Clin Res Cardiol (2015) 104:136–144
DOI 10.1007/s00392-014-0763-6

ORIGINAL PAPER

Outcome of super-responders to cardiac resynchronization therapy defined by endpoint-derived parameters of left ventricular remodeling: a two-center retrospective study

David Hürlimann · Susann Schmidt · Burkhardt Seifert · Ardan M. Saguner · Gerhard Hindricks · Thomas F. Lüscher · Frank Ruschitzka · Jan Steffel

Received: 12 May 2014 / Accepted: 26 September 2014 / Published online: 10 October 2014

Abstract

Aims Various studies have attempted to identify super-responders to cardiac resynchronization therapy (CRT) by echocardiographic parameters of reverse remodeling. However, scientific evidence regarding those parameters is scarce. This study aimed at validating the definition of super-response to CRT based on the following frequently employed echocardiographic parameters: left ventricular ejection fraction (LVEF), end-diastolic volume index (EDVI), and end-systolic volume index (ESVI).

Methods and results We retrospectively investigated echocardiographic data and outcomes of 542 patients after CRT implantation. The primary endpoint comprised all-cause mortality, heart transplantation, ventricular assist device implantation (VAD), and hospitalization for heart failure. Secondary endpoints were hospitalization for heart failure, and the combination of all-cause mortality, heart transplantation and VAD. Two approaches were employed defining super-response based on improvement of echocardiographic parameters: one derived from the negative predictive value (NPV) for clinical endpoints, and second from best quartiles of improvement. Using the NPV method, an absolute 25 % increase in LVEF, a relative 38 % reduction in EDVI, and 46 % in ESVI were calculated as optimal cut-offs identifying 4.9, 18.5, and 21.3 % as super-responders. The best quartiles method resulted in lower cut-off values, i.e. 14 % increase in LVEF, 26 % reduction in EDVI, and 36 % in ESVI. All cut-offs except LVEF $\geq$25% were significantly associated with improved outcomes after 5 years (median follow-up 35.7 months).

Conclusions NPV- and best quartile-based cut-offs validate previously applied empirical echocardiographic cut-offs to define super-response to CRT. These data provide evidence for using these empirical cut-offs in daily practice and facilitate inter-study comparability.

Keywords Cardiac resynchronization therapy · Cardiac failure · Super-responder · Cardiac devices · CRT device · Left ventricular remodeling

Introduction

Cardiac resynchronization therapy (CRT) has become a cornerstone in the treatment of patients with symptomatic heart failure, LV ejection fraction $\leq$35 % and a prolonged QRS duration ($\geq$120 ms) despite optimal medical therapy [1, 2]. However, the response rate to CRT may vary considerably among patients. Some patients, typically referred to as "super-responders", show striking reverse remodeling and an increase or even normalization of ejection fraction

D. Hürlimann and S. Schmidt contributed equally to the study.

D. Hürlimann · S. Schmidt · A. M. Saguner · T. F. Lüscher · F. Ruschitzka · J. Steffel
Department of Cardiology, Invasive Electrophysiology and Devices, University Heart Center Zurich, Zurich, Switzerland
e-mail: schmidtsusann@gmx.de

B. Seifert
Division of Biostatistics, Institute for Social and Preventive Medicine, University of Zurich, Zurich, Switzerland

G. Hindricks
Department of Electrophysiology, Heart Center Leipzig, Leipzig, Germany

J. Steffel (✉)
Division of Electrophysiology and Pacing, Department of Cardiology, University Heart Center Zurich, Zurich, Switzerland
e-mail: j.steffel@gmx.ch

or chamber size. The proportion of super-responders is reported to be in the range of 12–47 % of patients undergoing CRT implantation. [3–10].

The lack of a universal definition of super-response to CRT is one of the main reasons for the wide range of percentages observed in these studies. A number of investigations attempted to identify super-responders focusing on various echocardiographic parameters of reverse remodeling. Yu et al. [11], Ypenburg [6] and Poller [12] defined super-responder by an improvement in left ventricular end-systolic volume (LVESV), although different cut-offs were selected [6, 11]. Another study group used vectorcardiography parameters to assess response to CRT [13]. We have previously compared three definitions for super-responders defined by an absolute increase in LVEF ≥10 %, a decrease in end-systolic volume index (ESVI) by ≥30 % and end-diastolic volume index (EDVI) by ≥20 %, and found that either of these cut-off points are highly predictive for clinical improvement and survival after CRT implantation [3].

Common to all above-mentioned studies (including our previous work), however, was that both the parameters as well as the individual cut-offs used for defining super-response to CRT were more or less arbitrarily chosen, primarily based on previously published studies rather than endpoint-derived evidence. The aim of the current study, therefore, was to comprehensively determine cut-off values for three commonly used parameters defining echocardiographic super-response (improvement in LVEF, EDVI, ESVI), and to compare them among each other as well as with previously employed, empirically derived cut-off values.

Table 1 Baseline characteristics

	Mean ± SD
Clinical	
Men (%)	432/542 (79.9)
Age at implantation (years)	64.7 ± 11.0
Heart rate (bpm)	75.0 ± 18.3
nt-pro BNP (pg/ml)	4,314 (140–55,053)*
Coronary artery disease-*n* (%)	432/542 (79.9)
QRS duration (msec)	148.6 ± 34.6
Atrial fibrillation-*n* (%)	104/542 (19.2)
Time diagnosis-implantation (months)	48.4 ± 68.5
Echocardiography at time of CRT implantation	
End-diastolic volume index (EDVI) (ml/m^2)	106.9 ± 39.8
End-systolic volume index (ESVI) (ml/m^2)	79.5 ± 35.4
Left ventricular ejection fraction (LVEF) (%)	26.0 ± 8.4
RV/RA gradient	38.0 ± 13.2
Right ventricular fractional area change (%)	41.7 ± 13.8
Tricuspid annulus motion (TAM) (mm)	16.6 ± 5.8
Interventricular mechanical delay (msec)	37.5 ± 34.7
Echocardiography post implantation	
Time FU echo from implant (months)	9.0 ± 4.1
End-diastolic volume index (ml/m^2)	97.7 ± 36.4
Delta EDVI (ml/m^2)	−8.3 (−73.8–162.1)*
End-systolic volume index (ml/m^2)	68.2 ± 36.4
Delta ESVI (ml/m^2)	−13.8 (−77.2–413.5)*
LVEF (%)	32.7 ± 11.2
Delta LVEF (%)	6.6 ± 10.4
Manufacturer devices	
Biotronik (%)	114 (21.0)
Medtronic (%)	112 (20.7)
St. Jude Medical (%)l	298 (55.0)
Boston Scientific (%)	18 (3.3)

Categorical data are presented as number of patients (%), continuous data as mean (±SD) unless indicated. Asterisk median (range)

Methods

Study population

All patients ($n = 542$) receiving a de novo CRT implantation or CRT upgrade at the University Heart Center Zurich ($n = 182$) or at the Heart Center Leipzig ($n = 360$) between November 2000 and December 2012, in whom an echocardiogram between 1 and 30 months after implantation was available were included in the study. In rare cases, where no echocardiogram was performed, available data from magnetic resonance tomography or levocardiography were used. Overall, 823 patients had to be excluded due to incomplete or missing follow-up. Patients received devices and leads from Biotronik, Boston Scientific, Medtronic and St. Jude Medical (Table 1). The standard approach for LV lead positioning was via a transvenous access through the coronary sinus into either a posterolateral or lateral vein. If transvenous implantation was not possible, epicardial lead implantation was performed (30 patients, 5.5 %). Data on the clinical follow-up were retrieved from hospital records, as well as through contact with the patients' general practitioners, external cardiologists and the patients themselves. This retrospective study was approved by the ethics committee of the University of Zurich (KEK-ZH-Nr. 2011-0304) and the Institutional Review Board of the Heart Center Leipzig.

Endpoints and statistics

The primary endpoint of the study was the combined endpoint of all-cause mortality, heart transplantation, ventricular assist device implantation and hospitalization for heart failure. Additionally we evaluated hospitalization for heart failure as well as the combination of all-cause mortality, heart transplantation and ventricular assist device (VAD) implantation as secondary endpoints. Freedom from endpoints was assessed during 5 years from CRT implantation and was computed using Kaplan–Meier analysis with delayed entry at the time of echocardiography. Differences in survival curves between super-responders and non-responders were computed with the log-rank test using Stata 11.2 (Stata Corp, College Station, Texas, USA). All other calculations and graphics were performed using *R* Statistical Software (Foundation for Statistical Computing, Vienna, Austria). A p value of <0.05 was considered statistically significant.

Assessment of super-response

To determine the most useful parameter among LVEF, EDVI, and ESVI, the percentage change of each parameter (Delta LVEF, Delta EDVI, Delta ESVI) from baseline to first follow-up was computed. To determine cut-off values for defining a super-responder status after CRT implantation, two methods were applied.

Determination of super-responders based on negative predictive value

In contrast to the method based on best quartile, cut-offs for left ventricular remodeling were based on the negative predictive value (NPV), i.e. the probability of 5-year freedom from the primary endpoint for patients classified as super-responder. The package ‘survivalROC’ [14] was used first to compute sensitivity and specificity as a function of the cut-off value. The negative predictive value was then obtained using Bayes formula and plotted as a function of the left ventricular improvement. The cut-off for super-response was the value, which defined as many patients as possible with a NPV of at least 75 %. To evaluate the prognostic performance of parameters of left ventricular remodeling, ROC curves were plotted, the areas under the curves were computed, and sensitivities and specificities of super-responder definitions calculated. Afterwards freedom from endpoints was illustrated using Kaplan–Meier curves as described above.

Determination of super-response based on best quartile

In the “best quartile” method, super-response was defined by the top quartile of LVEF, EDVI or ESVI improvement, regardless of the patients’ clinical outcomes.

Results

Baseline characteristics and follow-up

The patients‘ baseline characteristics including echocardiographic and electrocardiographic parameters are given in Table 1. 345 (63.7 %) patients received a new CRT device, 118 (21.8 %) a pacemaker upgrade and 79 (14.6 %) an ICD upgrade. All patients were on optimal heart failure therapy at the time of implantation: 481 patients (88.7 %) were on angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, 463 (85.0 %) on beta blockers, 418 (77.1 %) on loop diuretics, 171 (31.5 %) on thiazides, 300 (55.4 %) on spironolactone, 70 (12.8 %) on nitrates, 36 (6.6 %) on calcium antagonists, 291 (53.7 %) on lipid lowering treatment, and 78 (14.4 %) patients were on amiodarone.

Mean follow-up was 35.7 ± 24.7 months (range 0.3–115.4 months). During this time, 248 patients (45.8 %) reached the combined endpoint, which included 160 deaths (29.5 %), 12 heart transplantations (2.2 %), 12 left ventricular assist device implantations (2.2 %), and 173 hospitalizations for heart failure (21.4 %, Table 2).

The mean time of echocardiographic follow-up was 9.0 ± 4.1 months. LVEF increased after CRT from 26.1 ± 8.5 to 32.7 ± 11.7 %. Accordingly, ESVI and EDVI decreased from 79.5 ± 35.4 to 68.2 ± 36.4 ml/m^2 and 106.9 ± 39.8 to 97.7 ± 41.2 ml/m^2, respectively.

Determination of super-responder status based on the NPV

Using the NPV-based method, an absolute increase in LVEF by 25 %, a reduction in EDVI by 38 %, and a reduction in ESVI by 46 % were calculated as the optimal cut-off values to define super-response (Fig. 1). These definitions yielded a NPV of 75 % and identified 4.9 % (22/452), 18.5 % (58/314) and 21.3 % (66/310) of patients, respectively, as super-responders. There was no relevant difference in the AUC between each parameter. The AUC for all parameters were considered useful at separating between the outcome of super-responders and non-super-responders (Delta LVEF AUC 0.67> Delta ESVI AUC

Table 2 Follow-up and endpoints

Follow-up (months)	35.7 ± 24.7
Combined endpoint	248 (45.8 %)
Death	160 (29.5 %)
Heart transplantation	12 (2.2 %)
Ventricular assist device	12 (2.2 %)
Congestive heart failure hospitalization	173 (31.9 %)

Data are presented as mean (±SD) and number of patients (%) for continuous and categorical variables, respectively

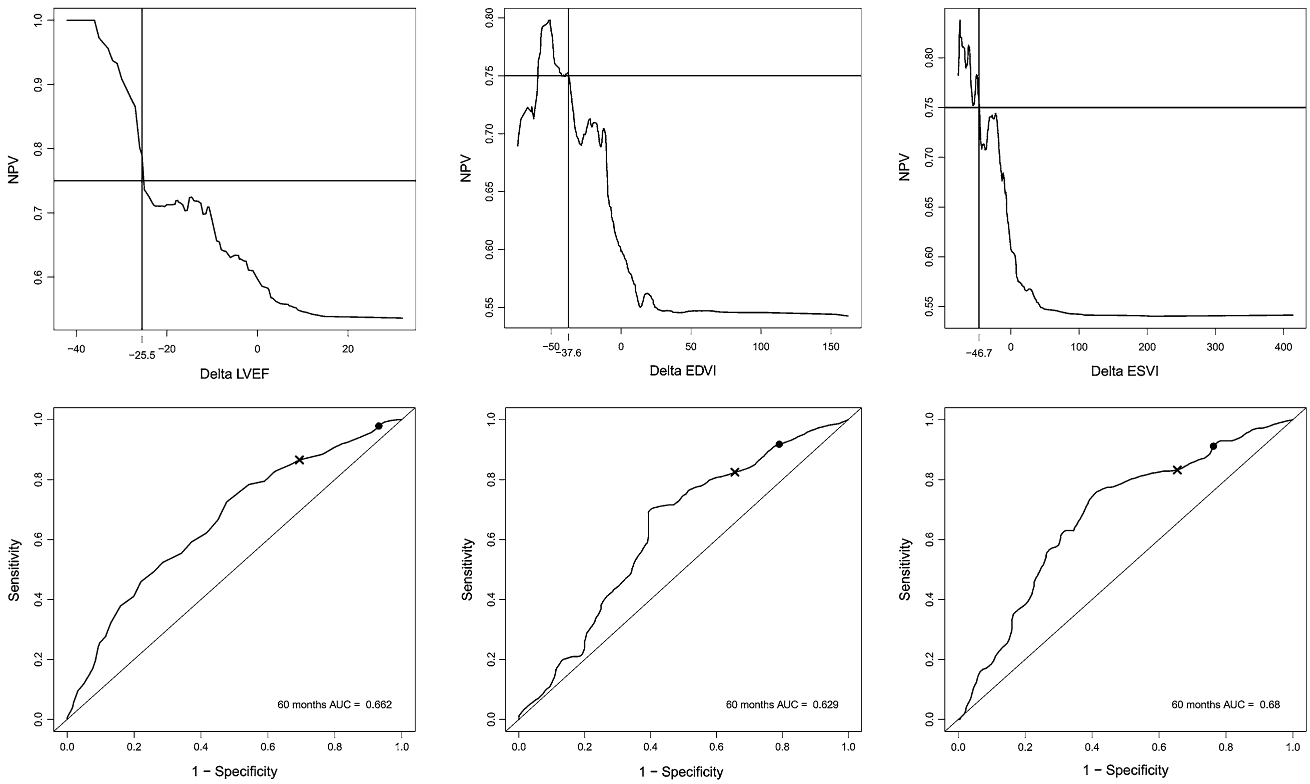

Fig. 1 NPV-based method. *Upper panel*: determination of optimal cut-off point for the definition of super-response. *Lower panel*: *ROC curves* (Delta LVEF, Delta EDVI, Delta ESVI). *point* NPV-based cut-off point, *cross* best quartile-based cut-off point

0.65> Delta EDVI 0.61). Super-responders as defined by a relative decrease of EDVI ≥38 % and ESVI ≥47 % were significantly less likely to reach the combined primary, as well as the secondary endpoints (Tables 3, 4, 5). In contrast, the cut-off value for LVEF improvement ≥25 % was not associated with a reduced probability of death, heart transplantation and implantation of a left ventricular assist device ($p = 0.072$.). The corresponding Kaplan–Meier estimates of event-free survival are shown in Fig. 2.

Determination of super-responder definition based on the best quartile

Using the method based on the best quartile, super-response was defined by an absolute improvement in LVEF of 14 %, a relative improvement in EDVI by 25 % or a relative improvement in ESVI by 36 %. Using these definitions, 133/337 (39.5 %), 104/255 (40.8 %) and 101/271 (37.3 %) of patients, respectively, were classified as super-responders (Tables 3, 4, 5). With this method, significant results were obtained regarding 5-years freedom from both the primary and secondary endpoints for all parameters and cut-offs investigated. The corresponding Kaplan–Meier estimates of event-free survival are illustrated in Fig. 3.

Discussion

We here for the first time used an objective approach to assess the optimal parameter and its cut-off point using an NPV-based analysis to determine whether different echocardiographic parameters of left ventricular remodeling based on clinical outcome data, rather than empiric values, may precisely predict super-response to CRT.

In our previous work [3], as well as in other studies, cut-off-points for all echocardiographic parameters were determined a priori, followed by outcome analysis to evaluate the influence of echocardiographic response on the clinical course [3]. The somewhat arbitrary determination of cut-off values is frequently problematic due to several reasons. First, there is no consensus regarding which echocardiographic parameter is most appropriate with a good reproducibility in daily clinical practice. Second, most of the cut-off points which were chosen in previous projects were empirically derived and predetermined [3–6, 8, 9, 11].

Our current study was undertaken to address these two shortcomings. Indeed, we were able to identify endpoint-derived cut-off values for the most frequently employed markers of LV remodeling.

Table 3 Outcome of super-responders according to improvement in delta LVEF

	NPV-based cut-off LVEF 25 %		Best quartile-based cut-off LVEF 14 %	
Δ LVEF				
Specificity (%)	6.9		30.6	
Sensitivity (%)	97.9		86.6	
	Super-responder	Non super-responder	Super-responder	Non super-responder
Combined endpoint				
n	27	447	119	351
5-years freedom (%)	75.6	43.3	72.2	36.0
CI	0.57–1.0	0.37–0.5	0.63–0.83	0.30–0.44
p value	0.033		<0.0001	
Death/heart transplantation/LVAD				
n	29	506	129	406
5-years freedom (%)	81.6	48.1	78.2	41.3
CI	0.67–1.0	0.42–0.56	0.70–0.87	0.35–0.49
p value	0.072		<0.0001	
CHF hospitalization				
n	27	443	119	351
5-years freedom (%)	90.0	64.2	83.6	59.0
CI	0.73–1.0	0.58–0.71	0.76–0.93	0.52–0.67
p value	0.037		0.0001	

Table 4 Outcome of super-responders according to improvement in delta EDVI

	NPV-based cut-off EDVI 38 %		Best quartile-based cut-off EDVI 26 %	
Δ EDVI				
Specificity (%)	21.7		34.4	
Sensitivity (%)	91.5		82.5	
	Super-responder	Non super-responder	Super-responder	Non super-responder
Combined endpoint				
n	56	316	99	270
5-years freedom (%)	76.1	39.8	68.5	36.8
CI	0.64–0.91	0.33–0.48	0.58–0.81	0.30–0.45
p value	0.032		0.008	
Death/heart transplantation/LVAD				
n	57	356	104	309
5-years freedom (%)	84.3	44.4	75.7	41.9
CI	0.74–0.96	0.37–0.53	0.66–0.87	0.35–0.51
p value	0.0099		0.017	
CHF hospitalization				
n	56	313	99	270
5-years freedom (%)	89.7	59.5	90.0	54.7
CI	0.81–1.0	0.52–0.68	0.83–0.97	0.47–0.64
p value	0.019		0.0001	

End-diastolic volume index

An improvement in EDVI may represent an important parameter when it comes to evaluating the response to CRT, as it reflects true reverse remodeling (i.e. a genuine reduction in left ventricular size). Celib et al. classified 22 out of 136 CRT patients (16.2 %) with a 27 % LVEDD reduction after an average follow-up of 9.4 months as

Table 5 Outcome of super-responders according to improvement in delta ESVI

	NPV-based cut-off ESVI 47 %		Best quartile-based cut-off ESVI 36 %	
Δ ESVI				
Specificity (%)	23.9		34.5	
Sensitivity (%)	90.8		83.2	
	Super-responder	Non super-responder	Super-responder	Non super-responder
Combined endpoint				
n	65	311	101	271
5-years freedom (%)	75.1	39.2	68.5	36.9
CI	0.64–0.89	0.33–0.47	0.58–0.80	0.3–0.46
p value	<0.0001		<0.0001	
Death/heart transplantation/LVAD				
n	68	349	106	311
5-years freedom (%)	84.1	43.5	76.3	41.8
CI	0.75–0.95	0.36–0.52	0.67–0.87	0.35–0.51
p value	<0.0001		<0.0001	
CHF hospitalization				
n	65	307	101	271
5-years freedom (%)	89.0	58.6	87.0	55.7
CI	0.80–0.99	0.51–0.67	0.79–0.96	0.48–0.64
p value	0.0001		<0.0001	

super-responders. Although patients were classified as super-responders with a LVEDD reduction beyond the 80th percentile, the latter was based on hypothesis rather than endpoint analysis [8].

Both of our methods measured higher cut-off values for relative decreases in EDVI than in our previous study (20 %) [3]. The NPV-based method with a higher cut-off point identified fewer patients as super-responders. Conversely, freedom from the combined endpoint, death/heart transplantation/left ventricular assist device, and hospitalization due to heart failure was slightly higher using the NPV- versus best quartile-based cut-off point.

End-systolic volume index

Improvements in ESVI have more often been employed than EDVI for identifying super-response after cardiac resynchronization therapy, and a link between improvement in ESVI and a survival benefit has frequently been postulated [11, 15, 16] [4, 6, 11, 17]. Similar to the other definitions, we received higher cut-off values for ESVI than previous studies. The associated AUC for cardiovascular mortality was 0.774, which is similar to the data from Yu et al. [11].

We obtained a threshold of ESVI improvement of 46 % with the NPV-based analysis and 36 % with the best quartile-based method. Comparing both methods, the percentage of super-responders for freedom from the combined endpoint, from death, heart transplantation and LVAD implantation, as well as freedom from CHF hospitalization was always higher using the NPV-based method as compared to the best quartile-based method, implying that the NPV-based method may be more capable in better identifying super-responders. However, the absolute number of super-responders was lower using the NPV-based method, resulting in a higher number of patients with a favorable clinical outcome who did not qualify as "super-responders" per this definition. As expected, a reduced absolute number of super-responders were identified with increasing absolute cut-off values.

Left ventricular ejection fraction

The best quartile-based cut-off for LVEF improvement (14 %) turned out to be identical to the one recently chosen for the analysis of MADIT-CRT (14 %) [7]. This may have been due to a similar approach for identification of super-responders using the top quartile of LVEF change. The concordance of both studies hence strongly indicates a high degree of reproducibility and, consequently, reliability of the received cut-off point.

In our previous study, 47 % patients were identified as super-responders as defined by an absolute increase in LVEF $\geq$10 %, which reached statistical significance for freedom from the combined endpoint and hospitalization, but not for freedom from all-cause mortality. Likewise, our

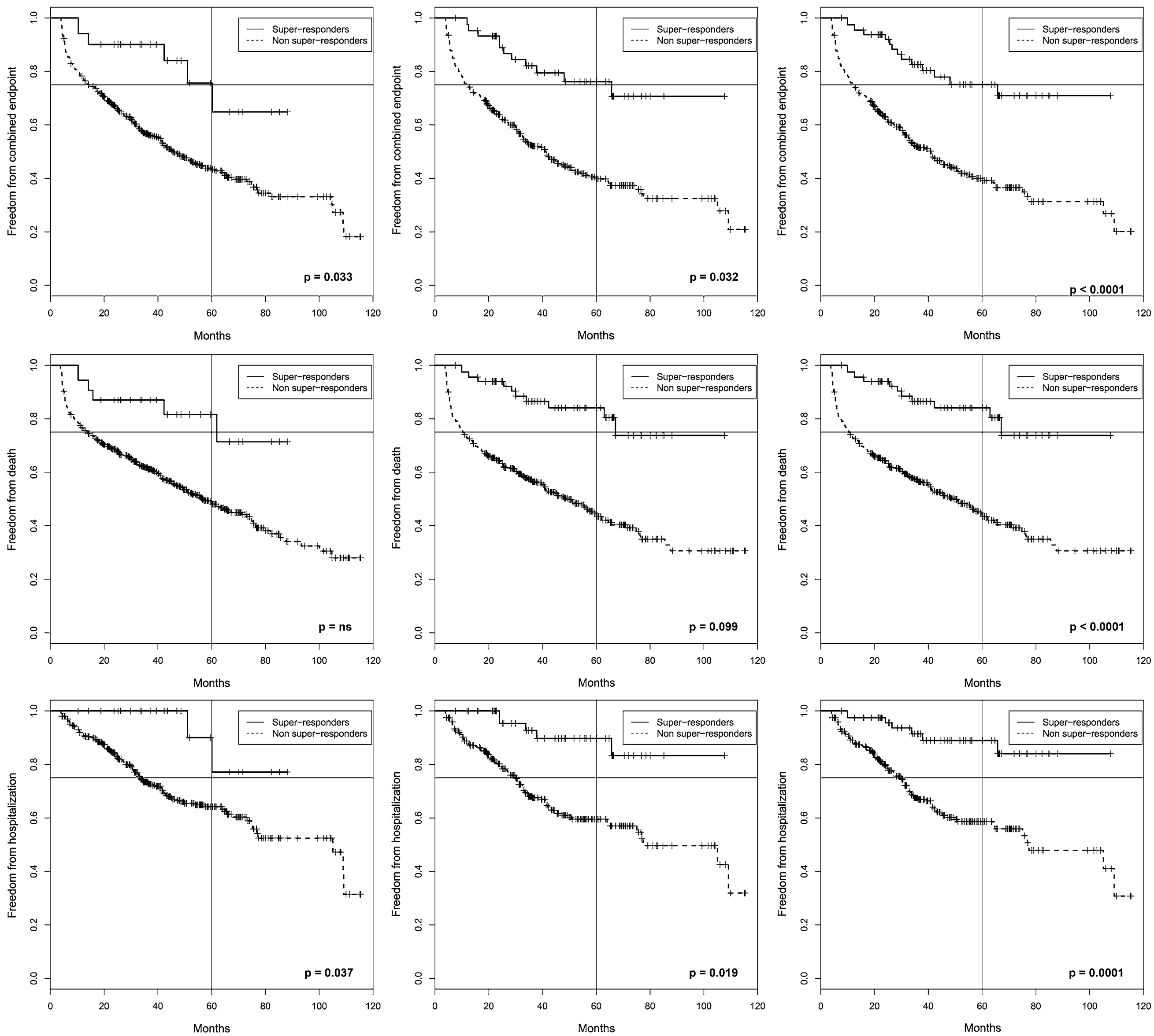

Fig. 2 NPV-based method: probability of freedom from the combined endpoint (*upper*), death/heart transplantation/ventricular assist device (*middle*) and hospitalization for heart failure (*lower panel*) for different definitions of super-responders: Δ LVEF >25 % (*left*); Δ EDVI <38 % (*middle*); and Δ ESVI <46 % (*right panel*)

present study demonstrates a significant reduction of all endpoints with both cut-off points, except for LVEF ≥25 % for the combined secondary mortality endpoint [3].

When comparing the NPV-based (≥25 %) with the best quartile-based threshold (≥14 %), we obtained fewer super-responders with the former due to the higher cut-off point. The fact that an improvement in LVEF of ≥25 % was not associated with a statistically significant reduction in the combined secondary endpoint may be due to the substantially lower specificity for the NPV-based cut-off (6.9 vs. 30.6 %), indicating that some patients with a pronounced response did not qualify as super-responders as per the NPV-based definition. Instead, this threshold clearly identified very pronounced super-responders regarding the hospitalization for the secondary endpoint heart failure, with only a few events occurring until 50 months after CRT implantation.

Limitations

This is a retrospective study, limited to patients who were followed-up at two large-scale tertiary care centers with mid-term follow-up to assess reverse remodeling. As a result, several patients who were implanted were not included in the analysis due to lack of follow-up data (external referrals etc.). These aspects, however, are

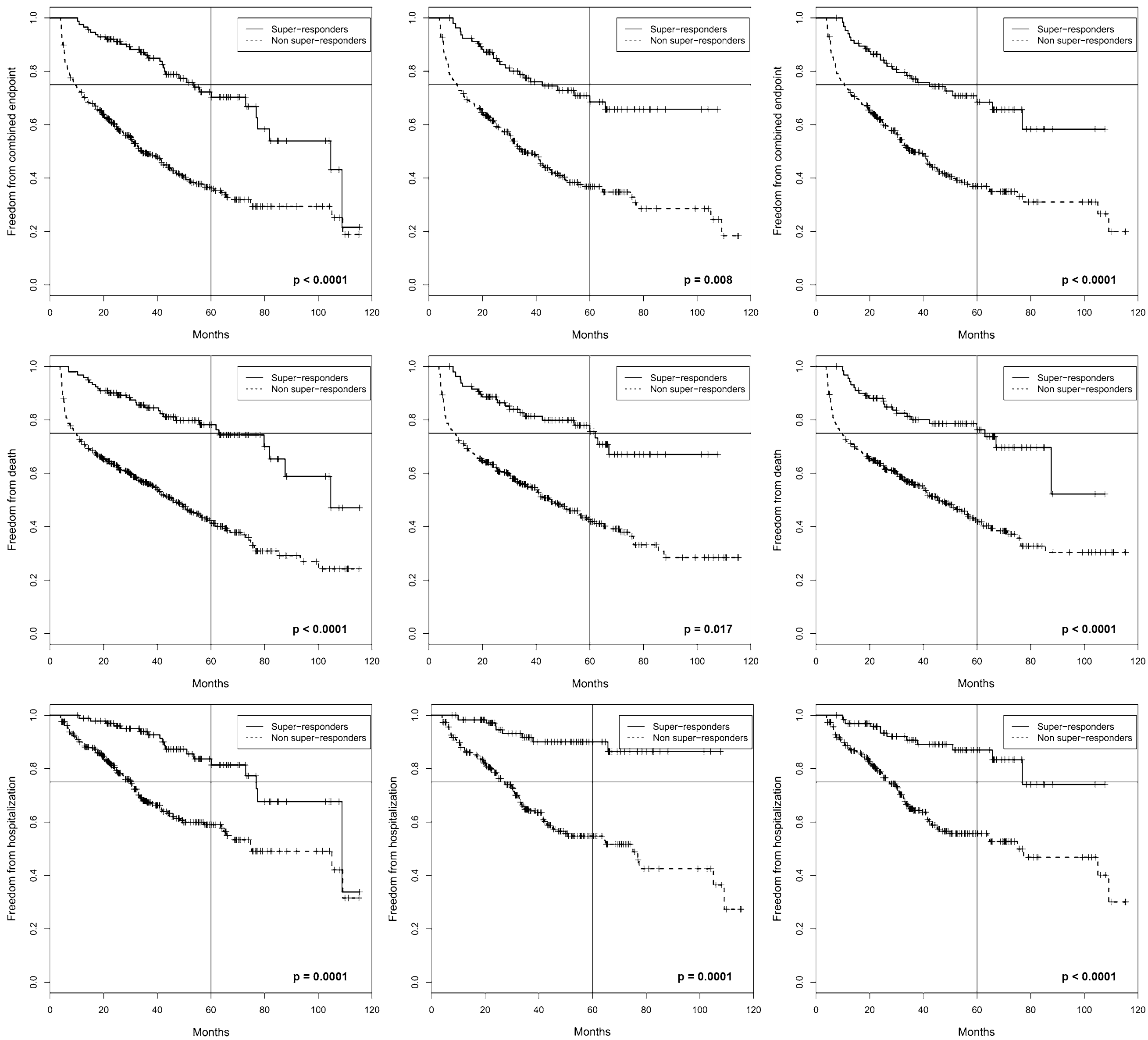

Fig. 3 Best quartile-based method: probability of freedom from the combined endpoint (*upper*), death/heart transplantation/ventricular assist device (*middle*) and hospitalization for heart failure (*lower panel*) for different definitions of super-responder: Δ LVEF >14 % (left); EDVI <25 % (*middle*) and ESVI <36 % (*right*)

inherent limitations of any "real world" investigation; conversely, they are potentially outweighed by the fact that patients were consecutively included without any pre-selection. Furthermore, for the main message of our paper, i.e. the comparison of NPV- vs. best quartile-based assessment of super-response, this aspect is of subordinate importance as patients served as their own controls. Overall, our findings are representative of current daily practice for CRT, and should therefore be of value for clinicians involved in the care of these patients. Subgroup analyses (e.g., analyzing only patients with sinus rhythm at implantation) were beyond the scope of our study.

Conclusions

All cut-offs, independent of the method by which they were assessed, were associated with a significant reduction in the combined primary endpoint of all-cause death, heart transplantation, ventricular assist device implantation, and hospitalization for heart failure, as well as the secondary endpoints (except LVEF ≥25 % for the mortality endpoint). Overall, the NPV-based method was not able to more "accurately" define super-response to CRT than the best quartile-based method comparing 5-years freedom from endpoints. Importantly, NPV- and best quartile-based cut-offs validate previously applied empirical echocardiographic cut-offs to define super-response to CRT and provide evidence for using these cut-offs in daily practice, and to facilitate inter-study comparability.

Conflict of interest David Hürlimann: Educational grants from Boston Scientific and Medtronic, Research grants from Biotronik, Medtronic and St. Jude Medical; Speaker honoraria and consulting fees from Biotronik, Medtronic, Sorin, St. Jude Medical.

Susann Schmidt: None.

Burkhardt Seifert: None.

Ardan M. Saguner: Educational and travel grants from Biotronik, Boston Scientific, St. Jude Medical and Sorin.

Gerhard Hindricks: Research support and speakers' honoraria from Biotronik and St. Jude Medical.

Thomas F. Lüscher: Research grants from Biotronik, Medtronic and St. Jude Medical.

Frank Ruschitzka: Research grants and consulting fees from Biotronik, speaker honoraria from Biotronik and Boston Scientific.

Jan Steffel: Research Grants from Biotronik, Medtronic and St. Jude Medical. Consulting fees from Biotronik, Boston Scientific, Medtronic, Sorin and St. Jude Medical.

References

1. Strickberger SA, Conti J, Daoud EG, Havranek E, Mehra MR, Pina IL, Young J (2005) Patient selection for cardiac resynchronization therapy: from the Council on Clinical Cardiology Subcommittee on Electrocardiography and Arrhythmias and the Quality of Care and Outcomes Research Interdisciplinary Working Group, in collaboration with the Heart Rhythm Society. Circulation 111(16):2146–2150. doi:10.1161/01.cir.0000161276.09685.4a
2. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P (2012) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 14(8):803–869. doi:10.1093/eurjhf/hfs105
3. Steffel J, Milosevic G, Hurlimann A, Krasniqi N, Namdar M, Ruschitzka F, Luscher TF, Duru F, Holzmeister J, Hurlimann D (2011) Characteristics and long-term outcome of echocardiographic super-responders to cardiac resynchronisation therapy: 'real world' experience from a single tertiary care centre. Heart (Br Card Soc) 97(20):1668–1674. doi:10.1136/heartjnl-2011-300222
4. Antonio N, Teixeira R, Coelho L, Lourenco C, Monteiro P, Ventura M, Cristovao J, Elvas L, Goncalves L, Providencia LA (2009) Identification of 'super-responders' to cardiac resynchronization therapy: the importance of symptom duration and left ventricular geometry. Europace 11(3):343–349
5. Castellant P, Fatemi M, Bertault-Valls V, Etienne Y, Blanc JJ (2008) Cardiac resynchronization therapy: "nonresponders" and "hyperresponders". Heart Rhythm Off J Heart Rhythm Soc 5(2):193–197. doi:10.1016/j.hrthm.2007.09.023
6. Ypenburg C, van Bommel RJ, Borleffs CJ, Bleeker GB, Boersma E, Schalij MJ, Bax JJ (2009) Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at midterm follow-up. J Am Coll Cardiol 53(6):483–490. doi:10.1016/j.jacc.2008.10.032
7. Hsu JC, Solomon SD, Bourgoun M, McNitt S, Goldenberg I, Klein H, Moss AJ, Foster E (2012) Predictors of super-response to cardiac resynchronization therapy and associated improvement in clinical outcome: the MADIT-CRT (multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy) study. J Am Coll Cardiol 59(25):2366–2373. doi:10.1016/j.jacc.2012.01.065
8. Celebi O, Knaus T, Blaschke F, Habedank D, Dohner W, Nitardy A, Stockburger M (2012) Extraordinarily favorable left ventricular reverse remodeling through long-term cardiac resynchronization: super-response to cardiac resynchronization. Pacing Clin Electrophysiol PACE 35(7):870–876. doi:10.1111/j.1540-8159.2012.03417.x
9. Rickard J, Kumbhani DJ, Popovic Z, Verhaert D, Manne M, Sraow D, Baranowski B, Martin DO, Lindsay BD, Grimm RA, Wilkoff BL, Tchou P (2010) Characterization of super-response to cardiac resynchronization therapy. Heart Rhythm Off J Heart Rhythm Soc 7(7):885–889. doi:10.1016/j.hrthm.2010.04.005
10. Wasmer K, Kobe J, Andresen D, Zahn R, Spitzer SG, Jehle J, Brachmann J, Stellbrink C, Martens E, Hochadel M, Senges J, Klein H, Eckardt L (2013) Comparing outcome of patients with coronary artery disease and dilated cardiomyopathy in ICD and CRT recipients: data from the German DEVICE-registry. Clin Res Cardiol Off J Ger Card Soc 102(7):513–521. doi:10.1007/s00392-013-0559-0
11. Yu CM, Bleeker GB, Fung JW, Schalij MJ, Zhang Q, van der Wall EE, Chan YS, Kong SL, Bax JJ (2005) Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. Circulation 112(11):1580–1586. doi:10.1161/circulationaha.105.538272
12. Poller WC, Dreger H, Schwerg M, Bondke H, Melzer C (2014) Not left ventricular lead position, but the extent of immediate asynchrony reduction predicts long-term response to cardiac resynchronization therapy. Clin Res Cardiol Off J Ger Card Soc 103(6):457–466. doi:10.1007/s00392-014-0672-8
13. Schau T, Koglek W, Brandl J, Seifert M, Meyhofer J, Neuss M, Grimm G, Bitschnau R, Butter C (2013) Baseline vectorcardiography as a predictor of invasively determined acute hemodynamic response to cardiac resynchronization therapy. Clin Res Cardiol Off J Ger Card Soc 102(2):129–138. doi:10.1007/s00392-012-0506-5
14. Heagerty PJ, Lumley T, Pepe MS (2000) Time-dependent ROC curves for censored survival data and a diagnostic marker. Biometrics 56(2):337–344
15. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ (1987) Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 76(1):44–51
16. Bax JJ, Schinkel AF, Boersma E, Elhendy A, Rizzello V, Maat A, Roelandt JR, van der Wall EE, Poldermans D (2004) Extensive left ventricular remodeling does not allow viable myocardium to improve in left ventricular ejection fraction after revascularization and is associated with worse long-term prognosis. Circulation 110((11 Suppl 1)):II18–II22. doi:10.1161/01.CIR.0000138195.33452.b0
17. Gold MR, Linde C, Abraham WT, Gardiwal A, Daubert JC (2011) The impact of cardiac resynchronization therapy on the incidence of ventricular arrhythmias in mild heart failure. Heart Rhythm 8(5):679–684. doi:10.1016/j.hrthm.2010.12.031