | 106 (57) | 0.191 | 52 (17) |
| **Ischemic, n (%)** | 97 (50) | 86 (46) | 77 (39) | 81 (43) | 0.191 | 260 (83) |
| **Prior CABG, n (%)** | 54 (28) | 40 (21) | 36 (18) | 34 (18) | 0.071 | 140 (45) |

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| | **LBBB Q1** | **LBBB Q2** | **LBBB Q3** | **LBBB Q4** | **p-value** | Non-LBBB patients (n=312) |
|---|---|---|---|---|---|---|
| | **(n=193)** | **(n=189)** | **(n=195)** | **(n=187)** | | |
| **Prior non-CABG revasc., n (%)** | 45 (23) | 51 (27) | 30 (15) | 37 (20) | **0.040** | 141(45) |
| **Prior MI, n (%)** | 71 (38) | 59 (32) | 57 (30) | 62 (34) | 0.387 | 221 (72) |
| **Past atrial arrhythmias, n (%)** | 24 (13) | 14 (7) | 17 (9) | 13 (7) | 0.220 | 40 (13) |
| **Past ventricular arrhythmias, n (%)** | 12 (6) | 10 (5) | 12 (6) | 11 (6) | 0.976 | 25 (8) |
| **Creatinine (mg/dL)** | 1.19 ± 0.33 | 1.10 ± 0.30 | 1.13 ± 0.31 | 1.18 ± 0.35 | **0.031** | 1.24 ± 0.47 |
| **QRS (ms)** | 158.6 ± 17.1 | 160.0 ± 18.1 | 163.7 ± 18.7 | 166.0 ± 19.7 | **<0.001** | 144.9 ± 14.0 |
| **Heart rate (bpm)** | 68.6 ± 12.0 | 70.9 ± 12.3 | 68.5 ± 10.7 | 65.3 ± 9.2 | **<0.001** | 66.0 ± 10.8 |
| **LVEF (%)** | 29.5 ± 3.5 | 29.1 ± 3.5 | 28.6 ± 3.3 | 22.1 ± 5.7 | **0.037** | 30.1 ± 3.3 |
| **LVEDV indexed by BSA (mL/cm$^2$)** | 119.1 ± 24.2 | 124.5 ± 29.6 | 129.0 ± 27.7 | 135.0 ± 34.0 | **<0.001** | 117.4 ± 20.9 |
| **LVESV indexed by BSA (mL/cm$^2$)** | 84.4 ± 19.5 | 88.7 ± 24.5 | 92.5 ± 22.2 | 97.2 ± 28.3 | **<0.001** | 82.3 ± 16.4 |
| **LAV indexed by BSA (mL/cm$^2$)** | 46.2 ± 9.7 | 45.1 ± 10.5 | 47.3 ± 9.6 | 48.2 ± 11.7 | **0.017** | 45.2 ± 10.4 |
| **BNP level (pg/mL) (median)** | 55.5 (31; 125) | 55 (23; 131) | 60 (28; 144) | 89 (33.5; 166) | **0.141** | 98 (35; 208) |

Values are given as percent of patients or mean ± SD. NYHA = New York Heart Association; CABG = Coronary Artery Bypass Graft; MI = myocardial infarction; LVEF = Left Ventricular Ejection Fraction; LVESV = Left Ventricular End-Systolic Volume; LVEDV = Left Ventricular End-Diastolic Volume; LAV = left atrial volume.

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LBBB patients with more pronounced LV dyssynchrony had wider QRS complexes and worse echocardiographic parameters; lower left ventricular ejection fraction, higher end-diastolic and end-systolic volumes. Non-LBBB patients had wider QRS-complex and significantly lower heart rate with increasing LV dyssynchrony.

The extent of LV dyssynchrony at baseline represented by quartiles was not predictive of higher incidence of VT/VF/Death or VT/VF in non-LBBB or LBBB patients (Figure 14 a, b).

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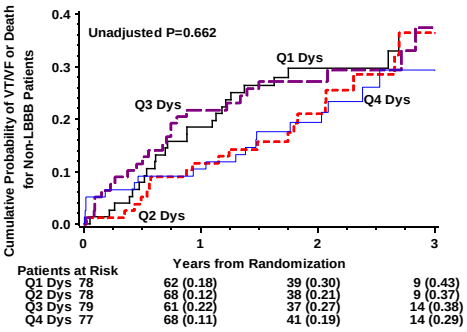
**Figure 14.** Kaplan–Meier Estimates of the Cumulative Probability of VT/VF/Death and VT/VF Episodes by Quartiles of LV Dyssynchrony at Baseline a. non-LBBB Patients, b. LBBB Patients

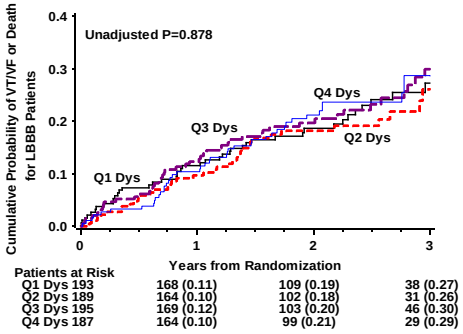
Non-LBBB

VT/VF/Death



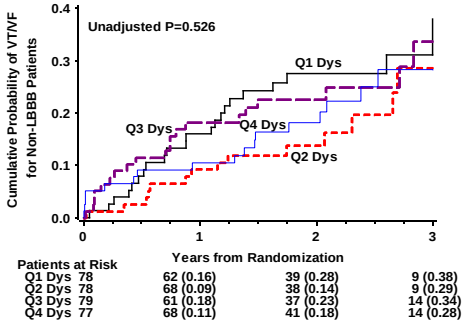

LBBB

VT/VF/Death



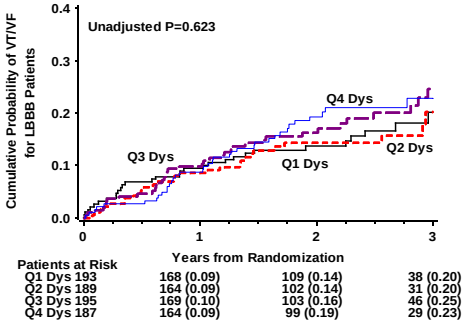

VT/VF

Non-LBBB




VT/VF

LBBB




When assessing in a multivariate model, non-LBBB, LBBB patients with increasing quartiles of baseline dyssynchrony did not show increased risk of VT/VF or death and VT/VF (Table 8a). Consistently to this, baseline dyssynchrony was not predictive of subsequent VT/VF/Death or VT/VF in ICD or CRT-D patients (Table 8b).

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CRT-D treatment did not modify the relationship between LV dyssynchrony and VT/VF/Death (p=0.27) or VT/VF (p=0.47) in the total patient population.

**Table 8.** Baseline LV Dyssynchrony and the Risk of Ventricular Arrhythmic Events in the Total Patient Population, a. Stratified by LBBB ECG pattern, b. Stratified by Treatment

a.

| **Baseline LV Dyssynchrony*** | | | | | | |
|---|---|---|---|---|---|---|
| **End point: VT/VF/Death (n=264)** | | | | | | |
| | **Non-LBBB patients** | | | **LBBB patients** | | |
| **Parameter** | **Hazard ratio** | **95%CI** | **p-value** | **Hazard ratio** | **95%CI** | **p-value** |
| **Baseline Dyssynchrony Q2** | 1.25 | 0.74 – 2.13 | 0.41 | 1.06 | 0.67 – 1.67 | 0.81 |
| **Baseline Dyssynchrony Q3** | 0.82 | 0.43 – 1.56 | 0.54 | 0.93 | 0.59 – 1.45 | 0.75 |
| **Baseline Dyssynchrony Q4** | 0.73 | 0.40 – 1.35 | 0.32 | 1.00 | 0.63 – 1.60 | 0.98 |
| **End point: VT/VF (n=211)** | | | | | | |
| | **Non-LBBB patients** | | | **LBBB patients** | | |
| **Parameter** | **Hazard ratio** | **95%CI** | **p-value** | **Hazard ratio** | **95%CI** | **p-value** |
| **Baseline Dyssynchrony Q2** | 1.04 | 0.57 – 1.90 | 0.90 | 1.21 | 0.70 – 2.06 | 0.50 |
| **Baseline Dyssynchrony Q3** | 0.81 | 0.41 – 1.60 | 0.54 | 1.12 | 0.67 – 1.89 | 0.67 |
| **Baseline Dyssynchrony Q4** | 0.76 | 0.40 – 1.45 | 0.41 | 1.24 | 0.72 – 2.13 | 0.43 |

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b.

| **Baseline LV Dyssynchrony*** | | | | | | |
|---|---|---|---|---|---|---|
| **End point: VT/VF/Death** | | | | | | |
| | **ICD patients** | | | **CRT-D patients** | | |
| **Parameter** | **Hazard ratio** | **95%CI** | **p-value** | **Hazard ratio** | **95%CI** | **p-value** |
| **Baseline Dyssynchrony Q2** | 1.18 | 0.68 – 2.05 | 0.56 | 1.07 | 0.68 – 1.69 | 0.77 |
| **Baseline Dyssynchrony Q3** | 1.25 | 0.73 – 2.16 | 0.42 | 0.65 | 0.39 – 1.07 | 0.09 |
| **Baseline Dyssynchrony Q4** | 0.95 | 0.55 – 1.75 | 0.98 | 0.83 | 0.51 – 1.35 | 0.46 |
| **End point: VT/VF** | | | | | | |
| | **ICD patients** | | | **CRT-D patients** | | |
| **Parameter** | **Hazard ratio** | **95%CI** | **p-value** | **Hazard ratio** | **95%CI** | **p-value** |
| **Baseline Dyssynchrony Q2** | 0.92 | 0.50 – 1.72 | 0.80 | 1.29 | 0.76 – 2.19 | 0.35 |
| **Baseline Dyssynchrony Q3** | 1.27 | 0.71 – 2.28 | 0.42 | 0.74 | 0.42 – 1.32 | 0.30 |
| **Baseline Dyssynchrony Q4** | 0.97 | 0.52 – 1.80 | 0.93 | 1.06 | 0.61 – 1.85 | 0.84 |

Q1 was used as reference group. The model is adjusted for treatment, age at enrollment, ventricular arrhythmia episodes in the past, female gender, QRS duration, left ventricular ejection fraction, previous revascularization, myocardial infarction in the past and LVESV index.

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#### 4.3.2.2 Change in Left Ventricular Dyssynchrony

At 12-month follow-up, CRT-D patients with LBBB (n=303) showed significant decrease in LV dyssynchrony as compared with baseline (134.7 ± 61.0 ms vs. 191.3 ± 63.0 ms, respectively, $p<0.001$). CRT-D patients with LBBB exhibited a greater decrease of LV dyssynchrony when compared to CRT-D patients with non-LBBB (n=125) (-56.5 ± 81.1 ms vs. -27.1 ± 85.0 ms, $p=0.002$).

The most relevant clinical characteristics in CRT-D patients with LBBB stratified by the change of LV dyssynchrony are listed in Table 9. Patients with improving LV dyssynchrony were more likely to be females, younger and had higher frequency of non-ischemic etiology of heart failure. The BNP level was significantly lower in patients with improving LV dyssynchrony. The left ventricular end-diastolic, end-systolic volume percent change and left atrial volume percent change were greater in patients with improving LV dyssynchrony, showing evidence of more pronounced left ventricular reverse remodeling. There was no difference in drug treatment among the patient groups. CRT-D patients with non-LBBB had significantly lower heart rate and trend towards less intraventricular conduction delay (IVCD) ECG pattern with improving LV dyssynchrony (data not shown).

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**Table 9.** Baseline Characteristics of CRT-D, LBBB Patients According to the Change in LV Dyssynchrony

| | **Dyssynchrony improving** | **Dyssynchrony worsening** | **p-value** |
|---|---|---|---|
| | **(n=237)** | **(n=66)** | |
| **Age, yrs** | 63.4±11.0 | 66.1±10.9 | 0.054 |
| **Female, n (%)** | 81 (34) | 12 (18) | **0.013** |
| **NYHA II, non-ischemic, n (%)** | 148 (62) | 28 (42) | **0.004** |
| **Ischemic, n (%)** | 89 (38) | 38 (58) | **0.004** |
| **Prior CABG, n (%)** | 34 (14) | 19 (29) | **0.007** |
| **Prior non-CABG, n (%)** | 43 (18) | 20 (30) | **0.033** |
| **Prior MI, n (%)** | 65 (28) | 31 (48) | **0.003** |
| **Past atrial arrhythmias, n (%)** | 12 (5) | 9 (14) | **0.026** |
| **QRS (ms)** | 162.9 ± 17.3 | 160.3 ± 18.7 | 0.249 |
| **Creatinine (mg/dL)** | 1.15 ± 0.35 | 1.23 ± 0.36 | 0.081 |
| **BNP level (pg/mL)(median, IQR)** | 67.5 (27.5; 143.5) | 117 (55; 235) | **0.011** |
| **LVEF (%)** | 29.5 ± 3.2 | 29.6 ± 3.4 | 0.546 |
| **LVEDV percent change** | -24.9 ± 11.9 | -21.0 ± 10.3 | **0.013** |
| **LVESV percent change** | -38.1 ± 15.1 | -32.8 ± 14.7 | **0.006** |
| **LAV percent change** | -32.3 ± 12.2 | -28.9 ± 9.7 | **0.011** |

Values are given as percent of patients or mean ± SD. NYHA = New York Heart Functional Class; LBBB = left bundle branch block; RBBB = right bundle branch block; IVCD = intraventricular conduction delay; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVEDV = left ventricular end-diastolic volume; LAV = left atrial volume.

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Bundle branch block pattern significantly modified the relationship between dyssynchrony and the outcome of VT/VF or death ($p = 0.03$), while non-significant interaction was found between bundle branch pattern and dyssynchrony with regard to VT/VF ($p = 0.07$). In CRT-D patients without LBBB, we observed no relationship between change in LV dyssynchrony and VT/VF/Death outcome and VT/VF events (Figure 15a). In CRT-D patients with LBBB, the decrease in LV dyssynchrony was associated with significantly lower incidence of VT/VF/Death ($p=0.014$) and VT/VF ($p=0.045$) (Figure 15b).

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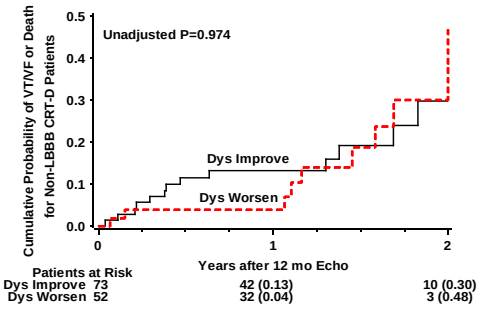
**Figure 15.** Kaplan–Meier Estimates of the Cumulative Probability of VT/VF/Death and VT/VF by Change in LV dyssynchrony in CRT-D a. non-LBBB and b. LBBB Patients

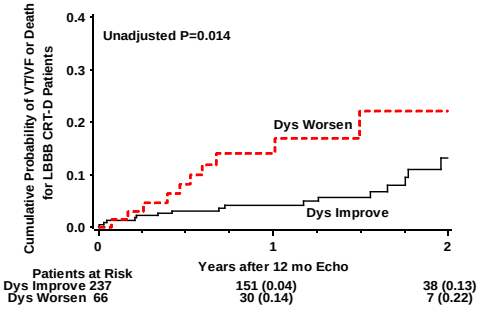
Non-LBBB

VT/VF/Death



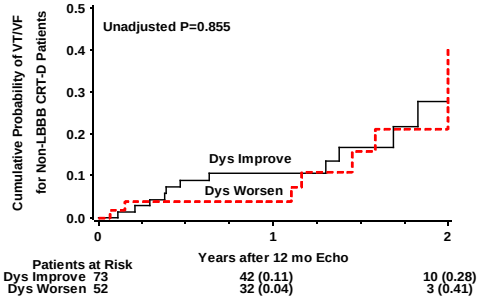

LBBB

VT/VF/Death



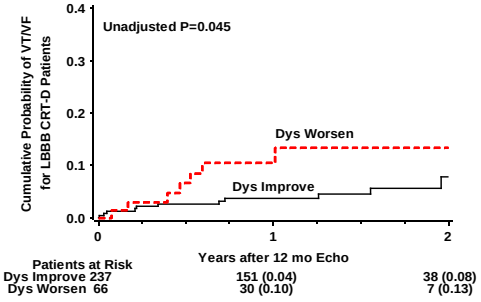

VT/VF

Non-LBBB




VT/VF

LBBB




At one-year, CRT-D patients with LBBB and improving LV dyssynchrony showed significant, 63% risk reduction of VT/VF or death (p=0.02) after adjustment for relevant clinical covariates (left ventricular ejection fraction, left ventricular end-diastolic volume change).

Consistent with these findings, CRT-D patients with LBBB and improving LV

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dyssynchrony exhibited significant, 68% lower risk of VT/VF events as compared to patients with unchanged or worsening LV dyssynchrony (p=0.02).

CRT-D patients with non-LBBB ECG pattern and improving LV dyssynchrony did not show decrease in the risk of VT/VF/Death (p=0.62) or VT/VF events (p=0.62) as compared to those with unchanged or worsening LV dyssynchrony (Table 10).

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**Table 10.** Change in LV Dyssynchrony and the Risk of Ventricular Arrhythmic Events in CRT-D LBBB and non-LBBB Patients

| **End point: VT/VF/Death** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Non-LBBB patients** | | | **LBBB patients** | | | **Interaction** |
| **Parameter** | **Hazard ratio** | **95%CI** | **p-value** | **Hazard ratio** | **95%CI** | **p-value** | **p-value** |
| **Dyssynchrony Improving: Worsening** | 1.25 | 0.52 – 3.00 | 0.62 | 0.37 | 0.16 – 0.82 | **0.02** | **0.03** |
| **Dyssynchrony Improving 5%: Worsening** | 1.33 | 0.55 – 3.25 | 0.53 | 0.42 | 0.18 – 0.95 | **0.04** | **0.046** |
| **Dyssynchrony Improving 15%: Worsening** | 1.52 | 0.63 – 3.70 | 0.62 | 0.36 | 0.18 – 0.87 | **0.02** | **0.02** |
| **End point: VT/VF** | | | | | | | |
| | **Non-LBBB patients** | | | **LBBB patients** | | | **Interaction** |
| **Parameter** | **Hazard ratio** | **95%CI** | **p-value** | **Hazard ratio** | **95%CI** | **p-value** | **p-value** |
| **Dyssynchrony Improving: Worsening** | 1.28 | 0.48 – 3.41 | 0.62 | 0.32 | 0.12 – 0.86 | **0.02** | 0.07 |
| **Dyssynchrony Improving 5%: Worsening** | 1.40 | 0.52 – 3.78 | 0.51 | 0.38 | 0.14 – 1.02 | **0.05** | **0.04** |
| **Dyssynchrony Improving 15%: Worsening** | 1.61 | 0.60 – 4.34 | 0.35 | 0.36 | 0.13 – 0.95 | **0.04** | **0.03** |

The model is adjusted for left ventricular ejection fraction, ischemic status and left ventricular end-diastolic volume percent change.

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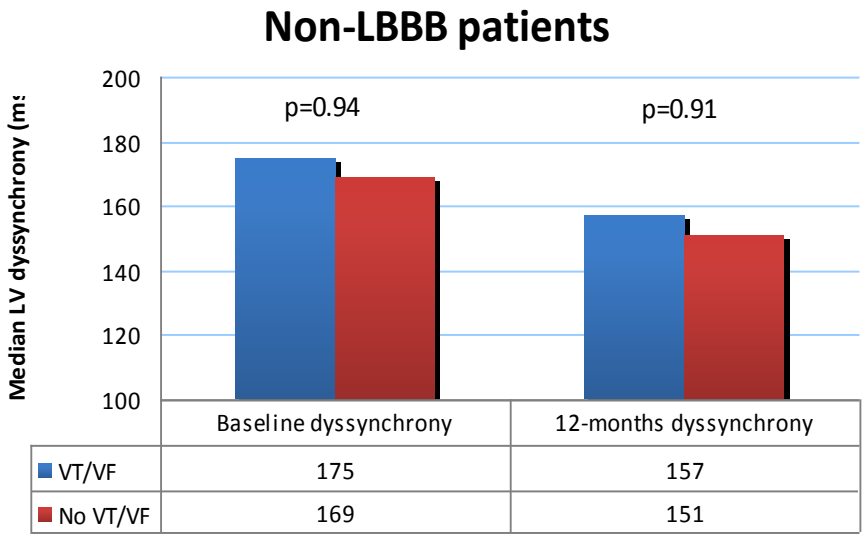
CRT-D LBBB patients with no VT/VF events exhibited a significant decrease in LV dyssynchrony as compared to patients with LBBB and VT/VF events, who did not decrease or even increased the degree of LV dyssynchrony from baseline (p=0.014). In CRT-D patients with non-LBBB the change in LV dyssynchrony was not associated with a decrease of VT/VF events (p=0.994) (Figure 16).

We also evaluated the effects of LV dyssynchrony improvement at one-year using 5% or 15% LV dyssynchrony percent change cut-off and consistent findings were revealed in CRT-D LBBB patients when analyzing the risk of VT/VF/Death or VT/VF (Table 10).

**Figure 16.** Baseline and 12-months Median LV Dyssynchrony in CRT-D a. Non-LBBB and b. LBBB Patients with Ventricular Arrhythmic Events or with No Events of VT/VF.

a.



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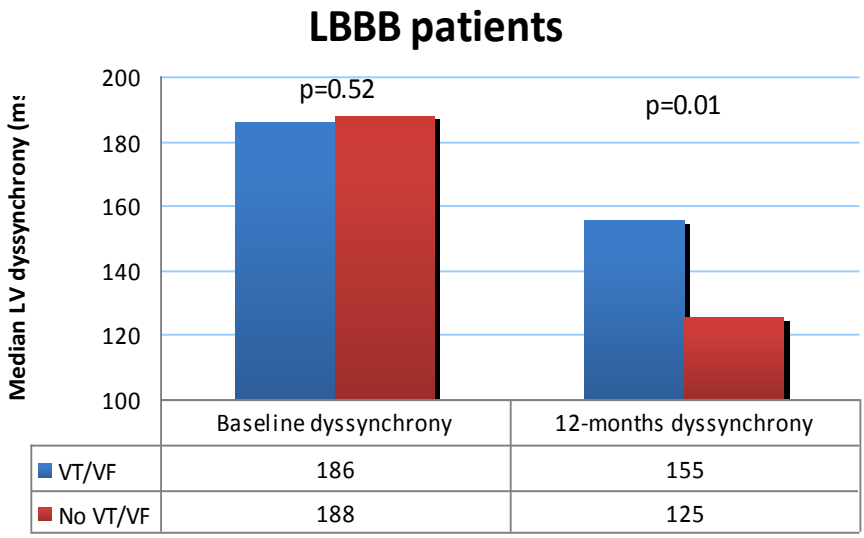
b.




## 4.4 New indications of CRT

### 4.4.1 *Chronic Right Ventricular Apical Pacing*

#### 4.4.1.1 Baseline Clinical Characteristics

In the current study, 107 patients (54%) had previously implanted pacemaker device, and 91 patients (44%) had implanted ICD devices at the time of the CRT upgrade. CRT upgrade was performed 5.4 ± 5.1 years after the initial device implantation. The most important baseline clinical characteristics are listed in Table 11.

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**Table 11.** Baseline clinical characteristics of ICD and PM patients upgraded to CRT.

| **Clinical parameters** | **ICD Patients (n= 91)** | **PM Patients (n= 107)** |
|---|---|---|
| Age at enrollment (years) | 68.6±9.5 | 68.5±9.3 |
| Female | 17 (19) | 20 (19) |
| Ischemic etiology | 55 (61) | 50 (48) |
| QRS (ms) | 171.4±26.2 | 186.3±30.4 ***** |
| Diabetes Mellitus | 29 (32) | 43 (41) |
| Hypertension | 58 (64) | 73 (69) |
| Prior MI | 65 (71) | 51 (48) * |
| Prior PCI | 32 (35) | 31 (29) |
| Prior CABG | 25 (28) | 21 (20) |
| Paroxysmal atrial fibrillation | 15 (17) | 18 (17) |
| Permanent atrial fibrillation | 30 (33) | 47 (44) |
| Ventricular arrhythmia in the past | 71 (78) | 10 (9) * |
| Creatinine (μmol/L) | 121.9 ± 39.5 | 126.5 ± 46.2 |
| Urea (mM/L) | 10.5 ± 5.6 | 12.0 ± 9.7 |
| **Medications** | | |
| Beta-blockers | 85 (93) | 94 (88) |
| ACEI/ ARB | 77 (85) | 92 (86) |
| Diuretics | 77 (85) | 88 (82) |
| Aldosterone antagonist | 64 (70) | 61 (57) |

$p < 0.05$ for comparison between ICD and PM patients. Values are given as percent of patients or mean ± SD. CABG = Coronary Artery Bypass Graft; PCI = Percutaneous Coronary Intervention; MI = myocardial infarction; ACEI= ACE-inhibitor; ARB = Angiotensin receptor blocker.

Patients with prior implanted ICD had a trend towards more frequent ischemic cardiomyopathy compared to PM patients (p= 0.07) and significantly higher incidence of prior myocardial infarction before CRT upgrade (p<0.001). Baseline paced QRS duration was

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significantly wider in patients with implanted PM as compared to those with previously implanted ICD (186.3 ± 30.4 vs. 171.4 ± 26.2 ms, p= 0.006). Baseline creatinine and urea level was similar in both groups. There was no significant difference in medication at baseline. Baseline echocardiographic parameters are shown in Table 12. Baseline left ventricular ejection fraction and left ventricular volumes were similar in both groups.

#### 4.4.1.2 Device Implantation

CRT upgrade procedure was performed using transvenous (n= 189, 95%), epicardial (n= 4, 2%) or transseptal (n=5, 3%) approach.

LV leads were implanted in the lateral or postero-lateral side-branch of the coronary sinus in 96 of 107 PM patients (89%) and in 81 of 91 ICD patients (89%), in the posterior location in 2 PM patients (2%), and in the anterior position in 6 PM patients (5%) and 5 ICD patients (5%). Epicardial LV lead placement was performed in 2 PM and 2 ICD patients, and transseptal approach was used in 2 PM and 3 ICD patients because of unsuccessful transvenous LV lead implantation.

CRT upgrade resulted in an immediate significant reduction of the QRS duration in both patient groups (ICD -36.6 ± 25.3 ms vs. -43.3 ± 24.8 ms, p=0.082). As noted earlier, baseline QRS duration was significantly longer in patients with previously implanted PM devices, therefore the net change was different however, the percent change was similar in both groups (ICD -21.1 ± 13.8 % vs. PM -22.8 ± 12.1%, p=0.276).

At the end of the device implantation, LV pacing, sensing parameters and LV impedance were within normal range. Patients did not manifest phrenic nerve stimulation. Device defibrillation threshold testing was successful in all patients.

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#### 4.4.1.3 Response to CRT Upgrade

*Clinical response*

After CRT upgrade, significant and similar improvement of NYHA functional class (ICD -0.67 ± 0.94 vs. PM -0.74 ± 0.77, p=0.745) was observed in both patient groups. Improvement of the functional status was accompanied by significantly improved quality of life, assessed by the EQ-5D visual analog scale (Table 12).

**Table 12.** Clinical response to CRT in PM and ICD patients.

| | **ICD patients** | | **PM patients** | | **p-value** |
|---|---|---|---|---|---|
| | **Before CRT** | **After CRT** | **Before CRT** | **After CRT** | |
| NYHA functional class | 3.2 ± 0.74 | 2.5 ± 0.68 | 3.1 ± 0.82 | 2.5 ± 0.68 | 0.745 |
| EQ-5D visual analog scale (0-100 scale) | 42.0 ± 20.9 | 60.6 ± 23.0 | 48.7 ± 22.4 | 64.4 ± 19.3 | 0.899 |
| QRS duration (ms) | 171.4±26.2 | 140.0±32.7 | 186.3±30.4 | 144.3±29.4 | 0.082 |
| LVEF (%) | 29.5 ± 6.8 | 33.8 ± 8.2 | 29.2 ± 8.3 | 36.6 ± 11.8 | **0.02** |
| LVEDD (mm) | 64.3 ± 9.3 | 65.6 ± 9.9 | 61.2 ± 11.7 | 62.1 ± 9.8 | 0.385 |
| LVESD (mm) | 53.4 ± 10.0 | 54.7 ± 9.5 | 52.0 ± 11.1 | 50.3 ± 11.7 | 0.099 |

NYHA = New York Heart Association; LVEF = Left Ventricular Ejection Fraction; LVESD = Left Ventricular End-Systolic Diameter; LVEDD = Left Ventricular End-Diastolic Diameter.

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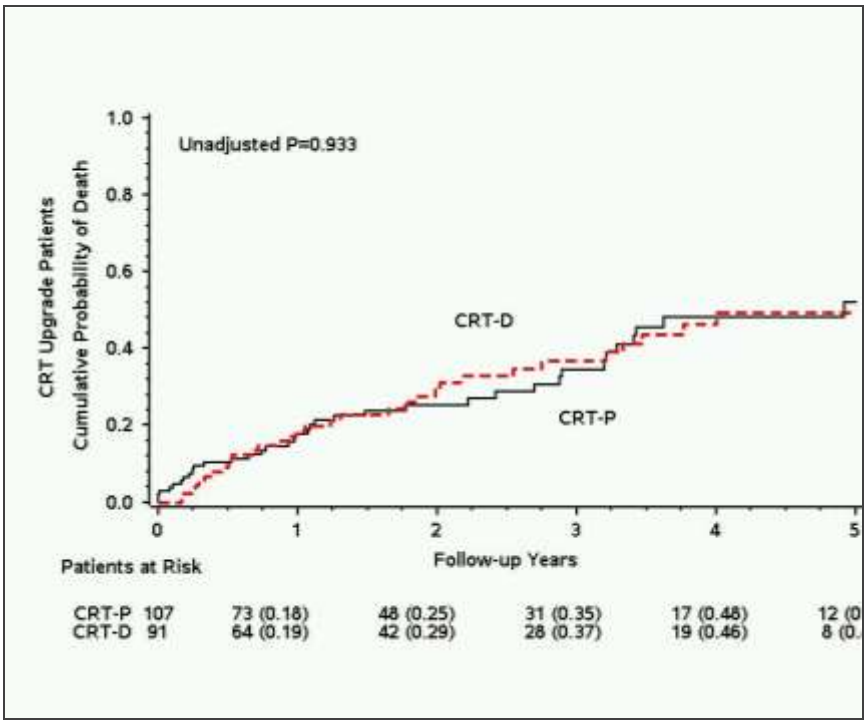
*Echocardiographic response*

After CRT upgrade, marked improvement of left ventricular ejection fraction was observed in PM ($p<0.001$) and ICD patients ($p=0.003$) as compared to baseline however, PM patients derived significantly greater increase in LVEF as compared to ICD patients ($p=0.02$). Reduction in left ventricular end-diastolic and end-systolic diameter did not reach statistical significance in both groups (Table 12).

*Survival response*

During the median follow-up of 21 months, 72 (36%) patients died of any cause (39 from PM, 33 from ICD group, $p=0.98$). Cumulative probability of death from any cause stratified by the previously implanted device is shown in Figure 17.

**Figure 17.** Cumulative probability of all-cause mortality in patients upgraded to CRT stratified by first implanted device (ICD or PM).



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There was no significant difference observed in mortality between PM and ICD patients during long-term follow-up (Kaplan-Meier 5-year cumulative event rate of PM 52% vs. 49%, p log-rank = 0.933).

Kaplan-Meier graphs presenting patients with ischemic and non-ischemic cardiomyopathy, stratified by previously implanted PM or ICD device are shown in Figure 18. Ischemic etiology did not modify the lack of association between the first implanted device and clinical outcome assessed by all-cause mortality.

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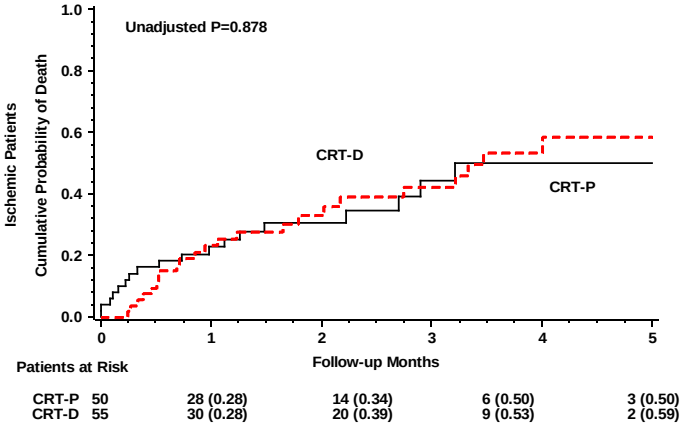
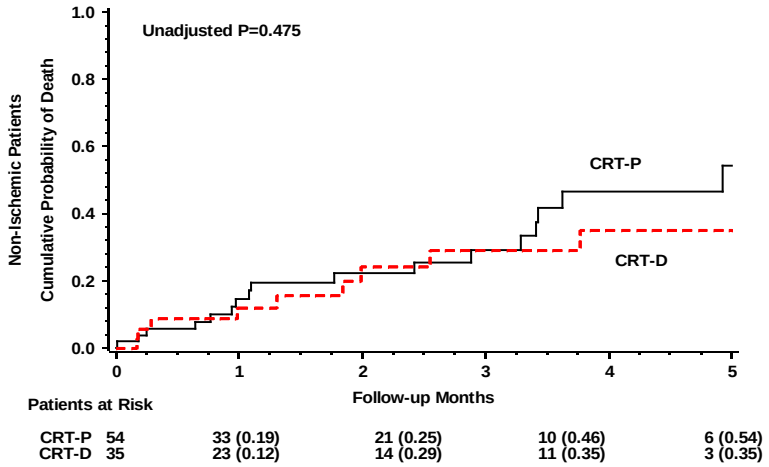
**Figure 18.** Cumulative probability of all-cause mortality in patients upgraded to CRT stratified by the first implanted device (ICD or PM) in ischemic cardiomyopathy, non-ischemic cardiomyopathy patients.




Multivariate model after adjustment for ischemic etiology of cardiomyopathy, baseline LVEF and baseline creatinine/urea ratio showed consistent result (ICD HR=1.18, 95 % CI: 0.60 - 2.29, p = 0.634).

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#### 4.4.1.4 Predictors of Mortality

Multivariate regression analysis revealed that ischemic etiology (HR=3.9, p=0.002), LVEF at baseline (HR=0.95, p=0.04) and baseline creatinine/urea ratio (p=0.0) are independent predictors of mortality in the total patient population (Table 13a).

In patients with previously implanted PM, LVEF at baseline influenced outcome positively, while ischemic etiology negatively (Table 13b). Every unit increment in baseline LVEF decreased subsequent all-cause mortality by 10 percent (p= 0.002). Ischemic etiology was associated with two-fold higher risk of death in PM patients, however this association showed only borderline significance (p=0.09).

In ICD patients, ischemic etiology was shown to be associated with increased mortality (Table 13c) (HR=7.2, p= 0.01). Every unit decrease in creatinine/urea ratio was associated with 18 % reduction in all-cause mortality (p=0.002).

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**Table 13.** Predictors of mortality a. in all patients, b. PM patients, c. ICD patients.

a. All patients.

| Parameter | Parameter Estimate | Standard Error | Chi-Square | Pr > ChiSq | Hazard Ratio | 95% Hazard Ratio Confidence Limits | |
|---|---|---|---|---|---|---|---|
| Ischemic etiology | 1.36676 | 0.43201 | 10.0090 | 0.0016 | 3.923 | 1.682 | 9.148 |
| Creatinine/urea ratio | -0.12435 | 0.04628 | 7.2201 | 0.0072 | 0.883 | 0.807 | 0.967 |
| LVEF at baseline | -0.04900 | 0.02347 | 4.3580 | 0.0368 | 0.952 | 0.909 | 0.997 |

b. PM patients.

| Parameter | Parameter Estimate | Standard Error | Chi-Square | Pr > ChiSq | Hazard Ratio | 95% Hazard Ratio Confidence Limits | |
|---|---|---|---|---|---|---|---|
| LVEF at baseline | -0.09997 | 0.03289 | 9.2408 | 0.0024 | 0.905 | 0.848 | 0.965 |
| Ischemic etiology | 0.69764 | 0.42316 | 2.7180 | 0.0992 | 2.009 | 0.877 | 4.604 |

c. ICD patients.

| Parameter | Parameter Estimate | Standard Error | Chi-Square | Pr > ChiSq | Hazard Ratio | 95% Hazard Ratio Confidence Limits | |
|---|---|---|---|---|---|---|---|
| Creatinine/urea ratio | -0.20371 | 0.06474 | 9.9025 | 0.0017 | 0.816 | 0.718 | 0.926 |
| Ischemic etiology | 1.97099 | 0.77239 | 6.5118 | 0.0107 | 7.178 | 1.580 | 32.617 |

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### 4.4.2 *Cardiac Resynchronization Therapy in Patients with Less Severe Ventricular Dysfunction*

At baseline, 914 patients (50.5%) had LVEF 26-30% (median=28.1%, Q1=27.1%, Q3=29.0%), and 199 patients (11%) comprised the LVEF group of ≤ 25% (median=23.2%, Q1=21.8%, Q3=24.2%). The subgroup of LVEF >30% included 696 (38%) patients (in the range of 30.1-45.3%, median=31.8%, Q1=30.8%, Q3=33.1%), as evaluated by the echocardiography core laboratory.

LVEFs identified by the enrolling centers were multiplies of 5 in 72% of cases, possibly due to the fact that most centers used estimates for this measure. There was a weak, but significant correlation between left ventricular ejection fractions identified by the centers and measured by the echocardiography core laboratory ($r^2$ = 10.5%, $p<0.001$). The distribution and correlation of LVEF identified by the enrolling centers and measured by the echocardiography core laboratory is shown in Figure 19.

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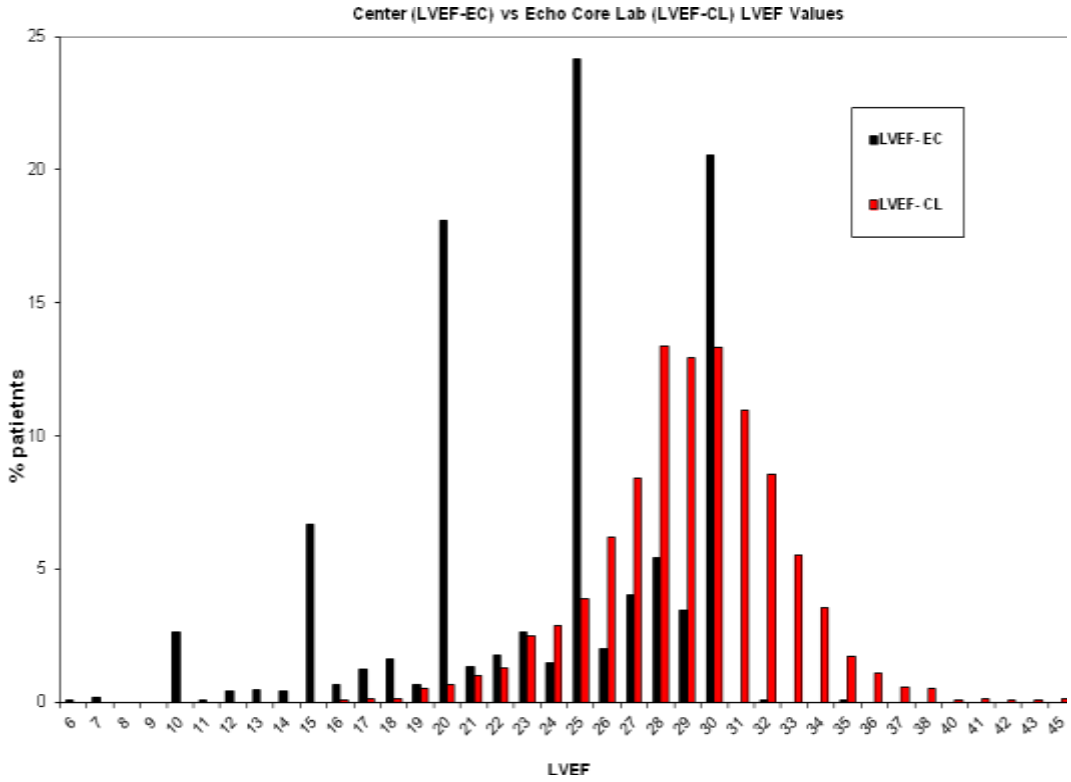
**Figure 19.** Distribution of baseline LVEF identified by the centers and measured by the echocardiography core laboratory in all patients.




Abbreviations: LVEF-EC - LVEF identified by the enrolling centers, LVEF-CL - LVEF measured by the echocardiography core laboratory.

Baseline clinical characteristics of patients with LVEF ≤ 25%, LVEF 26-30% and LVEF > 30% are shown in Table 14. Patients with increasing LVEF were older, more often females, they had lower heart rate, less often LBBB, more often RBBB and IVCD ECG pattern. There was a trend towards more frequent ischemic cardiomyopathy and less prior severe heart failure episode (> 3 months prior to enrollment) with less depressed LVEF. Baseline drug treatment was similar across LVEF ranges with lower use of diuretics and digitalis with increasing LVEF. Echocardiographic results showed gradually smaller left ventricular end-diastolic, end-systolic and left atrial volumes across LVEF groups, demonstrating less advanced stage of the disease.

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**Table 14.** Clinical characteristics of all patients with regard to baseline LVEF ranges.

| Clinical Characteristics | LVEF ≤ 25% | LVEF 26-30% | LVEF > 30% | p-value |
|---|---|---|---|---|
| Number of patients | **199** | **914** | **696** | |
| Age (years) | 61.4±11.0 | 64.3±10.8 | 65.3±10.4 | **<0.001** |
| Females | 36 (18%) | 220 (24%) | 195 (28%) | **0.012** |
| CRT-D treatment | 115 (58) | 554 (61) | 416 (60) | 0.755 |
| Ischemic NYHA I | 25 (13%) | 121 (13%) | 118 (17%) | 0.077 |
| Ischemic NYHA II | 74 (37%) | 388 (42%) | 267 (38%) | 0.162 |
| Non-Ischemic NYHA II | 100 (50%) | 405 (44%) | 311 (45%) | 0.300 |
| Worst NYHA > 2 (>3 months prior enrollment) | 24 (13%) | 102 (12%) | 56 (8%) | 0.063 |
| QRS complex (ms) | 166.6 ± 22.5 | 159.1 ± 20.0 | 154.4±17.6 | **<0.001** |
| LBBB | 168 (84%) | 656 (72%) | 450 (65%) | **<0.001** |
| RBBB | 9 (5%) | 111 (12%) | 106 (15%) | **<0.001** |
| IVCD | 22 (11%) | 146 (16%) | 139 (20%) | **0.006** |
| Heart rate | 69.8 ± 12.0 | 67.8 ± 10.6 | 67.0 ± 10.7 | **0.007** |
| Systolic blood pressure | 119.2 ± 17.5 | 121.9 ± 16.7 | 124.4 ± 18.1 | **<0.001** |
| ACE-inhibitors/ ARB | 163 (82) | 685 (75) | 546 (78) | 0.168 |
| Beta blocker | 180 (90%) | 854 (93%) | 653 (94%) | 0.236 |
| Diuretics | 142 (71%) | 653 (69%) | 446 (64%) | **0.035** |
| Digitalis | 68 (34) | 241 (26) | 156 (22) | **0.003** |
| LVEDV indexed by BSA | 150.7 ± 40.7 | 125.5 ± 26.7 | 112.9 ± 19.1 | **<0.001** |
| LVESV indexed by BSA | 116.6 ± 32.4 | 90.5 ± 19.8 | 76.6 ± 13.7 | **<0.001** |
| LAV indexed by BSA | 57.0 ± 10.7 | 48.4 ± 8.8 | 41.2 ± 7.9 | **<0.001** |

Values are given as percent of patients or mean ± SD. NYHA stands for New York Heart Association class, LBBB= left bundle branch block, RBBB= right bundle branch block, IVCD= intraventricular conduction delay, LVEF= left ventricular ejection fraction, LVESV= left ventricular end-systolic volume, LVEDV= left ventricular end-diastolic volume, LAV = left atrial volume, ACE-inhibitors= Angiotensin converting enzyme inhibitors, ARB= Angiotensin receptor blocker.

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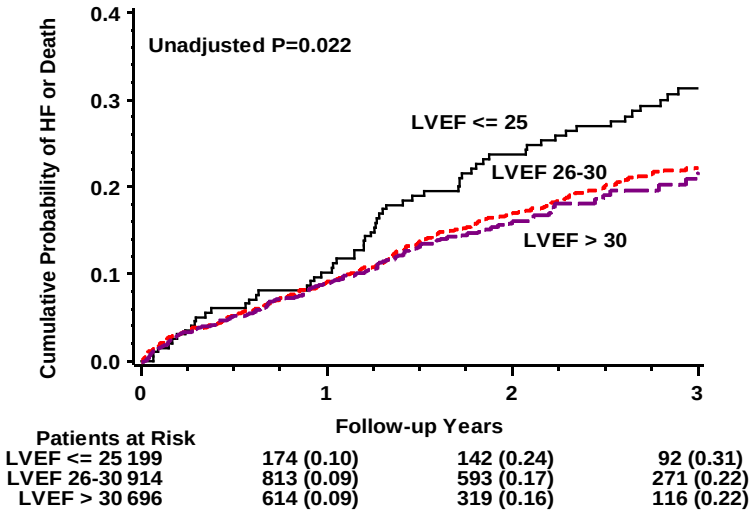
#### 4.4.2.1 Effect of Baseline LVEF on Primary Clinical Outcome during Follow-Up

The primary endpoint of HF or death was met in 375 patients (20.7%) with baseline LVEF measurements, 126 patients (7%) died, 78 (4.3%) of them of cardiac causes during the mean follow-up of 29.4 ± 11 months.

Patients with baseline LVEF ≤ 25% showed significantly higher cumulative incidence of HF or death episodes when compared to patients with LVEF 26-30% or LVEF> 30% (Figure 20).

**Figure 20.** Kaplan–Meier Estimates of the Cumulative Probability of HF/Death Episodes in all patients with LVEF ≤ 25%, LVEF 26-30 % and LVEF > 30%.




Multivariate Cox-model after adjustment for relevant clinical covariates: treatment, ischemic etiology of cardiomyopathy, NYHA class > 2 greater than 3 months prior enrollment, baseline heart rate and age at enrollment revealed similar findings. Patients with LVEF ≤ 25%

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had 55% higher risk of HF or death when compared to patients with LVEF 25-30% and 66% higher risk when compared to patients with LVEF > 30%. Patients with LVEF 26-30% and LVEF >30% demonstrated a similar risk of HF/Death. LVEF as a continuous measure was a surrogate marker of the primary end point, demonstrating a significant 5% reduction in the risk of HF/death for each unit increment in LVEF (Table 15).

**Table 15.** Baseline LVEF groups and the risk of HF/Death.

| Parameter | Hazard Ratio | 95% CI | p- value |
|---|---|---|---|
| **HF/Death** | | | |
| LVEF ≤ 25 %: LVEF 26-30% | 1.55 | 1.16 – 2.08 | **0.003** |
| LVEF ≤ 25 %: LVEF > 30% | 1.66 | 1.21 – 2.28 | **0.002** |
| LVEF 26-30 %: LVEF > 30% | 1.07 | 0.84 – 1.36 | 0.588 |
| LVEF (continuous) | 0.95 | 0.92 – 0.98 | **0.001** |

Model is adjusted for treatment, ischemic etiology of cardiomyopathy, NYHA class > 2 greater than 3 months prior enrollment, baseline heart rate and age at enrollment.

#### 4.4.2.2 Effect of CRT Therapy on the Primary Clinical Outcome by LVEF

Evaluating the treatment effects of CRT-D vs. ICD-only therapy, 1809 patients (1074 CRT-D- and 735 ICD- patients) with baseline LVEF data available were analyzed on an intention-to-treat basis.

Univariate Kaplan-Meier survival analysis showed that compared with ICD-only therapy, treatment with CRT-D showed borderline significance in decreasing the cumulative incidence of

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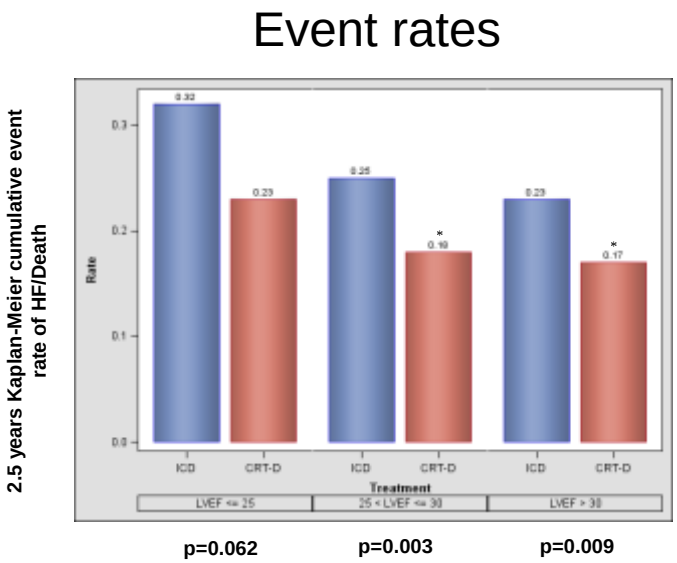
HF/Death in patients with LVEF ≤ 25% (p=0.062), while this effect was statistically significant among patients with LVEF 26-30% (p=0.003) and with LVEF 30% (p=0.009) (Figure 21).

**Figure 21.** Kaplan–Meier 2.5 years Event Rates of the Cumulative Probability of HF/Death Episodes by treatment arm in patients with LVEF ≤ 25%, LVEF 26-30% and LVEF > 30%.




p<0.05 for comparison between ICD and CRT-D treatment arm

Consistent with these findings, multivariate Cox-model after adjustment for relevant clinical covariates showed, that CRT-D treatment was associated with significant 43% reduction in the risk of HF or death in patients with LVEF ≤ 25% (p=0.03), 33% risk reduction in patients with LVEF 26-30% (p=0.007), and significant 44% risk reduction among those with LVEF >30% (p=0.003). The interaction p-value was not significant for all LVEF groups (all p-value for treatment-by-LVEF interactions >0.10), indicating that the clinical benefit of CRT-D was maintained regardless of baseline LVEF.

Evaluating the treatment effect of CRT-D in patients with LBBB, even more striking risk

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reduction of HF/Death was observed. LBBB patients with LVEF ≤ 25% showed 55%, significant risk reduction (p=0.006), LVEF 26-30% patients had 53% risk reduction (p<0.001) and those with LVEF>30% exhibited even more, 62% reduction the risk of HF/Death (p<0.001). Non-LBBB patients did not show benefit of CRT-D irrespective of their baseline LVEF (Table 16).

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**Table 16.** Treatment Effect of CRT-D stratified by baseline LVEF groups by the primary end point of HF/Death.

| **HF/Death** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **All patients** | | | **LBBB patients** | | | **Non-LBBB patients** | | |
| | Hazard ratio | 95%CI | p-value | Hazard ratio | 95%CI | p-value | Hazard ratio | 95%CI | p-value |
| LVEF ≤ 25% | 0.57 | 0.35-0.95 | **0.031** | 0.45 | 0.26-0.80 | **0.006** | 1.35 | 0.36-5.03 | 0.654 |
| LVEF 26-30% | 0.67 | 0.50-0.90 | **0.007** | 0.47 | 0.32-0.68 | **<0.001** | 1.38 | 0.81-2.37 | 0.238 |
| LVEF > 30% | 0.56 | 0.39-0.82 | **0.003** | 0.38 | 0.23-0.62 | **<0.001** | 0.98 | 0.53-1.84 | 0.956 |

Model is adjusted for: female, ischemic and QRS duration.

Interaction p-values with treatment are >0.1 in all patient groups and LVEF sub-groups.

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#### 4.4.2.3 The Magnitude of Echocardiographic Response to CRT-D by LVEF Groups

Echocardiographic response was assessed at 12-month follow-up in patients with implanted CRT-D, crossovers were excluded from this analysis (n=119).

Echocardiographic response to CRT-D was directly correlated to LVEF. Patients with LVEF ≤ 25% exhibited less decrease of left ventricular end-diastolic volume (LVEDV) percent change from baseline to one-year (-18.7 ± 11.6%), as compared to patients with LVEF 26-30% (-20.1 ± 10.7%) or to patients with LVEF > 30% (-22.3 ± 12.3% p=0.001). Furthermore, patients with LVEF > 30% showed a significantly greater reduction in LVEDV than patients with LVEF 26-30% (p=0.001).

Similarly, the degree of left ventricular end-systolic volume (LVESV) percent reduction with CRT-D therapy was also directly correlated to increasing LVEF groups (-31.4 ±13.5 % change vs. -32.0 ± 13.8 % -33.6 ± 17.1 percent change, p<0.001 for the overall difference). Patients with LVEF > 30% exhibited greater reduction in LVESV than patients with LVEF 26-30% (p=0.029).

Consistent findings were seen in left atrial volume reduction (-22.67 ± 10.9 % vs. -27.6 ± 11.6 % vs. -30.4 ± 12.5, p<0.001). Patients with LVEF > 30% gained more pronounced left atrial remodeling than those with LVEF 26-30% (p=0.001) (Figure 22).

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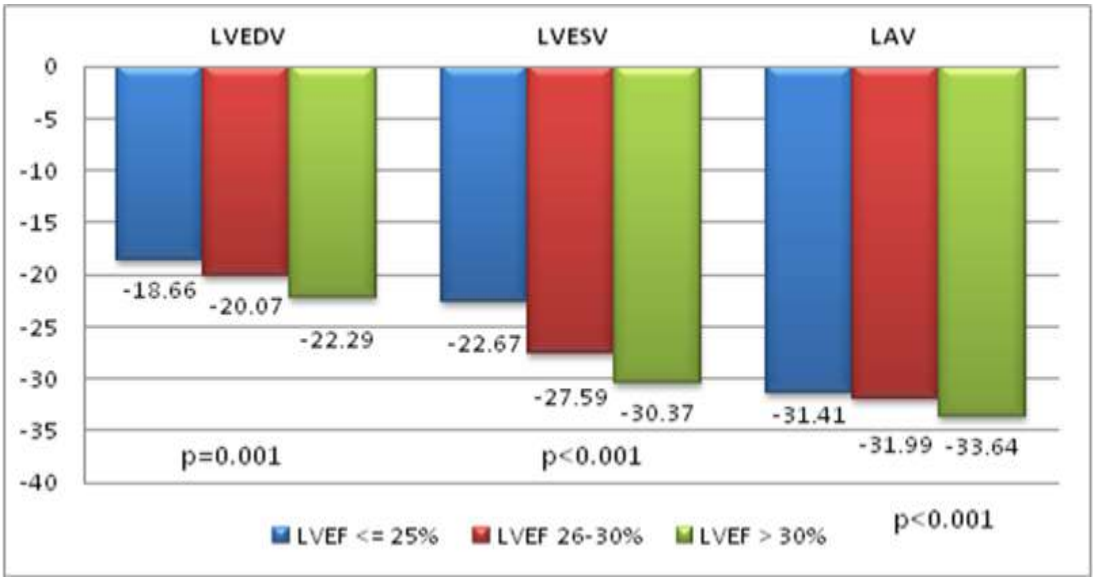
**Figure 22.** Effects of CRT-D on echocardiographic parameters after 1-year in patients with LVEF ranges of LVEF ≤ 25%, LVEF 26-30%, LVEF > 30%.




Abbreviations: LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LAV = left atrial volume.

We analyzed LV dyssynchrony data available in 587 of 955 CRT-D patients (61.5%). Patients with LVEF ≤ 25% exhibited greater baseline LV dyssynchrony (207.1 ± 63.1 ms) as compared to patients with LVEF 26-30% (194 ± 64.4 ms) or with LVEF >30% (175.5 ± 65.3 ms, p<0.001). However, the reduction in LV dyssynchrony at 12 months of follow-up was similar across LVEF groups (-13.4 ± 49.1 % vs. -19.0 ± 43.0 % vs. -14.0 ± 55.8 % change, p=0.93).

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# 5 Discussion

## 5.1 Current Practice of Cardiac Resynchronization Therapy

### 5.1.1 *Evaluating the Effects of CRT-P versus CRT-D in a CRT Registry*

We suggest analyzing high-volume single-center registry data that patients implanted with CRT-D or CRT-P gain similar clinical and echocardiographic improvement after CRT implantation and more importantly, the mortality benefit is the same. However, patients with ischemic cardiomyopathy had significant mortality reduction with implantation of a CRT-D device as compared to patients with a CRT-P.

Previous randomized multicenter clinical studies evaluated the mortality reduction of heart failure patients with NYHA functional class III, IV and implanted CRT-P or CRT-D device.[29, 35] The COMPANION trial assessed the effects of CRT-P or CRT-D compared to medical therapy however, the study did not aim to compare CRT-P effects directly to the benefits of CRT-D.[29]

This analysis is novel in suggesting provocative data of CRT-P and CRT-D might bear similar outcome in non-ischemic patients with heart failure patients. Only patients with ischemic etiology of cardiomyopathy showed significant benefit from implantation of a CRT-D device as compared to CRT-P. This might have been explained by the additional benefit of sudden cardiac death reduction in CRT-D patients. Further clinical studies are needed to confirm these findings in larger, randomized patient population.

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## 5.2 Refining Implantation Methods

### 5.2.1 *Prognostic Significance of Right Ventricular to Left Ventricular Interlead Sensed Electrical Delay in CRT Patients*

We showed that CRT patients with right to left ventricular interlead sensed electrical delay greater than 106.5 ms measured during the implantation procedure demonstrated significant mortality benefit as compared to patients with right to left ventricular interlead sensed electrical delay lower than 106.5 ms.

Earlier reports failed to predict left ventricular reverse remodeling using the right to left ventricular interlead electrical delay.[23-25] Sassone et al. studied 52 CRT patients and showed that right to left ventricular interlead electrical delay does not predict reverse remodeling defined as ≥ 15%.[23] Zuchelli et al. found that that CRT responders had longer right to left ventricular interlead electrical delay than patients with no Echocardiographic response.[25] Zuchelli et al.[25] and Kristiansen et al.[24] showed that interlead sensed electrical delay was correlated with intraventricular dyssynchrony.[24, 25]

The findings of the current analysis indicating that patients with greater distance between the right and left ventricular lead during implantation might derive more significant mortality benefit from CRT-D. Obviously, the right to left ventricular interlead electrical delay might also depends on the baseline QRS-duration. However, our results were consistent in the multivariate model after adjustment for baseline QRS duration.

Patients with shorter or longer right to left ventricular interlead electrical delays were different in terms of clinical characteristics, however all cofounders were taken into account in the multivariate model.

Possible limitation of this study is that patients were not randomized, and we might acknowledge the technical limitation of the measurement. However, all measurements were

performed on the same EP system, excluding the possibility of different filtering and adjusting of the signal and therefore possibly avoid major measurement errors.

### 5.2.2 *Electroanatomical Mapping-Guided Transseptal Endocardial LV Lead Implantation*

We reported the feasibility of electroanatomical mapping guided transseptal endocardial LV lead implantation in a small series of patients.

Experimental[42] and clinical[41] observations also suggested that endocardial pacing is more physiologic than epicardial pacing. Garrigue [70] and Jais [71] reported better hemodynamic results with higher aortic- and mitral time velocity integral, improvement of LV fractional shortening and reduction of regional electromechanical delay in patients with endocardial LV pacing. In our patient cohort we also reported significant improvement of the LV systolic function and additional marked improvement of the patient's functional status during long-term follow-up.

The drawbacks of this approach include the risk of transseptal catheterization, the current lack of appropriate implantation tools and the possible need for life-time anticoagulation, as previously reported.[34] However, anticoagulation is indicated in the majority of these patients due to severe LV systolic dysfunction and/or the presence of atrial fibrillation. Long-term follow-up data regarding thromboembolic or hemorrhagic complications were so far not available. Our study showed that during a 1.5 years follow-up no hemorrhagic or thromboembolic events occurred.

Using transseptal CRT approach, the LV lead crosses the atrial septum, mitral valve and is actively fixed to the LV endocardial surface. It is controversial whether mitral regurgitation might be worsened with this technique however, we did not observe any worsening of mitral regurgitation or echocardiographic evidence of the mitral valve being partially kept open. The risk of infective endocarditis might be increased,[72] but no data of more frequent endocarditis are

currently available in this patient population. We did not observe any lead infection during the follow-up period.

Clinical studies showed appropriate positioning of the LV lead to be of high importance to increase the number of CRT responders.[20, 73] Recent studies also demonstrated that an "individually" based LV pacing approach compared to conventional CS pacing, echo-guided or lateral area strategy might result in better short-term hemodynamic response in non-ischemic cardiomyopathy patients.[74] The authors reported benefit of endocardial pacing. Our study also emphasizes the positive effects of endocardial pacing. In our study, electroanatomical activation mapping was used to identify the latest activation area to find optimal LV lead position for CRT. Functional assay (dP/dt max) might be an alternative approach to guide LV lead implantation and the two approaches may give discordant result.[75] However, there are no long-term data available on these techniques.

Singh et al.[76] showed that clinical benefit from CRT was similar with LV leads along the anterior, lateral or posterior wall in mildly symptomatic heart failure patients. However, LV leads positioned in the apical region were associated with a subsequent worse outcome. Our study confirmed basal, mid-basal LV lead position to be associated with marked improvement of the LV systolic function and clinical status during a mean follow-up of 1.5 years.

One of the major limitations of this report is that the position of the LV lead cannot be tracked within the LV cavity using CARTO electroanatomical mapping system.

## 5.3 Effects of CRT on Ventricular Arrhythmias

### 5.3.1 *Left Ventricular Lead Location and the Risk of Ventricular Tachyarrhythmias*

Our analysis of the impact of LV lead position on the occurrence of ventricular tachyarrhythmic

events showed that the lateral-posterior LV lead position was associated with decreased risk of first VT/VF when compared to patients with ICD-only and to patients with an anterior LV lead location.

It is important to stress, that the majority (65%) of the anterior leads were placed at the basal part of the anterior left ventricular wall, whereas 35% were positioned on the mid-ventricular anterior wall. This suggests that the LV lead positioned at the basal anterior wall does not reduce VT/VF episodes despite the reverse remodelling of the left ventricle.

There is a report from Kleemann et al.,[77] who investigated LV lead position and potential arrhythmic events in 187 patients receiving CRT (anterior lead location was found in 40 patients). They did not find significant difference in the susceptibility to arrhythmic events regarding LV lead positioning. However, they compared anterior and apical lead locations with posterior and posterior-lateral positions. The incidence of sudden cardiac death was not different among the lead positions.

Several studies reported potential pro-arrhythmic effects of CRT independent from LV lead location. During CRT, pacing the right ventricle from the endocardium and the left ventricle (LV) from the epicardium may increase transmural heterogeneity of repolarization[42] and subsequently create QT and TDR prolongation, leading to the development of R-on-T extrasystoles and torsades de pointes (TdP).[41, 43] We did not observe significant differences in QRS duration changes (pre-implant versus one day after implant) or in the $QT_c$ and $JT_c$ interval changes in the pre-specified subgroups (data not shown). In our study, there was no evidence for any pro-arrhythmic effects of CRT, since none of the CRT subgroups showed more VT/VF events than ICD only patients.

Other studies suggest antiarrhythmic effects of CRT which might be partly explained by the CRT-induced reverse remodelling.[46-48, 78, 79] Higgins et al.[46] found that ICD therapy occurred

less often with biventricular pacing compared with no pacing. A possible mechanism might be the reduction of heterogeneity, avoidance of pause-dependent ventricular tachycardia or decrease of the norepinephrine level. McSwain et al.[80] did not find CRT to be associated with a measurable increase in the incidence of polymorphic VT or a decrease in monomorphic VT episodes analyzing arrhythmic events in two CRT-D trials. We observed decreased risk of first VT/VF events in patients with lateral-posterior LV lead position, but not in patients with anterior and particularly anterior-basal lead position despite similar amount of left ventricular reverse remodelling. The difference of the risk of arrhythmic events between anterior and lateral or posterior lead location was present after adjustment for clinical covariates. There were no significant differences between anterior and lateral-posterior LV lead locations regarding baseline LV volumes and LVEF. In both ischaemic, and non-ischaemic cardiomyopathy, lateral-posterior lead locations were associated with a lower risk of VT/VF as compared with anterior LV lead location.

The reason of why, at least in our study, the lateral-posterior LV lead positions bear a lower risk of ventricular tachyarrhythmic events whereas the risk remains unchanged with anterior LV pacing is difficult to explain. Although most clinical characteristics were similar with an anterior and lateral or posterior position, two baseline characteristics may have contributed to no suppression of VT/VF events with anterior LV pacing. The percentage of patients with RBBB ECG configuration was significantly higher in the anterior LV lead position compared with the lateral-posterior position. Pacing the anterior left ventricular wall in patients with RBBB may not reduce electrical heterogeneity to the same amount as in patients with LBBB ECG morphology. This is supported by our study on the impact of QRS morphology in the MADIT-CRT trial[81] and other trials in heart failure patients with mild to moderate heart failure.[82] Not only patients with LBBB had less heart failure or death than patients with RBBB

morphology, but also the incidence of VT/VF episodes was significantly lower in patients with LBBB morphology compared with non-LBBB patients.

The fact that patients with anterior LV lead positions had trend towards more frequent prior myocardial infarctions than patients with lateral and posterior positions might also contribute to the difference in VT/VF occurrence. Pacing the left ventricle in close proximity to scar tissue may enhance electrical instability.

We must acknowledge, that the question of why VT/VF events are significantly suppressed with a lateral or posterior but not with an anterior LV lead remains partly unanswered. In addition, our earlier findings of more heart failure events with apical lead location do not correlate with an increase in VT/VF events.[83]

Potential limitations of our analysis include the non-randomized fashion of this study, which might leave potential bias. We acknowledge that the groups analyzed were not equal in size and we found differences in baseline clinical characteristics among the groups however, our findings were coherent even after adjusting for potential imbalances of baseline clinical characteristics in the Cox multivariate model. Our results might warrant conducting further randomized trials in this field.

### 5.3.2 *Left Ventricular Dyssynchrony and the Risk of Ventricular Tachyarrhythmias*

Previous studies suggested that LV dyssynchrony might be related to cardiac events in heart failure patients.[84] Cho et al. demonstrated that mechanical dyssynchrony was a powerful predictor of mortality or cardiac events in heart failure patients with normal[85] and wide QRS.[86] Penicka,[87] Fauchier[88] and Bader et al.[89] reported that LV dyssynchrony was prognostic of cardiac end points. These studies analyzed heart failure patients without implantable devices (ICD or CRT) and used either radionuclide technique or pulsed-wave Doppler tissue Doppler

imaging to evaluate LV dyssynchrony.

Other studies however demonstrated that baseline LV dyssynchrony predicts favorable outcome after CRT implantation.[90, 91] Gorcsan et al. demonstrated that baseline LV dyssynchrony predicts EF response in patients implanted with CRT.[92] Recently, Augeer et al. demonstrated that patients with 3D assessed LV dyssynchrony showed better outcome after CRT.[93]

Haguaa et al. showed that mechanical dispersion assessed by strain echocardiography was an independent predictor of arrhythmia events in a smaller patient cohort after myocardial infarction treated with ICD. They excluded LBBB patients from this analysis.[94] Another paper from this group[95] showed similar effects in non-ischemic cardiomyopathy patients.

Our study is the first report to analyze VT/VF events and LV dyssynchrony in mild heart failure CRT LBBB patients compared to non-LBBB. While previous work has shown improvement in ventricular remodeling associated with improvement in synchrony,[66, 67, 96-98] we also demonstrated that improved synchrony translates to reduction of ventricular arrhythmic events in LBBB patients. The reduction of VT/VF episodes in LBBB patients with improving LV dyssynchrony might be explained by more homogenous left ventricular mechanical activation followed by the electrical resynchronization itself (mechanical to electrical feedback). Electrical resynchronization is characterized by more uniform alterations in refractoriness which might result in reduction of macroreentry arrhythmias.[88] The reduction in LV dyssynchrony might be correlated to reduction in LV volumes and favorable outcome as reported previously in this patient cohort.[66]

Patients with non-LBBB receiving CRT-D did not appear to benefit from improvement in LV dyssynchrony. One possible explanation for this lack of benefit might be the significant overlap of non-LBBB ECG pattern and patients with ischemic etiology, in whom there may be

more heterogeneous left ventricular activation and greater degree of ischemic scar which likely contributes to arrhythmogenesis. While CRT is able to reduce LV dyssynchrony and the heterogeneity of left ventricular activation, the arrhythmogenic potential represented by the scar tissue might remain the same.

Possible limitation of our study might be the higher variation of LV dyssynchrony measurements when compared to other established echocardiographic data (LVEF or LV volumes). However, speckle tracking imaging has better reproducibility than MRI tagging or other echo modalities to assess LV dyssynchrony.[99] In addition, we reported excellent reproducibility with this technique in our echocardiography laboratory.[84, 100]

We used an arbitrary definition of LV dyssynchrony improvement as any negative change in LV dyssynchrony compared to baseline LV dyssynchrony, as there is no defined LV dyssynchrony response cut-off for CRT patients established. However, when evaluating the effects of LV dyssynchrony change on the risk of VT/VF/Death or VT/VF using more conservative 5% and 15% LV dyssynchrony percent change cut-off, consistent results were found in CRT-D patients with LBBB.

## 5.4 New indications of CRT

### 5.4.1 *Chronic Right Ventricular Apical Pacing*

We demonstrated that CRT upgrade is feasible in patients with previously implanted ICD and patients gain similar benefit in survival as patients with an implanted PM upgraded to CRT. However the echocardiographic response, defined as the improvement in left ventricular ejection fraction was more pronounced in patients with a previously implanted PM.

Previous reports demonstrated the feasibility and safety of CRT upgrade in patients with

RV apical pacing compared to de novo CRT implantation[56] and showed improvement in quality of life,[55] reduction in LV dyssynchrony,[57] and significant reverse remodeling[53, 54] after CRT upgrade. However, none of these studies included patients with ICD. Our study is the first report of patients with implanted ICD upgraded to CRT.

Additionally, we investigated the predictors of mortality in patients upgraded to CRT. Consistent to previous studies,[101, 102] ischemic etiology was powerful predictor of mortality in CRT upgrade patients, in both PM and ICD subgroups. In ICD patients, ischemic etiology was the most powerful prognostic marker of all-cause mortality.

The prognostic significance of baseline left ventricular ejection fraction have been shown is several papers earlier.[58, 59] In this analysis we have confirmed these results.

Baseline creatinine/urea ratio is a reliable marker of pre-renal function which has been suggested to be associated with response to CRT.[103] In our study, it is shown to be a prognostic factor for long-term all-cause mortality in ICD and PM patients upgraded to CRT. In this analysis, baseline creatinine/urea ratio was a better surrogate marker of survival than baseline creatinine or urea alone.

### 5.4.2 *Cardiac Resynchronization Therapy in Patients with Less Severe Ventricular Dysfunction*

Previous smaller studies suggested that patients with severe HF (NYHA III and IV) and higher baseline LVEF could be eligible for CRT and showed improvement of clinical status and echocardiographic parameters.[104, 105] Recently, Chung et al. reported that 86 (24%) of 361 patients enrolled in the PROSPECT trial had LVEF of > 35% measured by the echocardiography core laboratory. They showed that CRT improved clinical composite score and was associated

with similar decrease of LVESV in patients with LVEF ≤ 35% or > 35%.[106] The REVERSE trial included patients with mild heart failure and LVEF < 40%,[6] however, the mean LVEF in the study was very low (26.8 ± 7.0 % in CRT-ON arm), indicating that the proportion of patients with better LVEF might have been small.

In contrast to the PROSPECT sub-study, our analysis showed that patients with LVEF > 30% exhibit even more pronounced echocardiographic response to CRT-D than patients with lower LVEF.

Notably, patients with LVEF > 30% showed similar clinical response to CRT-D as patients with lower LVEF, despite the fact that they had a higher frequency of RBBB and IVCD and less wide QRS durations, characteristics which were proven to be associated with unfavorable response in MADIT-CRT.[68] Furthermore, patients with LVEF > 30% had significantly smaller end-diastolic, end-systolic volumes indicating less advanced stage of the disease. This finding highlights the importance of heart failure progression prevention in this patient population.

We showed that LBBB patients derived significant improvement from CRT-D, while non-LBBB patients did not have better clinical outcome with CRT-D irrespective of their baseline LVEF. This finding is in agreement with our previous report.[68]

This is the first report that data are presented from a large patient cohort analyzing the impact of baseline LVEF, including those with LVEF > 30% on the primary end point of HF or death in patients with NYHA class I or II undergoing CRT implantation.

Possible limitations of this study include the fact that this is a post-hoc analysis and the fact that incomplete datasets or images with poor quality were excluded from the analysis and that some study patients with images at baseline might be deactivated from the study or die before the one-year re-assessment.

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# 6 Conclusions

## 6.1 Current Practice of Cardiac Resynchronization Therapy

### 6.1.1 *Evaluating the effects of CRT-P versus CRT-D in a CRT Registry*

We demonstrated that non-ischemic heart failure patients implanted with CRT-D or CRT-P gain similar clinical and echocardiographic improvement after CRT implantation and the mortality benefit is the same. Patients with ischemic cardiomyopathy implanted with CRT-D showed significant reduction in all-cause mortality as compared to ischemic patients implanted with a CRT-P device.

## 6.2 Refining Implantation Methods

### 6.2.1 *Prognostic Significance of Right Ventricular to Left Ventricular Interlead Sensed Electrical Delay in CRT Patients*

We showed that in CRT patients, right to left ventricular interlead sensed electrical delay greater than 106.5 ms measured during the implantation procedure is associated with significant all-cause mortality reduction as compared to patients with right to left ventricular interlead sensed electrical delay lower than 106.5 ms.

### 6.2.2 *Electroanatomical Mapping-Guided Transseptal Endocardial LV Lead Implantation*

We reported successful electroanatomical mapping-guided LV endocardial lead implantation in four patients after unsuccessful permanent transvenous or epicardial LV lead placement. Electroanatomical mapping to implant LV endocardial leads was proven a useful method, which might help identifying the optimal LV lead position for CRT.

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## 6.3 Effects of CRT on Ventricular Arrhythmias

### 6.3.1 *Left Ventricular Lead Location and the Risk of Ventricular Tachyarrhythmias*

Our study on LV lead position and its impact on VT/VF events in MADIT-CRT showed that CRT therapy with posterior or lateral left ventricular lead position is associated with reduced risk of ventricular arrhythmic events in comparison to anterior LV lead locations or ICD-only treated patients. However, CRT-D with anterior LV lead positions does not increase arrhythmic events, clearly indicating that CRT carries no pro-arrhythmic effects.

### 6.3.2 *Left Ventricular Dyssynchrony and the Risk of Ventricular Tachyarrhythmias*

Our study demonstrated that CRT-induced improvement in LV dyssynchrony in patients with LBBB is associated with significant risk reduction of VT/VF/Death and VT/VF compared to patients with no improvement or worsening LV dyssynchrony. In asymptomatic or mildly symptomatic heart failure patients with LBBB ECG pattern undergoing CRT implantation, lack of improvement in LV dyssynchrony with CRT might be helpful to identify patients at higher risk of subsequent ventricular tachyarrhythmias.

## 6.4 New indications of CRT

### 6.4.1 *Chronic Right Ventricular Apical Pacing*

We showed that CRT upgrade is feasible in patients with previously implanted ICD and patients get similar benefit in survival like those with previously implanted PM upgraded to CRT. However, the echocardiographic response was more pronounced in patients with previously implanted PM compared to the ICD patient population.

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### 6.4.2 *Cardiac Resynchronization Therapy in Patients with Less Severe Ventricular Dysfunction*

We have proven that the clinical benefit of CRT is present regardless of LVEF groups in patients enrolled in MADIT-CRT, including those with LVEF > 30% beyond the eligibility criteria. The echocardiographic response was directly correlated with increasing LVEF indicating that patients with better baseline LVEF may derive benefit from cardiac resynchronization therapy.

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# 7 Summary

Cardiac resynchronization therapy has been shown an effective therapeutic treatment option in patients with heart failure, wide QRS and severely depressed LVEF. However, the effects of CRT on ventricular arrhythmias or in patients with chronic RV pacing are unknown. We also aimed to evaluate possible new indications for CRT and refining current implantation methods.

We demonstrated that HF patients implanted with CRT-D or CRT-P gain similar clinical, echocardiographic improvement and mortality benefit. Patients with ischemic cardiomyopathy implanted with CRT-D showed significant reduction in all-cause mortality as compared to CRT-P. In CRT patients, right to left ventricular interlead sensed electrical delay is a powerful prognostic marker of all-cause mortality. We reported successful electroanatomical mapping-guided LV endocardial lead implantation in a small series of patients. We showed that CRT therapy with posterior or lateral left ventricular lead position is associated with reduced risk of ventricular arrhythmic events in comparison to anterior LV lead location or ICD-only treated patients. We demonstrated that CRT-induced improvement in LV dyssynchrony in patients with LBBB is associated with significant risk reduction of VT/VF/Death and VT/VF.

We also showed that CRT upgrade is feasible in patients with previously implanted ICD as compared to patients with previously implanted PM. We have proven that the clinical benefit of CRT is present in patients enrolled in MADIT-CRT with LVEF > 30% beyond the eligibility criteria, indicating that patients with better baseline LVEF may derive benefit from cardiac resynchronization therapy.

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# 8 Összefoglalás

A CRT kezelés bizonyítottan hatásos terápia súlyos szívelégtelen, széles QRS-sel és jelentősen csökkent bal kamra funkcióval rendelkező betegek esetében. Azonban, a reszinkronizációs kezelés hatása kamrai ritmuszavarokra vagy krónikus jobb kamrai ingerléssel élő betegekre jelenleg kevéssé ismert. Célom volt továbbá lehetséges új CRT indikációk felkutatása és a jelenlegi implantációs technika finomítása.

Dolgozatomban igazoltam, hogy CRT implantáción átesett betegekben, mind CRT-P, mind CRT-D esetében jelentős klinikai, echocardiográphiás javulás és mortalitás csökkenés figyelhető meg. Mindemellett, ischemiás cardiomopathiás betegekben a CRT-D kezelés a mortalitás szignifikáns csökkenésével járt együtt, CRT-P betegekkel összehasonlítva. CRT beültetésre kerülő betegekben a kettős jel távolság a mortalitás kitűnő prognosztikai faktornak vizonyult. Egy kisebb betegpopuláción igazoltam az elektroanatómiai térképezéssel vezérelt bal kamrai endocardialis transseptalis elektróda implantáció sikerességét. Kimutattam továbbá, hogy CRT-s betegekben a lateralis vagy posterior elektróda pozíció a kamrai ritmuszavarok előfordulásának jelentős csökkenésével jár, anterior elektróda pozícióval, illetve ICD-s betegekkel összehasonlítva. Igazoltam, hogy bal Tawara szár-blokkos betegekben a CRT-indukált dyssynchronia csökkenése a kamrai ritmuszavarok jelentős csökkenésével jár együtt.

Bizonyítottam, hogy CRT upgrade sikeresen elvégezhető korábban ICD készülékkel implantált betegek esetében. Demonstráltam továbbá, hogy CRT kezelés hatásos 30%-os bal kamrai ejekciós frakció feletti betegek esetében, mely alapul szolgálhat a CRT beültetés jelenlegi indikációs körének bővítésére.

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# 10 Publications

## 10.1 Publications closely related to the present thesis

### 10.1.1 *Original articles*

**1. V Kutyifa**, B Merkely, S Szilagyi, E Zima, A Roka, A Kiraly, I Osztheimer, L Molnar, G Szeplaki, L Geller. (2012) Usefulness of electroanatomical mapping during transseptal endocardial left ventricular lead implantation. EUROPACE 14:(4) pp. 599-604.

**IF: 1.839**

**2. V Kutyifa**, A Kloppe, W Zareba, SD Solomon, S McNitt, A Barsheshet, S Polonsky, B Merkely, B Lemke, VK Nagy, AJ Moss, I Goldenberg. (2012) The Influence of Left Ventricular Ejection Fraction on the Effectiveness of Cardiac Resynchronization Therapy in MADIT-CRT. JACC. Accepted for publication. **IF: 14.292**

**3. V Kutyifa**, W Zareba, S McNitt, J Singh, WJ Hall, S Polonsky, I Goldenberg, DT Huang, B Merkely, PJ Wang, AJ Moss, HU Klein. (2012) Left Ventricular Lead Location and the Risk of Ventricular Arrhythmias in the MADIT-CRT trial. European Heart Journal, 2012 Oct 10. [Epub ahead of print] **IF: 10.478**

**4. V Kutyifa**, P Bogyi, E Zima, VK Nagy, S Szilagyi, G Szeplaki, L Geller, B Merkely. (2012) Effects of Upgrading to Cardiac Resynchronization Therapy in Pacemaker and Implantable Cardioverter Defibrillator Patients and Predictors of Long-Term Outcome. Journal of Cardiovascular Electrophysiology, *submitted*

**5. V Kutyifa**, AC Pouleur, D Knappe, AA Ahmad, M Gibisnki, PJ Wang, S McNitt, B Merkely, I Goldenberg, SD Solomon, A J Moss, W Zareba. (2012) Dyssynchrony and the Risk of Ventricular Arrhythmias. JACC Cardiovascular Imaging, *under minor revision*

**6. V Kutyifa,** OA Breithardt. How to assess the nonresponder to cardiac resynchronization therapy-a comprehensive stepwise approach. (2012) REVISTA ESPANOLA DE CARDIOLOGIA. 65:(6) pp. 504-510. Review **IF: 2.157**

**7.** A Apor, **V Kutyifa**, B Merkely, S Szilagyi, P Andrassy, H Huttl, M Hubay, A Roka, L Geller. (2008) Successful cardiac resynchronization therapy after heart transplantation. EUROPACE. 10:(8) pp. 1024-1025. **IF: 1.706**

## 10.2 Publications not related to the present thesis

### 10.2.1 *Original articles*

**1.** B Merkely, A Róka, **V Kutyifa,** L Boersma, A Leenhardt, A Lubinski, A Oto, A Proclemer, J Brugada, PE Vardas, C Wolpert. (2012) Tracing the European course of cardiac resyncronization therapy from 2006 to 2008. EUROPACE. 12:(5) pp. 692-701.

**IF: 1.839**

**2.** L Molnar, G Szűcs, E Zima, S Szilágyi, **V Kutyifa,** D Becker, L Geller, B Merkely. (2009) Successful management and long term outcome of an accidental subclavian artery injury with a 9 french dilator during pacemaker implantation with collagen-based closure device. JOURNAL OF INTERVENTIONAL CARDIAC ELECTROPHYSIOLOGY 25:(3) pp. 217-218.

**IF: 1.056**

**3.** S Szilágyi, B Merkely, E Zima, **V Kutyifa,** G Szűcs, G Fülöp, L Molnár, Z Szabolcs, L Gellér. (2008) Minimal invasive coronary sinus lead reposition technique for the treatment of phrenic nerve stimulation. EUROPACE 10:(10) pp. 1157-1160. **IF: 1.706**

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**4.** S Szilágyi, B Merkely, A Róka, E Zima, G Fülöp, **V Kutyifa,** G Szűcs, D Becker, A Apor, L Geller. (2007) Stabilization of the coronary sinus electrode position with coronary stent implantation to prevent and treat dislocation. JOURNAL OF CARDIOVASCULAR ELECTROPHYSIOLOGY 18:(3) pp. 303-307. **IF: 3.475**

**5.** A Nemes, T Forster, ML Geleijnse, **V Kutyifa,** K Neu, OI Soliman, FJ Ten Cate, M Csanády. (2007) The additional prognostic power of diabetes mellitus on coronary flow reserve in patients with suspected coronary artery disease. DIABETES RESEARCH AND CLINICAL PRACTICE 78:(1) pp. 126-131. **IF: 1.823**

10.2.2 ***Articles in Hungarian***

**1. V Kutyifa,** B Merkely, Z Pozsonyi, K Hosszú, Sz Szilágyi, Gy Balázs, A Tóth, P Sármán, L Geller. (2008) Intracardiac echocardiography-guided cardiac tumor mass biopsy. Orvosi Hetilap Sep 28;149(39):1857-9. Article in Hungarian.

**2.** VK Nagy, **V Kutyifa,** A Apor, E Edes, A Nagy, B Merkely. (2012) Balkamra hipertrófia és remodeling vizsgálata élsportolókban. CARDIOLOGIA HUNGARICA 42:(1) pp. 11-16.

10.2.3 ***Book chapters***

**1. V Kutyifa,** B Merkely. Gyógyszertámogatás a klinikum szemszögéből. Medicina Kiadó.

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