Optimization of cardiac resynchronization therapy for the treatment of chronic heart failure: response of patients and new indications

PhD thesis

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Introduction

Cardiac resynchronization therapy has been shown to reduce hospitalization and all-cause mortality and to improve cardiac function and heart failure symptoms, quality of life and functional class in patients with decreased ejection fraction and prolonged QRS.

However approximately 30-40% of patients fail to improve and develop reverse remodeling after CRT implantation, and they consistently show significantly higher risk for mortality and heart failure events.

Decreasing the rate and early selection of such patients are crucial in the long-term outcome of patients and to decde by further therapeutic options.

Biomarkers might be feasible in optimal patient selection and to detect non-reponse as well.

There are also implantational parameters that could further improve the effect of resynchronization. During lead implantations, right to left ventricular activation delay may also reflect the distance of both leads, moreover shows the electrical dyssynchrony and prolonged activation pattern derived from the slow conduction due to e.g. a scar tissue. Those studies, which used right to left activation delay, also showed significant improvement in echocardiographic response and in clinical outcome in patients with longer measured activation delay. However, none of these studies looked specifically at sub-groups of LBBB and non-LBBB patients.

Several studies suggested that only patients with typical LBBB ECG morphology derive a significant benefit from cardiac resychronization. Although right ventricular pacing could reveal ventricular dyssynchrony similar to LBBB, data are scarce regarding the benefit of upgrade CRT in patients with previously implanted conventional pacemakers or implantable cardioverter defibrillators.

The most recent guidelines are referred upgrade procedures as a IIb B evidence level, however there have been no conclusive data on this field. Thus our investigator initiated trial, the BUDAPEST CRT study will be the first multicenter, randomized trial with investigtes chronic heart failure patients with a pacemaker or implantable cardioverter defibrillator and permanent or intermittent right ventricular pacing.

Aims

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

1. In order to optimize the patient selection and early assessment of the response to CRT, the serum levels of a novel biomarker, CT-apelin were measured.

Its predictive value for the echocardiographic response was investigated and compared to the gold standard NT-proBNP levels at baseline and 6 months after resynchronization.

2. Moreover we examined the impact of an easily measured parameter during the implantation, the RV-LV activation delay.

Its predictive role in the functional, echocardiographic and clinical outcome such as heart failure, all-cause mortality or laboratory parameters including NT-proBNP and renal function was assessed by the baseline QRS morphology of patients who underwent CRT implantation.

3. We would also focus on those questions, which are not entirely covered by the current ESC guidelines: patients who have an already implanted conventional pacemaker or ICD and referred to CRT upgrade.

By concluding the available evidences of the literature, we analysed the clinical outcome and long-term survival after upgrading compared to de novo implantation.

4. However conclusive data will be provided by the BUDAPEST-CRT Upgrade Study, which investigates the all-cause mortality, heart failure events and echocardiographic response as primary endpoint besides functional response and safety after 12 months. The actual status and design of this investigator initiated trial is shown.

Methods

For a better interpretation, those studies in which optimal patients selection and intraoperative parameters were evaluated are shown in Part 1, and the question of CRT upgarde is discussed in Part 2 separately in the Methods and Results sections.

1. Patient populations

1.1 Patient population in Part1

Between 2009 and 2010 a prospective, observational, cohort study was designed at the Heart and Vascular Center. Patients with ischemic and non-ischemic etiology with low left ventricular ejection fraction (EF≤35%), a prolonged baseline QRS interval (≥120 ms) and symptoms of HF (NYHA II-IVa functional class) despite optimal medical treatment were enrolled, the inclusion and exclusion criteria were in line with the current guidelines.

In the investigation of optimal patient selection by serum biomarker measurements, from the total included patient cohort those who were unable to give serum samples for biomarker assessments were censored. The study was approved by the Institutional Scientific Ethics Committee.

1.2 Patient population in the BUDAPEST CRT upgrade study in Part2

From November 2014 patients are enrolled to the study regardless of the heart failure etiology with reduced LVEF (≤ 35%), symptoms (NYHA functional class II-IVa) despite optimal medical treatment with single or dual chamber pacemakers or ICD devices implanted at least 6 months before the inclusion (with ≥20% RV pacing over 90 days prior to enrolment and wide paced QRS duration ≥150 ms) with sinus rhythm, atrial fibrillation/flutter or atrial tachycardia as per protocol. Exclusion and inclusion criteria are listed in Table 1. Those subjects, who proved to be eligible for the study, could be randomized in a 3:2 manner (CRT-D:ICD).

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

Inclusion criteria	Exclusion criteria
1. Age: over 18 years 2. Cardiomyopathy with LVEF ≤35%, ischemic or non-ischemic 3. Single or dual chamber PM or ICD implanted ≥6 months prior to enrolment (battery depletion or another indication for upgrade is not required)	1. CABG or PCI ≤3 month ago or planned 2. AMI ≤3 month ago 3. Unstable angina 4. Planned cardiac transplant 5. Acute myocarditis 6. Infiltrative or hypertrophic cardiomyopathy 7. Severe primary mitral, aortic or tricuspid valve

4. RV pacing ≥20% in the prior ≥90 days (use of algorithms to avoid ventricular pacing is recommended, per discretion of the clinician) 5. Paced QRS duration ≥150 ms 6. Symptomatic heart failure with NYHA functional class II-IVa ≥3 months prior to enrolment, despite optimized medical therapy 7. Informed consent	stenosis or insufficiency 8. Tricuspid valve prosthesis 9. Severe right ventricular dysfunction (RV basal diameter > 50mm) 10. Chronic severe renal dysfunction (creatinine >200 μmol/l) 11. Pregnant women or planned pregnancy 12. Any comorbidity that is likely to interfere with the conduct of the study 13. Participation in another trial 14. Patients unable or unavailable for follow-ups 15. Intrinsic QRS with typical LBBB morphology

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

2. Follow ups and investigations

In our prospective study each visits included a physical examination, assessment of the NYHA functional class, transthoracic echocardiography, detailed laboratory tests with serum biomarker measurments, 6 minute walk test and EQ5D quality of life measurements extended with device interrogations after the implantation. Investigations were performed at the baseline visit and 6 months after CRT/ICD implantation.

While in the BUDAPEST-CRT upgrade study, eligible patients undergo a baseline evaluation including clinical history, physical examination, NYHA class, 12-lead ECG with paced (paced VVI or DDD 70 bpm and non-paced QRS complexes using VVI 40 bpm settings), transthoracic echocardiography, device interrogation (RV pacing percentage and Holter data), quality of life assessment (EQ5D), 6 minute walk test and optional NT-pro-BNP measurement. Patients are followed up for 12 months after randomization. Regular, in-office follow-ups will be performed at 1, 6 and 12 months.

In each studies echocardiography was performed according to current standards in a left lateral position using Philips iE33 echocardiography system equipped with an S5-1 transducer (Philips Healthcare, Best, The Netherlands). Measurements were performed by the same person offline. Left ventricular ejection fraction was calculated by the biplane Simpson method.

By performing ECGs, the assessment of QRS width and morphology were mandatory in each study. After all of the ECGs has been recorded, the same person assessed the data and fill our electronical database retrospectively.

During BUDAPEST CRT study the digital formation of ECGs, pacemaker interrogation files and echocardiographic images are uploaded to the Biobankok server in the Heart and Vascular Center and will be analysed retrospectively by the corelab.

3. Serum biomarker measurements

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

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

4. Device implantation and programming

4. 1 Device implantation procedure in Part 1

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

4. 2 Upgrade procedure in BUDAPEST CRT UPGRADE study

Upgrade procedures need to be performed within 14 business days after randomization. During the procedure, duration time of the upgrade, X-ray dosage, details of the implanted leads, adverse events and RV-LV AD are mandantory to report. Patients with an existing ICD, who are randomized to the ICD arm, may not need a procedure unless a generator replacement, a system revision is necessary or the PI decides on upgrading to CRT-D in RV only pacing mode. Decisions about lead extraction are also based on the physicians' discretion by actual recommendations. Use of Boston Scientific Corporation (Marlborough, MA, USA) ICDs or CRT-D is preferred, but not mandatory. In the CRT-D arm, the left ventricular lead is recommended to be implanted in the lateral or postero-lateral side branch of the coronary sinus. Transvenous implantation is strongly preferred; however, alternative methods are also accepted if the transvenous attempt fails.

4.3 RV-LV AD measurement at implantations

After positioning both ventricular leads, intraoperative RV-LV activation delay measurements were performed by connecting to an electrophysiology system (Biotronik Reality SN6151087, Berlin, Germany). The right to left interventricular sensed delay was measured by the time delay of the peak activation in the right and left ventricular sensed signals phrased in milliseconds.

4.4 Device programming during BUDAPEST CRT upgrade study

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

5. Endpoints

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

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

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

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

Heart failure events were defined as symptoms and signs of heart failure that required intravenous diuretic treatment during an in-hospital stay. We also evaluated the clinical outcome as changes of ejection fraction, distance walked during the 6-minute walk test and NT-proBNP serum levels after 6-month.

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

patients with RV-LV AD < 86 ms

and those with RV-LV AD ≥ 86 ms

Thereafter they were further grouped by their baseline LBBB morphology:

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

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

Our analyses were extended by RV-LV AD as a continuous parameter on NT-proBNP and clinical outcome of HF/death, we evaluated the changes in NT-proBNP at 6-month by RV-LV AD quartiles along with the incidence of HF/death.

5.3 Endpoints and study selection in the meta-analysis of patients after CRT upgrade compared to de novo CRT implantation

The systematic review was performed according to the PRISMA Statement and a predefined review protocol was published in the PROSPERO database under the registration number of CRD42016043747. A comprehensive search of PubMed, Research Gate, and Google Scholar databases was performed from January 2006 to June 2016 focusing on full-sized, peer-reviewed, English language papers or abstracts reporting data on (i) all-cause mortality (ii) reporting heart failure events; (iii) reporting echocardiographic (i.e. LVEF, EDV) or clinical (NYHA class) or ECG (QRS width) parameters of reverse remodeling.

5.4 Endpoints in the BUDAPEST-CRT upgrade study

The primary endpoint of the study is a composite endpoint of heart failure events, all-cause mortality, or less than 15% reduction in echocardiography determined left ventricular end-systolic volume from baseline to 12-month.

Secondary endpoints are the composite of heart failure events and all-cause mortality, all-cause mortality alone, the changes of echocardiographic parameters (left ventricular end-diastolic volume or left ventricular ejection fraction) from baseline to 12 month.

Tertiary endpoints are the success and safety of implantation procedures, the change of NYHA class, quality of life assessed by EQ-5D questionnaire, 6-minute walk test and the changes of NT-pro-BNP serum levels from baseline to 12 months.

6. Statistics and methods for analyses

Statistical analyses were performed by Graph Pad version 6.0 and 7.0 (Graph Pad Inc., CA, USA), SPSS version 9 (IBM, NY, USA) or Comprehensive Meta-Analysis 3.3 (Biostat, Inc., USA).

Continuous variables with normal distributions are expressed as mean±SD, while those with non-normal distributions as medians with interquartile range (IQR). Categorical variables are shown with numbers and percentages (n, %). Baseline clinical characteristics were compared by unpaired t-test for normally distributed continuous variables, the Mann–Whitney U-Test for non-normally distributed variables, while $\chi 2$ - test or Fisher exact test was used for dichotomous variables, as appropriate.

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

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

In the meta-analyses heterogeneity between individual trial estimates was assessed by the Q statistic and I2 statistic. Since, there was significant heterogeneity in the design and patient's characteristics of the studies included into the meta-analyses, it was assumed that the true effect size varies from one study to the next, and hence the random-effect model was used. Since we did not have access to individual patient data from all studies reviewed, the median of delta values for LVEF, EDV, NYHA and QRS were calculated and compared between the two patient groups separately by using the Mann-Whitney U test.

Results

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

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

Baseline clinical characteristics

From those patiens who underwent a successful CRT implantation between September 2009 and December 2010, 81 patients were included in the current study. Mean age of the recruited patients was 64.9±10.5 years, with a mean ejection fraction of 28.5±6.5%, and mean QRS width of 167.7 ± 29.8 ms. Eighty-six percent of the patients had typical LBBB morphology and 59% had CRT-D device. Seventy-five percent of the patients were in NYHA class III functional state and 59 % had ischemic etiology before CRT implantation. No significant differences were found between responder and non-responder patients in baseline clinical variables, medical history, echocradiographic parameters or baseline serum biomarkers.

Response and prognosis

During the mean follow-up time of 795 ± 99 days, 7 (9%) patients died. Based on the pre-defined classification of response, 15 (18.5%) patients proved to be non-responders. In line with the definition of response, left ventricular volumes significantly decreased (ESV: 179.1 ± 64.9 vs. 117.9 ± 58.9, p<0.0001, EDV: 248.6± 80.2 vs. 196.7 ± 77.5, p<0.0001) and left ventricular function significantly improved (EF: 28.1 ± 6.0 vs. 41.3 ± 7.9) in responder patients after CRT implantation, while these parameters remained unchanged in the non-responder group after 6 months. According to Cox-regression analysis, non-responders had an almost four-fold higher risk for mortality compared with responders (HR: 3.75; 95% CI: 1.00-13.97; p=0.049). This impact on mortality persisted also in the multivariate model, with non-response to CRT prevailing as an independent predictor of mortality (adjusted HR: 4.54, 95% CI: 1.14-18.15, p=0.03)(Figure 1).

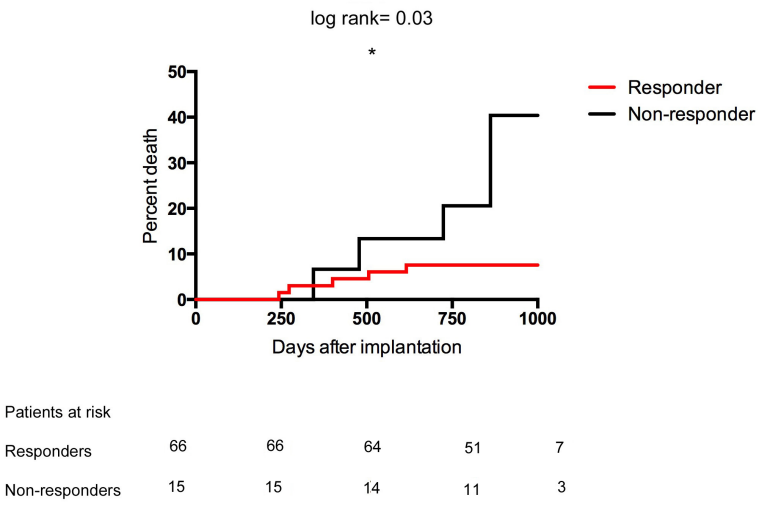

Figure 1: All-cause mortality in responder and non-responder patients

Biomarkers to identify non-responders

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

At six months, serum CT-apelin significantly decreased in responders (from 549.5 ng/ml [IQR: 279.0-868.8] to 211.0 ng/ml [IQR: 113.8-416.8]; p<0.0001), while it remained unchanged in non-responder patients (from 472.5 ng/ml [IQR: 307.8-700.3] to 541.0 ng/ml [IQR: 278.3-831.0]; p=0.80). Similarly, NT-proBNP levels significantly decreased in responders at 6 months (median: 2561 pg/ml, IQR: 1173-4616 to 1253 pg/ml IQR: 516-2519; p=0.007), while it remained unchanged in non-responder patients (median: 3126 pg/ml [IQR: 1238-4492] to 2676 pg/ml [IQR: 1947-4354]; p=0.91)(Figure 2).

In ROC analysis, both 6-month CT-apelin and NT-proBNP levels significantly discriminated between responder and non-responder patients (CT-apelin: AUC 0.78; 95%CI: 0.59-0.97; p<0.01, NT-proBNP: AUC 0.75; 95%CI: 0.62-0.88; p=0.005). According to the highest sensitivity and specificity, the optimal cutoffs to diagnose non-response were 268.5 ng/ml for CT-apelin and 1348.5 pg/ml for NT-proBNP.

When patients were classified into groups according to optimal cutoff values, patients with high serum CT-apelin showed a 10 times higher odds for non-response (OR: 10.3, 95% CI; 1.16-91.43; p=0.04), while higher NT-proBNP levels indicated a 16-fold odds for non-response in our patient cohort (OR: 16.0, 95% CI; 1.96-130.68; p=0.01).

However, Multivariate ROC testing suggested the superiority of CT-apelin over NT-proBNP (CT-apelin: AUC 0.78; 95%CI: 0-59-0.97; p=0.013 vs. NT-proBNP: AUC 0.67; 95%CI: 0.49-0.85; p=0.13, Figure 3) that was also confirmed in multivariate logistic regression analysis (CT-apelin: p=0.01, NT-proBNP: p=0.41).

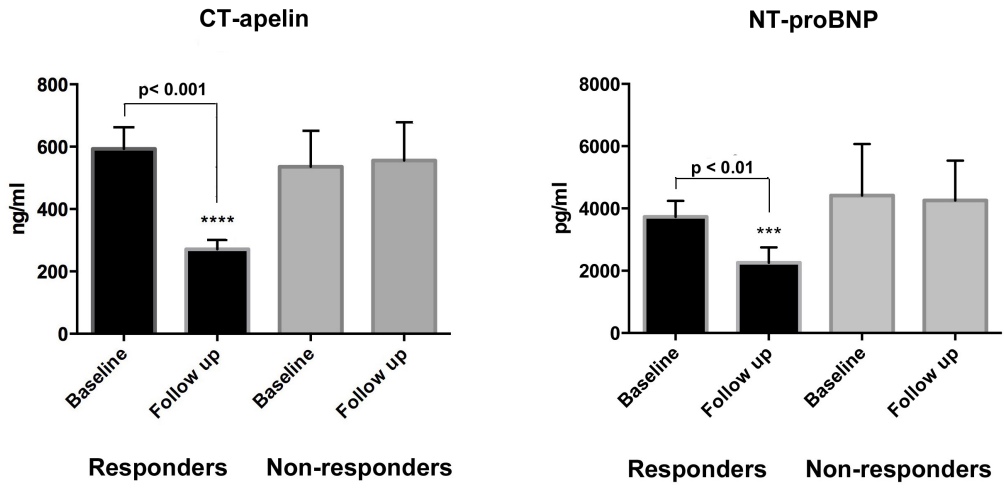

Figure 2. Serum biomarker changes in responder and non-responder patients

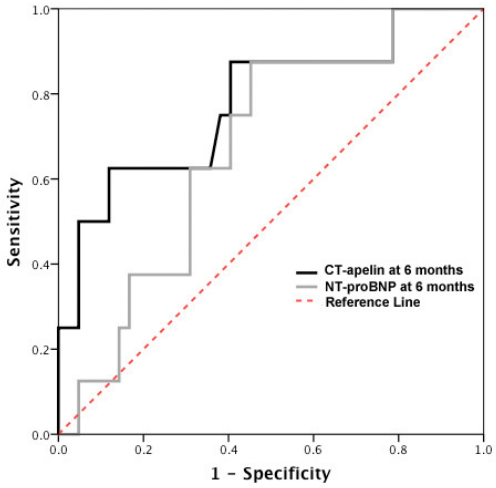

Figure 3. Receiver–Operator Characteristic Curve analysis comparing the diagnostic performance of 6-month serum CT-apelin and NT-proBNP levels on identifying non-responders to CRT

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

Baseline clinical characteristics

Altogether 125 patients were enrolled in the current investigation, the mean age of the study participants was 67.0 ± 8.6 years, the mean EF was 28.2 ± 6.5%. Majority of the patients (71%) were in NYHA functional class III, 62% of them had LBBB and 60% had ischemic cardiomyopathy. The RV-LV AD measurements were ranged between 40 and 175ms, the mean value was 106.10 ± 29.98 ms in the entire patient cohort, 109.80 ± 30.31 ms in the LBBB group, 100.0 ± 28.72 ms in the non-LBBB group (p=0.07). Baseline clinical characteristics of patients with an RV-LV AD below or equal and above 86 ms (lower quartile) showed no major differences among patients with a shorter or longer RV-LV AD in clinical or echocardiographic parameters.

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

RV-LV AD and clinical outcome in the total patient cohort

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

(37%) patients died with RV-LV AD < 86 ms, and 25 patients (26%) with RV-LV AD ≥ 86 ms.

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

Multivariate Cox-regression analysis confirmed the independent role of RV-LV AD, patients with RV-LV AD ≥ 86ms had a 56% significantly lower risk of HF or death (HR: 0.44; 95% CI: 0.23-0.82; p=0.001) and a 52% lower risk of all-cause mortality (HR: 0.48; 95% CI: 0.23-1.00; p=0.05), compared to those with a shorter RV-LV AD after adjustment for relevant clinical covariates (such as LBBB morphology, etiology and age).

RV-LV AD and clinical outcome by LBBB ECG pattern

These findings were more pronounced in patients with an LBBB ECG pattern. Patients with an LBBB and an RV-LV AD ≥ 86 ms at implantation had a significantly lower cumulative probability of HF/death when compared to those with shorter activation delay (RV-LV AD < 86 ms) and to those patients with non-LBBB (p<0.001). This difference was translated into a 77% reduction in the risk of HF or death (HR: 0.23; 95% CI: 0.11-0.49; p < 0.001), after adjustment for relevant clinical covariates.

Furthermore, there was a significantly lower cumulative probability of all-cause mortality in LBBB patients with a longer RV-LV activation delay at implantation (RV-LV AD ≥ 86ms), compared to those with shorter activation delay (RV-LV AD <86ms) and to those patients with non-LBBB (p=0.01). This translated into a 65% risk reduction in all-cause mortality in the multivariate models (HR: 0.35; 95% CI: 0.16-0.75; p=0.007).

In patients with non-LBBB, there was no significant difference in HF or death or in all-cause mortality by RV-LV AD groups measured at CRT implantation (HF/death HR=0.63; 95% CI: 0.26-1.49; p=0.29, death HR=0.43; 95% CI: 0.15-1.20; p=0.11)

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

At 6-month follow up, 33 (55%) of the patients with RV-LV AD ≥ 86 ms and LBBB performed their 6-minute walk test over 300 meters, compared to 23 of those patients (35%) with RV-LV AD < 86 ms or with a non-LBBB (55% vs. 35%; p=0.03). In patients with RV-LV AD ≥ 86 ms and LBBB, better laboratory parameters were observed at 6-month after CRT implantation regarding NT-proBNP (1216 pg/ml (IQR: 326.9 / 2630) vs. 1887 pg/ml (IQR: 1140 / 3300); p = 0.03), serum creatinine (96.3±

56.6 umol/l vs. 122.1 ± 46.9 umol/l; p = 0.01) and blood urea nitrogen (7.6 ± 4.7 mg/dl vs. 10.9 ± 5.6 mg/dl; p = 0.001), as compared to non-LBBB patients or to those with LBBB and RV-LV AD < 86 ms. Patients with RV-LV AD ≥ 86 ms and LBBB showed the greatest improvement in left ventricular ejection fraction (EF: 28.0 ± 7.1% to 36.3 ± 12.3%; p < 0.001) 6-month after CRT implantation.

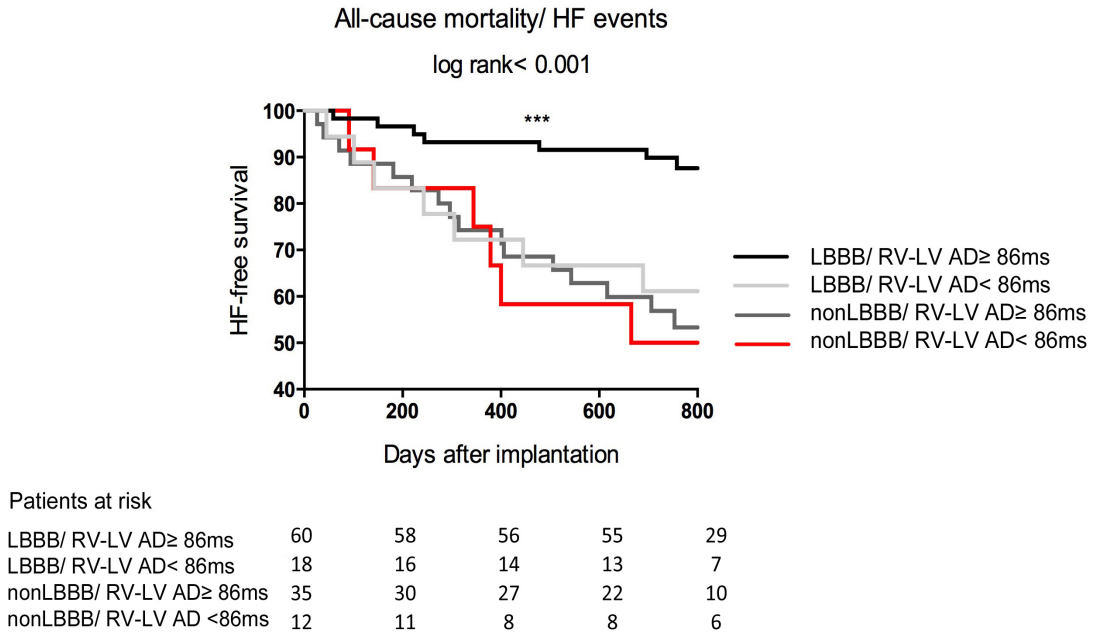

Figure 4. Kaplan-Meier Cumulative probability of HF/Death by LBBB ECG morphology and RV-LV activation delay**.**

When we assessed the effects of RV-LV AD on changes of NT-proBNP and incidence of HF/death by RV-LV quartiles, we found a linear increase in the degree of reduction in NT-proBNP 6-month after CRT towards the longer RV-LV AD quartile sub-groups. In parallel with the improvement in NT-proBNP, there was a linear decrease in the incidence of HF/death (Figure 5).

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

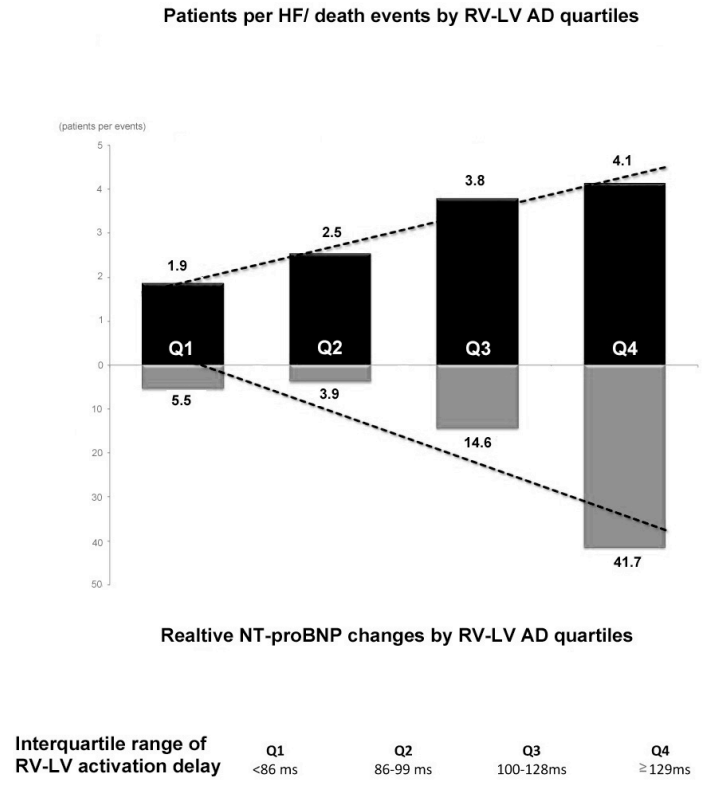

Figure 5. Incidence of patients per HF/death events and relative changes of NT-proBNP by RV-LV AD quartiles

Part 2 - The question of CRT upgrade

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

A total of 17 reports were selected for the current analysis comprising 6628 CRT recipients, of whom 4549 patients had de novo resynchronization therapy and 2079 patients underwent an upgrade procedure. Most of them were observational, retrospective or prospective cohort studies, and the vast majority were single-center observations with the exception of four dual/multicenter studies and one based on a European survey.

Regarding the investigated patient population, the mean ejection fraction was by definition lower than 35% in all studies, with severe symptoms (NYHA III-IVa). More than 50% of the studies found significant differences in the following baseline parameters between de novo vs. upgarde CRT groups: age, atrial fibrillation and QRS duration. In the upgrade group, patients were generally older, more likely to have atrial fibrillation and they had wider (paced) QRS.

All-cause mortality and heart failure events

Crude mortality rates were available in 6157 patients from 12 studies, while unadjusted or adjusted hazard ratios were available for 1734 and 1229 patients in three and four studies, respectively. All-cause mortality did not differ following an upgrade to CRT compared to de novo implantations (RR 1.10, 95% CI, 0.99 to 1.22, p=0.08, I2=36.5%)(Figure 6). Pooled analyses of the unadjusted or adjusted hazard ratios revealed similar findings (crude HR 1.07, 95% CI, 0.72 to 1.57, p=0.74, I2=73.65%)(adjusted HR: 0.81, 95% CI, 0.36 to 1.81, p=0.61). In studies that provided relevant information, the unadjusted risk of heart failure events was significantly higher in patients with de novo implantations (RR 1.15, 95% CI, 1.04 to 1.27, p=0.01, I2=46.5%).

Left ventricular reverse remodeling, clinical improvement

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

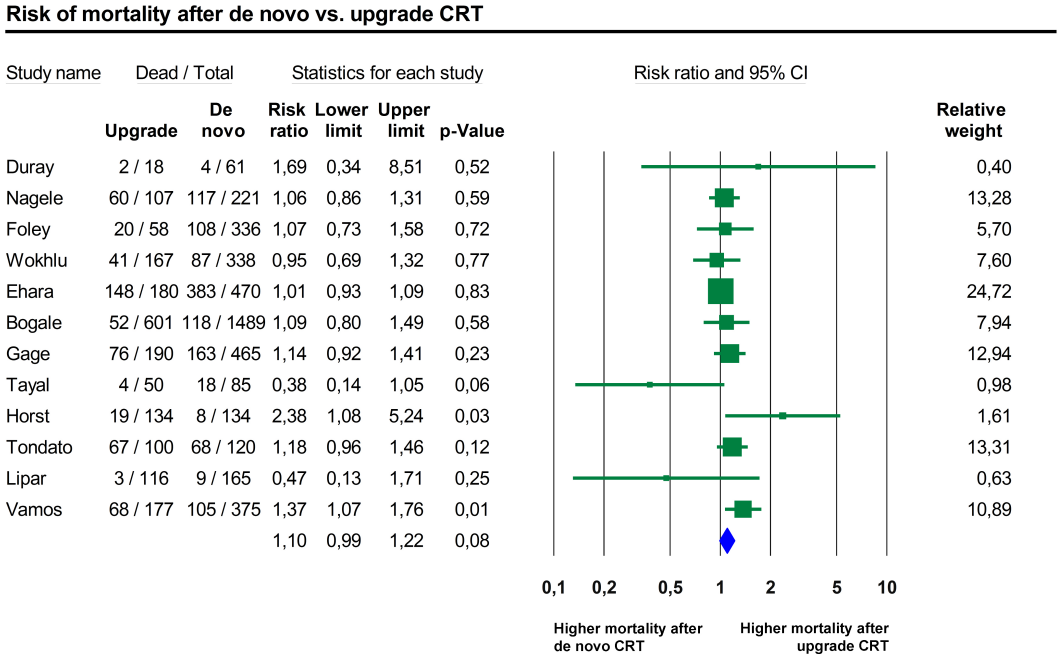

Figure 6. Risk of all-cause mortality (Risk Ratio) after de novo vs. upgrade CRT

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

Enrolment and baseline clinical characteristics

Altogether 26 centers are participating in the study, 20 European (from Hungary, Czech Republic, Germany Poland, Russia, Serbia and Slovenia) and 6 Isreali sites.

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

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

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

Success rate and safety of upgrade procedures

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

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

Follow up, heart failure events and all-cause mortality

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

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

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

CONCLUSIONS

However, cardiac resynchronization is an effective device therapy of chronic systolic heart failure, there have been still a large amount of patients who could not show a beneficial response after CRT implantation.

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

In our cohort less than 20% of heart failure patients failed to develop reverse remodeling and became non-responders to resynchronization, showing an elevated risk for all-cause mortality compared to responders. Thus it is essential to detect such patients as soon as possible. Our results showed, baseline levels of serum biomarkers: CT-apelin and NT-proBNP were not associated with non-response. Therefore, these biomarkers are ineligible as predictors of success before device implantation. However when six-month levels of both CT-apelin and NT-proBNP were investigated, a significant association with non-response was found, suggesting the possible role of such biomarkers in identifying high risk patients, where CT-apelin showed the superiority over NT-proBNP. These findings are rational, while the response to CRT is multifactorial, but these biomarkers may give additional information to define non-responders assigning the most vulnerable patients.

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

The intraoperative right to left ventricular activation delay, which reflects not only the the distance of right and left ventricular leads but also shows the electrical dyssynchrony and prolonged activation pattern derived from the slow conduction, had a predictive value for the outcome. Our results showed, in LBBB patients with a longer or equal to 86 ms right to left ventricular activation delay, a significantly lower risk of composite of heart failure events and death occured and lower risk of all-cause mortality alone compared to those with non-LBBB or those with LBBB and shorter than 86ms right to left ventricular activation delay. Moreover our results show that right to left ventricular activation delay predicts the improvement in left ventricular ejection fraction, NT-proBNP and functional outcome in LBBB patients. Thus simple assessment of intraventricular right to left ventricular activation delay could tailor the procedure to achieve the optimal position with a longer activation delay.

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

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

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

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

List of publications

Publications related to the dissertation

1. **Kosztin A***; Kutyifa V*; Nagy KV; Gellér L; Zima E; Molnár L; Szilágyi Sz; Özcan EE; Széplaki G; Merkely B:
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   Europace [Epub ahead of print 2016 Oct 6] **IF: 4.021**

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