Europace Advance Access published June 27, 2015

Europace
doi:10.1093/europace/euv117

CLINICAL RESEARCH

Longer right to left ventricular activation delay at cardiac resynchronization therapy implantation is associated with improved clinical outcome in left bundle branch block patients

Annamaria Kosztin†, Valentina Kutyifa†, Vivien Klaudia Nagy, Laszlo Geller, Endre Zima, Levente Molnar, Szabolcs Szilagyi, Emin Evren Ozcan, Gabor Szeplaki‡, and Bela Merkely‡,*

Heart and Vascular Center, Semmelweis University, Varosmajor 68, Budapest H-1122, Hungary

Received 6 November 2014; accepted after revision 8 April 2015

Aims Data on longer right to left ventricular activation delay (RV-LV AD) predicting clinical outcome after cardiac resynchronization therapy (CRT) by left bundle branch block (LBBB) are limited. We aimed to evaluate the impact of RV-LV AD on N-terminal pro–B-type natriuretic peptide (NT-proBNP), ejection fraction (EF), and clinical outcome in patients implanted with CRT, stratified by LBBB at baseline.

Methods and results Heart failure (HF) patients undergoing CRT implantation with EF $\leq$ 35% and QRS $\geq$ 120 ms were evaluated based on their RV-LV AD at implantation. Baseline and 6-month clinical parameters, EF, and NT-proBNP values were assessed. The primary endpoint was HF or death, the secondary endpoint was all-cause mortality. A total of 125 patients with CRT were studied, 62% had LBBB. During the median follow-up of 2.2 years, 44 (35%) patients had HF/death, 36 (29%) patients died. Patients with RV-LV AD $\geq$ 86 ms (lower quartile) had significantly lower risk of HF/death [hazard ratio (HR): 0.44; 95% confidence interval (95% CI): 0.23–0.82; $P = 0.001$] and all-cause mortality (HR: 0.48; 95% CI: 0.23–1.00; $P = 0.05$), compared with those with RV-LV AD $<$ 86 ms. Patients with RV-LV AD $\geq$ 86 ms and LBBB showed the greatest improvement in EF (28–36%; $P < 0.001$), NT-proBNP (2771–1216 ng/mL; $P < 0.001$), and they had better HF-free survival (HR: 0.23, 95% CI: 0.11–0.49, $P < 0.001$) and overall survival (HR: 0.35, 95% CI: 0.16–0.75; $P = 0.007$). There was no difference in outcome by RV-LV AD in non-LBBB patients.

Conclusion Left bundle branch block patients with longer RV-LV activation delay at CRT implantation had greater improvement in NT-proBNP, EF, and significantly better clinical outcome.

Keywords RV-LV activation delay • Clinical response • Cardiac resynchronization therapy response

Introduction

Cardiac resynchronization therapy (CRT) has been shown to improve cardiac function, heart failure (HF) symptoms, and to reduce hospitalization and all-cause mortality in patients with mild to severe HF and a prolonged QRS.[1–3]

Recent studies have suggested that patients with a left bundle branch block (LBBB) ECG morphology derive a significant benefit

* Corresponding author. Tel: +361 458 68 10; fax: +361 458 68 17, *E-mail address*: merkely.bela@kardio.sote.hu

† The first two authors contributed equally to the analysis and the drafting of the present manuscript.

‡ The last two authors contributed equally to the study design and coordination of the study.

What's new?

- We evaluated the role of RV-LV activation delay (RV-LV AD) during CRT implantation by baseline LBBB ECG morphology.
- There was greater reduction in mortality and heart failure events with a longer RV-LV AD at device implantation and LBBB.
- Patients with an LBBB ECG morphology and a longer RV-LV AD had significantly greater improvement in reverse remodelling, and NT-proBNP.

from the implantation of CRT, while in patients with a non-LBBB [right bundle branch block (RBBB), or intraventricular conduction delay], the benefit is less if at all discernible.[4,5]

It has been proposed that optimal left ventricular (LV) lead placement is an important determinant of response to CRT. The location of the left and right ventricular leads affects clinical outcome, and the incidence of ventricular tachyarrythmias.[6] Furthermore, few smaller studies have indicated that the electrical delay of the LV lead sensed signal from the beginning of QRS duration (Q-LV), or the distance between the electrical signals of the right to left ventricular activation delay (RV-LV AD) predicted echocardiographic improvement and clinical outcome.[7–9]

However, there have been no studies conducted evaluating the impact of RV-LV AD on N-terminal pro–B-type natriuretic peptide (NT-proBNP) and prior studies on RV-LV AD did not assess the differential effect in subgroups of LBBB and non-LBBB patients.

Therefore, the aim of this study was three-fold: (i) to evaluate the impact of RV-LV activation delay on the biomarker of NT-proBNP, (ii) on the echocardiographic improvement in ejection fraction (EF), and (iii) on clinical outcome assessing HF or death, and all-cause mortality in patients undergoing CRT implantation, by baseline LBBB ECG pattern.

Methods

Patient population and follow-up

A prospective, observational, cohort study was designed including patients with mild to severe chronic systolic HF (EF $\leq$ 35%) and a prolonged QRS (QRS $\geq$ 120 ms) undergoing successful CRT implantation at the Heart and Vascular Center, Semmelweis University, Budapest, Hungary. The study was conducted between September 2009 and December 2010.

Inclusion criteria included CRT indication according to actual guidelines, with an EF under 35%, a prolonged baseline QRS interval ($\geq$120 ms), and symptoms of HF [New York Heart Association (NYHA) II–IV ambulatory functional class] on optimal medical treatment. Exclusion criteria were patients with a known malignant disease, those with an inflammatory disorder, or those with HF based on a genetic condition. We have also excluded patients who were geographically unstable, or did not provide consent to the study. The protocol was approved by the Institutional Research Subjects Review Board. All patients provided written informed consent before inclusion in the study.

Laboratory tests, echocardiographic examination, and physical assessment were performed at baseline and 6 months after CRT implantation. Patients were followed for a median of 2.2 years and clinic follow-up data, and the National Hungarian Health Care Fund database was utilized to assess whether the patients were alive at the end of the follow-up period.

ECG morphology criteria

Left bundle branch block was defined on 12-lead ECGs that were performed at inclusion and were analysed by the same physicians. Left bundle branch block was defined as QRS duration >120 ms; QS or rS in lead V1; broad R waves in leads I, aVL, V5, or V6; and absent q waves in leads V5 and V6.

Right bundle branch block required QRS duration >120 ms; rsr, rsR, rSR, or qR in leads V1 or V2; and occasionally, a wide R wave and wide S waves in leads I, V5, and V6. Intraventricular conduction delay was defined as QRS >120 ms without typical features of LBBB or RBBB.

Device implantation procedure

Cardiac resynchronization therapy implantation was performed using a transvenous approach according to current standards. During device implantation, a coronary venous angiogram was performed to determine the coronary sinus branch suitable for LV lead placement. Left ventricular leads were implanted in the lateral position in 94 (75%) patients, in the posterior position in 28 (23%) patients, and in the anterior position in 3 (2%) patients.

After LV lead positioning, LV pacing threshold, sensing parameters, and LV impedance values were obtained and the pacing output was programmed to achieve an adequate pacing safety margins. In patients with intraoperative LV lead dislodgement or phrenic nerve stimulation, repositioning and stabilization of the coronary sinus lead was performed using coronary stent implantation, as previously described.[10,11] The location of the LV and RV leads was left to the physician's discretion. The right ventricular lead was recommended to be implanted in a septal position, and the left ventricular lead was recommended to be implanted in a posterolateral or lateral position whenever there was a suitable coronary sinus branch available. Left ventricular and RV lead positions were assessed by chest X-rays in the right and left anterior oblique views and reported by the implanting physician.

Right to left ventricular activation delay measurement

The RV-LV activation delay measurements were performed after positioning the right and left ventricular leads, they were connected to an electrophysiology system (Biotronik, 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. Right to left ventricular activation delay was captured in milliseconds.

Follow-up in the study

Patients had a clinic visit every 6 months and at any meaningful clinical event until the end of the study. Dates of death and HF episodes were registered into the database.

Clinic visit included a physical examination, assessment of the NYHA functional class, echocardiography, and a device interrogation. Heart failure events were defined as symptoms and signs suggestive of HF that prompted intravenous diuretic administration during an in-hospital stay. All-cause mortality was assessed using the clinic follow-up data and the National Health Fund Death Registry index.

Echocardiography

Echocardiography was performed according to current standards in a left lateral position using Philips iE33 echocardiography system equipped with an S5-1 transducer (Philips Healthcare, Best, The Netherlands).

Image acqusition was performed according to current recommendations.[12] Measurements were performed offline using the QLAB software (Philips Healthcare). Left ventricular end-systolic and end-diastolic volumes were measured, and EF was calculated by the biplane Simpson method.[12]

Definitions and endpoints

Patients were categorized into two groups by the lower quartile of RV-LV AD (86 ms) measured during CRT implantation: (i) those with RV-LV AD $<$ 86 ms and (ii) those with RV-LV AD $\geq$ 86 ms.

After assessing the role of RV-LV AD in the total patient cohort, patients were further grouped by their baseline LBBB morphology, as pre-specified. Right to left ventricular activation delay subgroups were compared among LBBB patients only, and then among non-LBBB patients only. Then, we combined patients with LBBB and RV-LV AD $<$ 86 ms with patients with non-LBBB ('CRT non-responders') and compared them to patients with LBBB but RV-LV AD $\geq$ 86 ms ('CRT responders'). We also evaluated the changes in EF, in the distance walked during the 6-min walk test and in the level of NT-proBNP at 6-month follow-up in CRT responders and CRT non-responders.

Furthermore, we assessed the changes in the biomarker NT-proBNP and clinical outcome of HF/death and death by quartiles of RV-LV AD to evaluate RV-LV AD as a continuous parameter.

The primary composite endpoint of the current study was HF episodes requiring hospitalization or all-cause mortality during the follow-up. The secondary endpoint was death from any cause.

Statistical analysis

The statistical analysis was performed using the Graph Pad Prism 5.0 software (Graph Pad Inc., CA, USA) and the SPSS software (IBM, NY, USA). Continuous variables with a normal distribution are presented as mean $\pm$ standard deviation, while parameters without a normal distribution are shown as median and interquartile range (IQR). Categorical variables are expressed as frequencies and percentages. Unpaired *t*-tests were used for comparisons of normally distributed continuous variables while not normally distributed variables were compared using the Mann–Whitney test. For categorical variables, Fisher's exact tests were performed to assess the differences between the groups.

Time-to-event data were presented by Kaplan–Meier survival curves using the log-rank test. Cox proportional hazards model was used to determine independent predictors of all-cause death at 3 years after adjustment for relevant clinical covariates. Hazard ratios (HRs) with a 95% confidence interval (95% CI) were determined for clinical endpoints.

All statistical tests were two-sided, a *P*-value of $<$0.05 was considered statistically significant. The statistical analysis was performed by the first author of the paper, Annamaria Kosztin.

Results

Baseline clinical characteristics

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

Baseline clinical characteristics of the patients with an RV-LV AD $\leq$86 and $>$86 ms (lower quartile) are listed in *Table 1*. Notably, there were no major differences among patients with a shorter or longer RV-LV AD in clinical or echocardiographic parameters. After we further dichotomized the patient cohort by LBBB morphology, we assessed the baseline clinical characteristics in patients with LBBB and RV-LV AD $\geq$ 86 ms and compared with the group of remaining patients such as LBBB and RV-LV AD $<$ 86 ms and patients with non-LBBB together (*Table 2*).

Right to left ventricular activation delay and functional outcome 6 months after cardiac resynchronization therapy implantation

At 6-month follow-up, 33 (55%) patients with RV-LV AD $\geq$ 86 ms and LBBB performed their 6-min walk test over 300 m, compared with 23 of those patients (35%) with RV-LV AD $<$ 86 ms or with a non-LBBB (55 vs. 35%; $P = 0.01$) (*Table 3*).

In patients with RV-LV AD $\geq$ 86 ms and LBBB, better laboratory parameters were observed at 6 months after CRT implantation with an NT-proBNP median value of 1216 (IQR: 326.9/2630) vs. 1887 (IQR: 1140/3300); $P = 0.03$, a creatinine value of 96.3 $\pm$ 56.6 vs. 122.1 $\pm$ 46.9; $P = 0.01$ and a blood urea nitrogen value of 7.6 $\pm$ 4.7 vs. 10.9 $\pm$ 5.6; $P = 0.001$, when compared with non-LBBB patients or to those with LBBB and RV-LV AD $<$ 86 ms (*Table 3*). Patients with RV-LV AD $\geq$ 86 ms and LBBB showed the greatest improvement in left ventricular EF (28.0 $\pm$ 7.1–36.3 $\pm$ 12.3; $P < 0.001$) 6 months after CRT implantation.

Right to left ventricular activation delay and clinical outcome in the total patient cohort

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

Patients with RV-LV AD $\geq$ 86 ms had significantly lower cumulative probability of HF/death when compared with those with RV-LV AD $<$ 86 ms ($P = 0.004$) (*Figure 1A*). The cumulative probability of all-cause mortality was significantly lower in patients with a longer activation delay (RV-LV AD $\geq$ 86 ms) compared with those with shorter delay (RV-LV AD $<$ 86 ms, $P = 0.003$) (*Figure 1B*).

Multivariate Cox-regression analysis confirmed the independent role of RV-LV AD first as a continuous parameter (*Table 4*) and then by 86 ms (*Table 5*) in predicting HF or death or all-cause mortality in the total patient population after adjustment for relevant clinical covariates, namely for LBBB ECG morphology, HF aetiology and age at enrolment. Patients with RV-LV AD $\geq$ 86 ms 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 with those with a shorter RV-LV activation delay at CRT implantation (*Table 5*).

Table 1 Baseline clinical characteristics of CRT patients by RV-LV AD of 86 ms at device implantation

	RV-LV AD ≥ 86 ms (*n* = 95)	RV-LV AD < 86 ms (*n* = 30)	*P*-Value
Age in years (mean ± SD)	67.1 ± 8.3	66.5 ± 9.7	0.73
Female gender, *n* (%)	18 (19%)	6 (20%)	1.00
CRT-D, *n* (%)	53 (56%)	20 (67%)	0.39
RV-LV AD (ms; mean ± SD)	117.67 ± 23.85	69.47 ± 13.19	NA
Baseline medical history			
Ischaemic aetiology, *n* (%)	56 (60%)	19 (63%)	0.25
Hypertension, *n* (%)	65 (70%)	22 (73%)	0.65
Diabetes mellitus, *n* (%)	31 (32%)	6 (20%)	0.25
Secondary prevention, *n* (%)	5 (4%)	5 (17%)	0.06
Prior myocardial infarction, *n* (%)	31 (32%)	14 (47%)	0.19
CABG, *n* (%)	17 (18%)	7 (23%)	0.60
Baseline clinical assessment			
Sinus rhythm at enrolment, *n* (%)	64 (67%)	18 (60%)	0.51
QRS at baseline (ms, mean ± SD)	166.4 ± 27.7	170.0 ± 33.9	0.57
LBBB ECG morphology, *n* (%)	60 (63%)	18 (60%)	0.23
RBBB ECG morphology, *n* (%)	0 (0%)	2 (7%)	0.06
IVCD ECG morphology, *n* (%)	35 (37%)	10 (33%)	0.83
NYHA II, *n* (%)	16 (17%)	2 (6%)	0.24
NYHA III, *n* (%)	69 (73%)	23 (77%)	0.81
NYHA IVa, *n* (%)	10 (10%)	5 (17%)	0.35
Six-min walk test (m, mean ± SD)	307.4 ± 128.8	268.1 ± 128.6	0.22
Systolic blood pressure (mmHg, mean ± SD)	119.9 ± 17.5	122.5 ± 20.8	0.52
Diastolic blood pressure (mmHg, mean ± SD)	74.4 ± 9.3	77.7 ± 12.0	0.12
Heart rate at baseline (b.p.m., mean ± SD)	75.8 ± 46.4	73.7 ± 11.3	0.59
Baseline drug treatment			
Beta blocker, *n* (%)	86 (91%)	24 (83%)	0.19
ACE inhibitor or ARB, *n* (%)	91 (96%)	27 (93%)	0.36
Spironolactone, *n* (%)	69 (74%)	18 (62%)	0.25
Loop diuretics, *n* (%)	77 (82%)	23 (80%)	0.61
Laboratory parameters			
NT-proBNP (ng/mL; med, IQR)	2608.0 (1596/4945)	2815.0 (1232/4732)	0.88
Creatinine (μmol/L; med, IQR)	106.8 ± 34.8	118.0 ± 41.6	0.20
BUN (mmol/L; mean ± SD)	9.2 ± 1.4	10.7 ± 7.0	0.18
Echocardiography parameters			
LVEF (%, mean ± SD)	28.5 ± 5.5	28.1 ± 6.9	0.82
LV end-diastolic volume (mL, mean ± SD)	249.6 ± 49.3	253.4 ± 82.7	0.86
LVESV (mL, mean ± SD)	181.4 ± 50.4	184.0 ± 67.4	0.85

RV-LV AD, right to left ventricular activation delay; CABG, coronary artery bypass graft; VF, ventricular fibrillation; LBBB, left bundle branch block; RBBB, right bundle branch block; IVCD, intraventricular conduction delay; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; BUN, blood urea nitrogen.

Right to left ventricular activation delay and clinical outcome by left bundle branch block ECG pattern

The findings were even more pronounced in patients with an LBBB ECG pattern. Patients with an LBBB and an RV-LV AD ≥ 86 ms at implantation had a significantly lower cumulative probability of HF/death when compared with those with shorter activation delay (RV-LV AD < 86 ms) and to those patients with non-LBBB ($P < 0.001$) (*Figure* 2*A*). 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 ≥ 86 ms), compared with those with shorter activation delay (RV-LV AD < 86 ms)

Table 2 Baseline clinical characteristics of CRT patients by RV-LV AD of 86 ms and LBBB morphology

	RV-LV AD ≥ 86 ms LBBB patients (n = 60)	RV-LV AD < 86 ms LBBB and non-LBBB patients (n = 65)	P-Value
Age in years (mean ± SD)	67.5 ± 7.9	66.3 ± 9.6	0.49
Female gender, *n* (%)	16 (27%)	8 (12%)	0.07
CRT-D, *n* (%)	32 (53%)	41 (63%)	0.28
RV-LV AD (ms; mean ± SD)	121.30 ± 23.56	92.05 ± 28.50	NA
Baseline medical history			
Ischaemic aetiology, *n* (%)	30 (50%)	45 (69%)	0.04*
Hypertension, *n* (%)	40 (67%)	47 (72%)	0.56
Diabetes mellitus, *n* (%)	16 (27%)	21 (32%)	0.23
Secondary prevention, *n* (%)	2 (3%)	8 (12%)	0.10
Prior myocardial infarction, *n* (%)	17 (28%)	28 (43%)	0.10
CABG, *n* (%)	7 (12%)	17 (26%)	0.04*
Baseline clinical assessment			
Sinus rhythm at enrolment, *n* (%)	49 (82%)	33 (51%)	0.001***
QRS at baseline (ms, mean ± SD)	167.3 ± 24.5	167.2 ± 33.3	0.98
LBBB ECG morphology, *n* (%)	N/A	18 (28%)	N/A
RBBB ECG morphology, *n* (%)	N/A	2 (3%)	N/A
IVCD ECG morphology, *n* (%)	N/A	45 (69%)	N/A
NYHA II, *n* (%)	9 (15%)	6 (9%)	0.41
NYHA III, *n* (%)	46 (77%)	44 (68%)	0.32
NYHA IVa, *n* (%)	5 (8%)	15 (23%)	0.01*
Six-min walk test (m, mean ± SD)	316.0 ± 132.6	282.9 ± 125.2	0.22
Systolic blood pressure (mmHg, mean ± SD)	119.8 ± 18.9	121.1 ± 17.8	0.70
Diastolic blood pressure (mmHg, mean ± SD)	74.5 ± 9.4	75.7 ± 10.5	0.54
Heart rate at baseline (b.p.m., mean ± SD)	76.8 ± 13.8	77.0 ± 20.8	0.97
Baseline drug treatment			
Beta blocker, *n* (%)	54 (90%)	56 (88%)	0.59
ACE inhibitor or ARB, *n* (%)	58 (97%)	60 (94%)	0.44
Spironolactone, *n* (%)	42 (70%)	45 (70%)	1.00
Loop diuretics, *n* (%)	45 (75%)	55 (86%)	0.19
Laboratory parameters			
NT-proBNP (ng/mL; med, IQR)	2608 (1063/4664)	2612.0 (1739/5049)	0.21
Creatinine (μmol/L; med, IQR)	101.9 ± 45.0	116.1 ± 36.8	0.06
BUN (mmol/L; mean ± SD)	9.0 ± 4.7	10.1 ± 5.4	0.21
Echocardiography parameters			
LVEF (%, mean ± SD)	27.6 ± 7.6	28.0 ± 6.6	0.77
LV end-diastolic volume (mL, mean ± SD)	263.1 ± 86.1	233.5 ± 69.1	0.08
LVESV (mL, mean ± SD)	194.5 ± 70.0	168.3 ± 56.4	0.04*

RV-LV AD, right to left ventricular activation delay; CABG, coronary artery bypass graft; VF, ventricular fibrillation; LBBB, left bundle branch block; RBBB, right bundle branch block; IVCD, intraventricular conduction delay; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; BUN, blood urea nitrogen.
N/A, not applicable due to the definition of the groups.
*$P < 0.05$.
***$P < 0.001$.

and to those patients with non-LBBB ($P = 0.01$) (*Figure 2B*). This translated into a 65% risk reduction in all-cause mortality in the multivariate models (HR: 0.35; 95% CI: 0.16–0.75; $P = 0.007$) (*Table 5*).

In patients with non-LBBB, there was no significant difference in HF or death or in all-cause mortality by RV-LV AD groups measured at CRT implantation (HF/death HR = 0.63; 95% CI: 0.26–1.49; $P = 0.29$, death HR = 0.43; 95% CI: 0.15–1.20; $P = 0.11$) (*Table 5*).

Clinical outcome by right to left ventricular activation delay after normalization to QRS

Our analyses were extended by RV-LV AD to QRS duration (RV-LV AD/QRS), while in a recent publication its percentage value was considered as feasible parameter with higher diagnostic value in

Table 3 Clinical parameters at 6 months after CRT implantation

	RV-LV AD ≥ 86 ms LBBB patients (n = 60)	RV-LV AD < 86 ms LBBB and non-LBBB patients (n = 65)	*P*-Value
Clinical assessment			
Six-min walk test >300 m, *n* (%)	33 (55%)	23 (35%)	0.03*
Systolic blood pressure (mmHg, mean ± SD)	127.4 ± 19.3	122.2 ± 24.8	0.27
Diastolic blood pressure (mmHg, mean ± SD)	77.2 ± 9.4	73.2 ± 12.0	0.08
Laboratory parameters			
NT-proBNP (ng/mL; med, IQR)	1216 (326.9/2630)	1887 (1140/3300)	0.03*
Creatinine (μmol/L; med, IQR)	96.3 ± 56.6	122.1 ± 46.9	0.01*
Blood urea nitrogen (mmol/L; mean ± SD)	7.6 ± 4.7	10.9 ± 5.4	0.001**

*$P < 0.05$.
**$P < 0.01$.

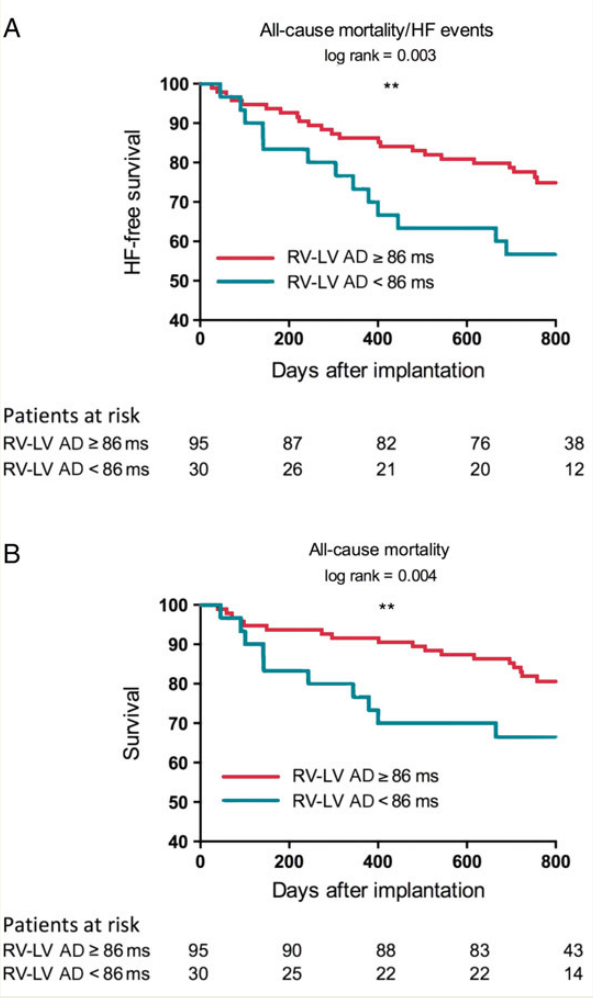

Figure 1 Kaplan–Meier cumulative probability of HF/death (*A*) and death (*B*) by RV-LV AD.

predicting the clinical response and purely evaluates the adequacy of LV lead placement for effective CRT.[13]

The univariate model showed RV-LV AD/QRS is also an independent factor of the primary endpoint of HF and death in LBBB patients (HR: 0.08; 95% CI: 0.01–1.02; $P = 0.05$). These results were also confirmed by multivariate Cox-regression analysis: by using the optimal cut-off value of percentage RV-LV AD/QRS which was 64%. Those who have higher RV-LV AD to QRS ≥ 64% have lower risk for HF events or death in the total patient cohort (HR: 0.43; 95% CI: 0.23–0.81; $P = 0.10$) and in LBBB patients as well (HR: 0.28; 95% CI: 0.10–0.80; $P = 0.017$). The lowest cumulative probability of HF/death was observed in patients with higher percentage of RV-LV AD/QRS and LBBB morphology (HR: 0.21; 95% CI: 0.08–0.54; $P = 0.001$) compared with non-LBBB or low RV-LV AD/QRS patients. In multivariate analyses, models were adjusted for age and ischaemic aetiology (data not shown).

Functional outcome, NT-proBNP 6 months after cardiac resynchronization therapy implantation and clinical outcome by right to left ventricular activation delay quartiles

To further assess the effects of RV-LV AD as a continuous parameter on NT-proBNP and clinical outcome of HF/death, we evaluated the changes in NT-proBNP at 6 months by RV-LV AD quartiles along with the incidence of HF/death. We found a linear increase in the amount of reduction in NT-proBNP 6 months after CRT towards the longer RV-LV AD quartile subgroups. In parallel with the improvement in NT-proBNP, there was a linear decrease in the incidence of HF/death (*Figure 3*).

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 with those, who had shorter activation delay or non-LBBB morphology (*Table 3*). Significant differences were found in changes in serum creatinine after 6 months (96.3 ± 56.6 vs. 122.1 ± 46.9 μmol/L; $P = 0.01$), and

Table 4 Univariate models to evaluate the clinical outcome of CRT patients by continuous value of RV-LV AD and LBBB ECG morphology at baseline

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

*$P < 0.05$.
***$P < 0.01$.

Table 5 Multivariate models to evaluate the clinical outcome of CRT patients by RV-LV AD and LBBB ECG morphology at baseline

	Hazard ratio	95% confidence interval	*P*-Value
Primary endpoint: HF event or death			
RV-LV AD $\geq$ 86 ms vs. $<$86 ms in all patients (95 vs. 30 patients)	0.44	0.23–0.82	0.001**
RV-LV AD $\geq$ 86 ms vs. $<$86 ms in LBBB (60 vs. 18 patients)	0.18	0.63–0.52	0.001**
RV-LV AD $\geq$ 86 ms vs. $<$86 ms in non-LBBB (35 vs. 12 patients)	0.63	0.26–1.49	0.29
RV-LV AD $\geq$ 86 ms in LBBB vs. Others (60 vs. 65 patients)	0.23	0.11–0.49	$<$0.001*
Secondary endpoint: all-cause mortality			
RV-LV AD $\geq$ 86 ms vs. $<$86 ms in all patients (95 vs. 30 patients)	0.48	0.23–1.00	0.05*
RV-LV AD $\geq$ 86 ms vs. $<$86 ms in LBBB (60 vs. 18 patients)	0.37	0.12–1.18	0.09
RV-LV AD $\geq$ 86 ms vs. $<$86 ms in non-LBBB (35 vs. 12 patients)	0.43	0.15–1.20	0.11**
RV-LV AD $\geq$ 86 ms in LBBB vs. Others (60 vs. 65 patients)	0.35	0.16–0.75	0.007*

Models are adjusted for age at enrolment, ischaemic aetiology of heart failure, and for LBBB ECG pattern in the model on the total patient population.
*$P < 0.05$.
**$P < 0.01$.

more pronounced in BUN (7.6 ± 4.7 vs. 10.9 ± 5.4 mmol/L; $P = 0.001$).

Discussion

The main findings of our study are that LBBB patients with an RV-LV activation delay of $\geq$86 ms have a significantly lower risk of HF or death and lower risk of all-cause mortality compared with those with non-LBBB ECG morphology combined with LBBB and RV-LV AD $<$ 86 ms. In non-LBBB patients, RV-LV AD was not predictive of clinical outcome. Furthermore, we found that RV-LV AD has an independent role in predicting improvement in left ventricular EF, NT-proBNP, and functional outcome in LBBB patients undergoing CRT implantation.

In this study, we used 86 ms as a cut-off value for RV-LV AD, the lower quartile of RV-LV AD to predict the primary composite endpoint, which was pre-specified in our analysis. D'onofrio *et al.*[9,13] published similar results in 301 patients who underwent CRT implantation and had LBBB morphology. In this article, ROC curves showed 80 ms as the optimal cut-off value of RV-LV AD and 65% of its normalization to QRS. Those patients who had greater RV-LV AD than 80 ms or RV-LV AD to QRS than 65% had significantly better outcome in echocardiographic reverse remodelling, which was defined as $>$15% end-systolic volume change. Their results are in line with our findings, the normalization of AD to QRS is also a feasible parameter in selecting patients who might benefit from CRT implantation. Those who have higher RV-LV AD to QRS and LBBB morphology have the lowest risk for HF events or death. The assessment of these parameters has higher importance in the subgroup of patients who have narrower QRS.

In another study by Kristiansen *et al.*,[8] they used an RV-LV interlead sensed electrical delay of $\geq$85 ms and showed differences in echocardiographic response and in clinical outcome. However, none of these studies looked specifically at subgroups of LBBB and non-LBBB patients.

Other studies used a different approach of evaluating successful resynchronization with CRT. Gold *et al.*[14] were focusing on the

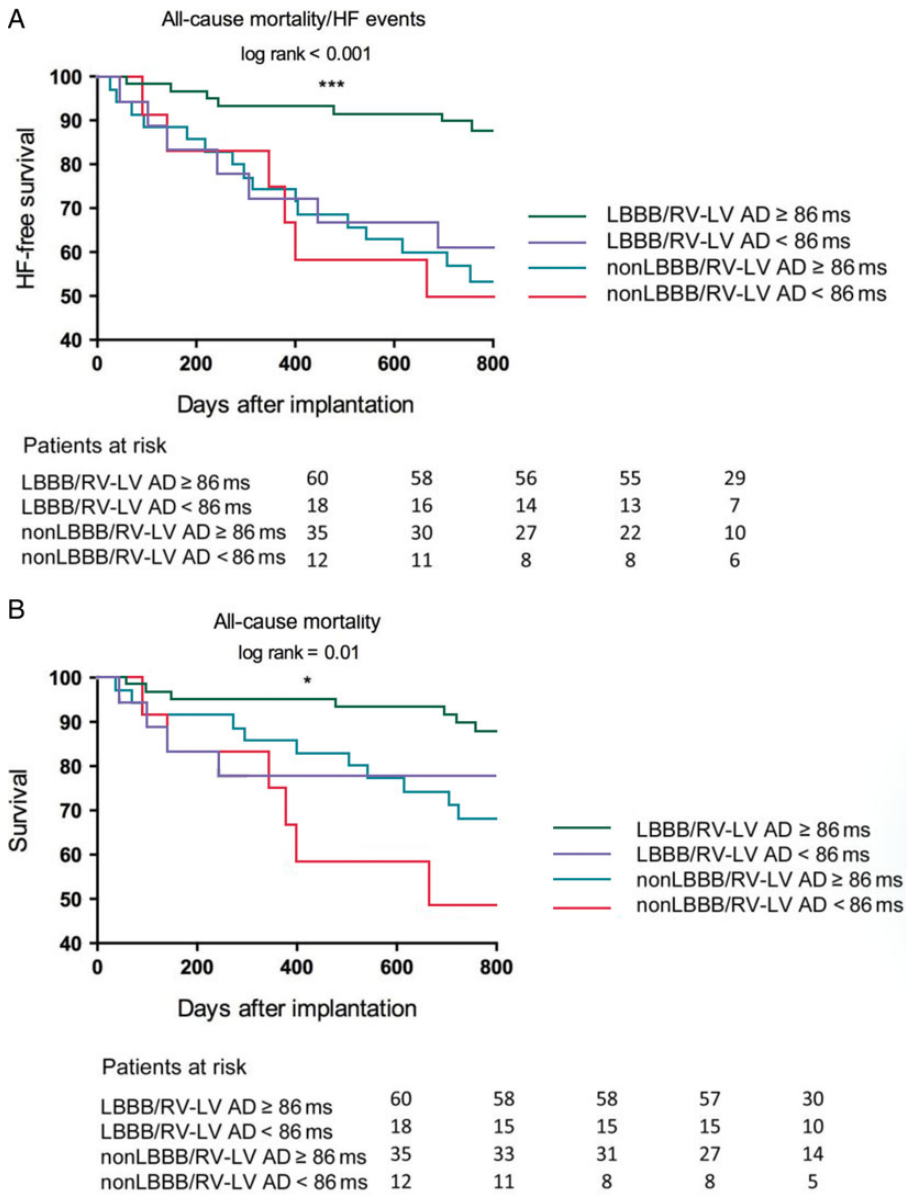

Figure 2 Kaplan–Meier cumulative probability of HF/death (*A*) and death (*B*) by RV-LV AD and LBBB ECG morphology.

association of clinical outcome and ventricular electrical delay measured by Q-LV in 426 patients with advanced HF, measuring LV lead activation time from the beginning of the QRS. Similarly to our results they found significant differences in functional parameters such as ESV reduction and in the quality-of-life 6 months after CRT implantation in those patients who had a greater Q-LV time than the median of 95 ms.

Right to left ventricular activation delay, the parameter used in our study is however a more comprehensive measurement providing information not only about the LV lead, but also about the RV lead position. Several studies have indicated that the location of the right ventricular lead plays a role in the clinical outcome of CRT patients.[15]

Furthermore, RV-LV activation delay may reflect slow conduction, as it is frequently seen in patients with ischaemic heart disease and extensive scarring of the posterior or lateral wall. However, we did not have data available on this in our cohort.

At the same time, it seems that RV-LV AD may point to significant electrical dyssynchrony that could be better surrogate marker for CRT benefit than mechanical dyssynchrony. A recent editorial suggests LBBB as an electrical disease, and CRT as a potent therapy for this electrical disease.[16] Therefore, it is sensible that patients with non-LBBB did not derive a significant benefit in our study, despite short or long RV-LV AD at implantation. The disease process may be more complex in patients with non-LBBB and needs further investigation.

This study is in line with several previous studies[5,17,18] suggesting that best response to CRT is achieved in patients with a 'left bundle branch block cardiomyopathy' with optimal positioning of the left

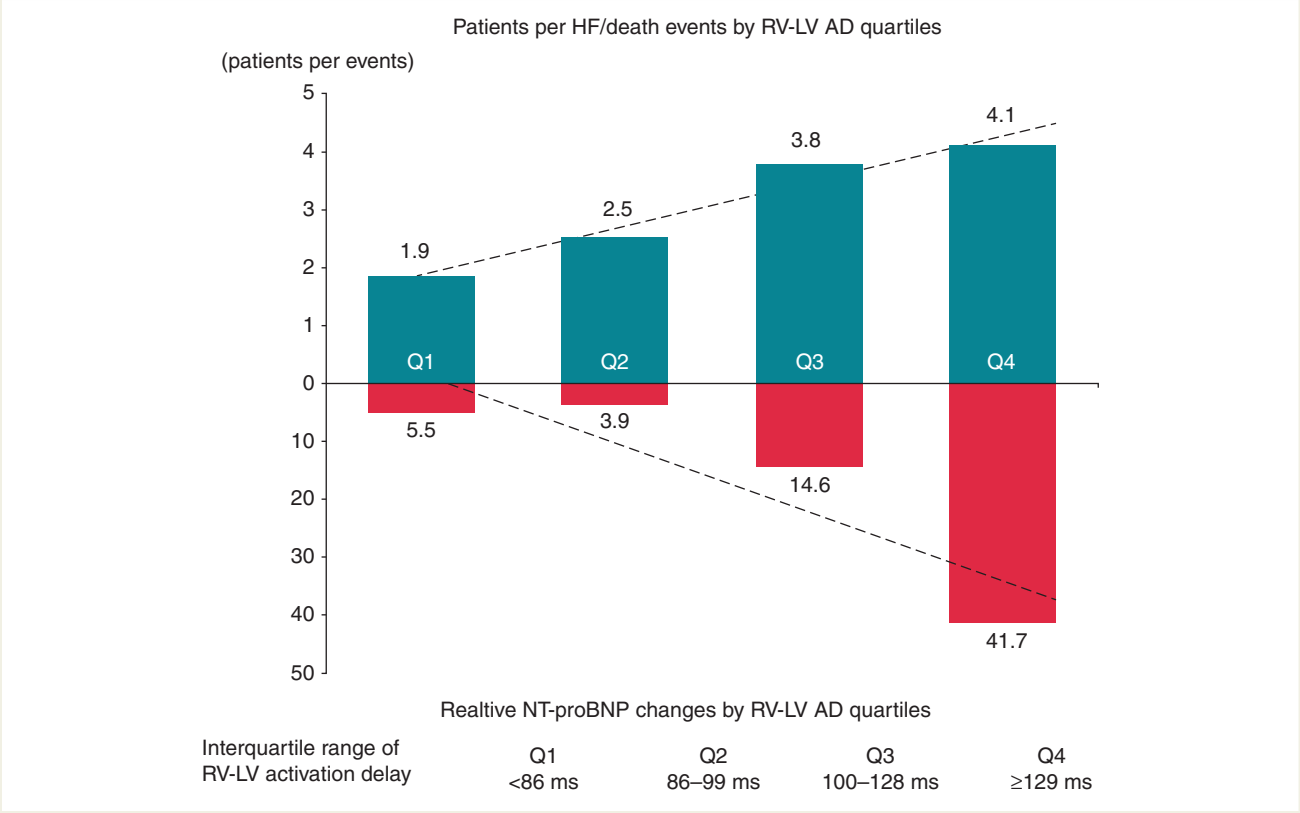

Figure 3 Incidence of HF/death and changes in NT-proBNP at 6 months by RV-LV AD quartiles.

ventricular lead. However to our knowledge, this is one of the first studies evaluating the effect of RV-LV activation delay in patients undergoing CRT by their baseline LBBB ECG pattern. Some of the previous studies adjusted the multivariate models for LBBB, but there were no pre-specified subgroup analysis performed in patients with a baseline LBBB or non-LBBB.

Moreover, in the current study the beneficial outcome was reflected in the decrease of prerenal dysfunction, independently of the baseline renal function values. In patients with longer RV-LV AD and LBBB morphology, serum creatinine and BUN values were significantly lower than in those with shorter RV-LV AD or non-LBBB ECG morphology.

Several trials assessed the independent risk factor of impaired renal function for mortality and morbidity in chronic HF.[19,20] The markers of prerenal dysfunction were also discussed in mildly symptomatic[21] and in advanced HF[22] after resynchronization. However, the association of RV-LV AD and the latter changes in renal function have not been directly investigated.

Our study has certain limitations, RV-LV AD may have been influenced by baseline QRS duration and by the suitable coronary sinus side branches. However, as a sensitivity analysis, we adjusted our models for QRS duration and our results were similar. Furthermore, suitable vein distribution for LV lead implantation is a known bias for all CRT studies and therefore needs to be acknowledged. Alternatively, minimal invasive techniques, e.g. mini-thoracotomy LV lead implantation[23] or transseptal LV endocardial pacing could be used to further maximize RV-LV AD and optimize CRT outcome. However, such methods have not become widely used in the past due to the relative invasive nature of the procedure. Furthermore we included only 125 patients in our study, and a small proportion of them had non-LBBB. Therefore, we may have a limited power to assess differences among non-LBBB patients by RV-LV AD. Further studies are warranted to evaluate the value of RV-LV AD in non-LBBB patients. Besides we adjusted our models for potential confounders, however, other unmeasured confounders may have influenced our results.

Conclusions

In conclusion, a longer RV-LV activation delay at CRT implantation was associated with improvement in EF, NT-proBNP, and with better HF-free survival and overall survival in patients with LBBB, but not in those with a shorter RV-LV activation delay, or in those with a non-LBBB. Simple assessment of RV-LV activation delay during CRT implantation might be a useful method to improve outcomes after CRT.

Funding

The study was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences (Gabor Szeplaki, Laszlo Geller) and the Hungarian Scientific Research Found (OTKA 105555). Funding to pay the Open Access publication charges for this article was provided by the Arrhythmia Research Foundation.

Conflict of interest: L.G. has received consultant fees/honoraria from Biotronik, Medtronic, St. Jude Medical, and Johnson & Johnson; Boston Scientific. E.Z. has received consultant fees/honoraria from Boston Scientific, Innomed, Biotronik, Medtronic, and St. Jude Medical for lectures, training, and participation in clinical trials. B.M. has received consultant and speaker fees/honoraria from Biotronik, Boston Scientific, Medtronic, and St. Jude Medical.

References

1. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T *et al.* Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–50.
2. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L *et al.* The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–49.
3. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP *et al.* Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;**361**:1329–38.
4. Birnie DH, Ha A, Higginson L, Sidhu K, Green M, Philippon F *et al.* Impact of QRS morphology and duration on outcomes after cardiac resynchronization therapy: results from the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT). *Circ Heart Fail* 2013;**6**:1190–8.
5. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M *et al.* Effectiveness of cardiac resynchronization therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation* 2011;**123**:1061–72.
6. Kutyifa V, Zareba W, McNitt S, Singh J, Hall WJ, Polonsky S *et al.* Left ventricular lead location and the risk of ventricular arrhythmias in the MADIT-CRT trial. *Eur Heart J* 2013;**34**:184–90.
7. Thebault C, Donal E, Meunier C, Gervais R, Gerritse B, Gold MR *et al.* Sites of left and right ventricular lead implantation and response to cardiac resynchronization therapy observations from the REVERSE trial. *Eur Heart J* 2012;**33**:2662–71.
8. Kristiansen HM, Hovstad T, Vollan G, Keilegavlen H, Faerestrand S. Clinical implication of right ventricular to left ventricular interlead sensed electrical delay in cardiac resynchronization therapy. *Europace* 2012;**14**:986–93.
9. D'Onofrio A, Botto G, Mantica M, La Rosa C, Occhetta E, Verlato R *et al.* The interventricular conduction time is associated with response to cardiac resynchronization therapy: interventricular electrical delay. *Int J Cardiol* 2013;**168**:5067–8.
10. Szilagyi S, Merkely B, Roka A, Zima E, Fulop G, Kutyifa V *et al.* Stabilization of the coronary sinus electrode position with coronary stent implantation to prevent and treat dislocation. *J Cardiovasc Electrophysiol* 2007;**18**:303–7.
11. Szilagyi S, Merkely B, Zima E, Kutyifa V, Szucs G, Fulop G *et al.* Minimal invasive coronary sinus lead reposition technique for the treatment of phrenic nerve stimulation. *Europace* 2008;**10**:1157–60.
12. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA *et al.* Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;**18**:1440–63.
13. D'Onofrio A, Botto G, Mantica M, LA Rosa C, Occhetta E, Verlato R *et al.* Incremental value of larger interventricular conduction time in improving cardiac resynchronization therapy outcome in patients with different QRS duration. *J Cardiovasc Electrophysiol* 2014;**25**:500–6.
14. Gold MR, Birgersdotter-Green U, Singh JP, Ellenbogen KA, Yu Y, Meyer TE *et al.* The relationship between ventricular electrical delay and left ventricular remodelling with cardiac resynchronization therapy. *Eur Heart J* 2011;**32**:2516–24.
15. Kutyifa V, Bloch Thomsen PE, Huang DT, Rosero S, Tompkins C, Jons C *et al.* Impact of the right ventricular lead position on clinical outcome and on the incidence of ventricular tachyarrhythmias in patients with CRT-D. *Heart Rhythm* 2013;**10**:1770–7.
16. Goldenberg I, Kutyifa V, Klein HU, Cannom DS, Brown MW, Dan A *et al.* Survival with cardiac-resynchronization therapy in mild heart failure. *N Engl J Med* 2014;**370**:1694–701.
17. Zareba W. Cardiac resynchronization therapy: forget QRS duration but do not forget QRS morphology. *J Electrocardiol* 2013;**46**:145–6.
18. Brenyo A, Zareba W. Prognostic significance of QRS duration and morphology. *Cardiol J* 2011;**18**:8–17.
19. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S *et al.* Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation* 2006;**113**:671–8.
20. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS *et al.* Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol* 2004;**43**:61–7.
21. Goldenberg I, Moss AJ, McNitt S, Barsheshet A, Gray D, Andrews ML *et al.* Relation between renal function and response to cardiac resynchronization therapy in Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). *Heart Rhythm* 2010;**7**:1777–82.
22. Boerrigter G, Costello-Boerrigter LC, Abraham WT, Sutton MG, Heublein DM, Kruger KM *et al.* Cardiac resynchronization therapy improves renal function in human heart failure with reduced glomerular filtration rate. *J Card Fail* 2008;**14**:539–46.
23. Kutyifa V, Merkely B, Szilagyi S, Zima E, Roka A, Kiraly A *et al.* Usefulness of electroanatomical mapping during transseptal endocardial left ventricular lead implantation. *Europace* 2012;**14**:599–604.