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Association between frequent cardiac resynchronization therapy optimization and long-term clinical response: a *post hoc* analysis of the Clinical Evaluation on Advanced Resynchronization (CLEAR) pilot study

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Aims The long-term clinical value of the optimization of atrioventricular (AVD) and interventricular (VVD) delays in cardiac resynchronization therapy (CRT) remains controversial. We studied retrospectively the association between the frequency of AVD and VVD optimization and 1-year clinical outcomes in the 199 CRT patients who completed the Clinical Evaluation on Advanced Resynchronization study.

Methods and results From the 199 patients assigned to CRT-pacemaker (CRT-P) (New York Heart Association, NYHA, class III/IV, left ventricular ejection fraction $<35\%$), two groups were retrospectively composed *a posteriori* on the basis of the frequency of their AVD and VVD optimization: Group 1 ($n = 66$) was composed of patients 'systematically' optimized at implant, at 3 and 6 months; Group 2 ($n = 133$) was composed of all other patients optimized 'non-systematically' (less than three times) during the 1 year study. The primary endpoint was a composite of all-cause mortality, heart failure-related hospitalization, NYHA functional class, and Quality of Life score, at 1 year. Systematic CRT optimization was associated with a higher percentage of improved patients based on the composite endpoint (85% in Group 1 vs. 61% in Group 2, $P < 0.001$), with fewer deaths (3% in Group 1 vs. 14% in Group 2, $P = 0.014$) and fewer hospitalizations (8% in Group 1 vs. 23% in Group 2, $P = 0.007$), at 1 year.

Conclusion These results further suggest that AVD and VVD frequent optimization (at implant, at 3 and 6 months) is associated with improved long-term clinical response in CRT-P patients.

Keywords Cardiac resynchronization therapy optimization frequency • Atrioventricular delay • Interventricular delay • Long-term clinical response • SonR^{TM} • Echocardiography

Introduction

Cardiac resynchronization therapy (CRT) is recognized in today's treatment guidelines as a standard of care for patients with heart failure (HF).[1] However, about 40% of CRT patients are commonly considered non-responders to the therapy.[2–4] Attempts to improve the responders' rates have taken a number of routes.

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What's new?

- Findings on the long-term association between CRT optimization (AVD and VVD) frequency and patients' clinical outcomes
- These findings are observed irrespective of the optimization method used, either echocardiography or device-based using SonR™

Perhaps the most frequent one is to refine selection criteria to exclude patients unlikely to respond: those with right bundle branch block, severe kidney insufficiency, and high burden of scar.[5,6] A second approach is to optimize the lead position,[7] but an optimal placement of the left ventricular (LV) lead is not always possible, depending on coronary venous anatomy, lead stability and other factors such as scar tissue. A third option is to optimize the programming of the CRT device, particularly the stimulation rate, paced and sensed atrioventricular delay (AVD), and interventricular delay (VVD).

The optimization of CRT programming involves a variety of techniques. The most commonly used techniques are echocardiography based. They often result in a time-consuming process, requiring high cost and labour intensity.[8–13] Consequently, CRT is often not optimized in clinical practice.[11] In an attempt to overcome these difficulties, device manufacturers are developing automated sensing methods and algorithms for assessing cardiac performance and adapting CRT delivery according to patients' changing needs, allowing a more rapid, simplified, and automated or semi-automated approach to CRT optimization. The SmartDelay™ (Boston Scientific Corporation, and QuickOpt™) uses the timing of intracardiac electrograms (IEGM) intervals to calculate the optimal AVD, while SonR™ (Sorin Group, Saluggia, Italy) uses a hemodynamic sensor selecting the VVD that yields maximal contractility to determine the optimal AVD.[12,13] To calculate the optimal AVD, the algorithms developed to date either use the timing of intracardiac electrograms (IEGM) intervals (SmartDelay™, Boston Scientific Corporation, and QuickOpt™), or a hemodynamic sensor (SonR™, Sorin Group, Saluggia, Italy).[12,13]

However, to date, the benefit and clinical value of the optimization of CRT programming remains unclear. Echocardiographic-based methods have shown acute hemodynamic benefits, but long-term clinical benefit remains to be assessed.[13] Also, inconclusive long-term results were reported with device-based methods algorithm such as QuickOpt™ (FREEDOM[14] trial) and Smart Delay™ (SMART-AV[15] trial). The Clinical Evaluation on Advanced Resynchronization (CLEAR) pilot study[16] was the first phase III trial showing potential trends towards a long-term clinical benefit of AVD and VVDs optimization with SonR™ vs. optimization left to investigators' discretion as per their standard of practice. Based on a composite endpoint close to the one used in the FREEDOM trial, the CLEAR results showed 76% of patients clinically improved with regular optimizations with SonR™ vs. 62% ($P = 0.028$) of patients improved when optimized according to standard of practice, at 1 year. Nevertheless, despite these encouraging findings, it appeared that only 57% of patients randomized to SonR™ were effectively optimized during the study; a limitation of this primary analysis which could have led to the underestimation of the clinical benefit of CRT programming optimization.

We present in this manuscript a non-randomized, retrospective analysis on the CLEAR population aimed to assess the association between the optimization frequency and long-term clinical outcomes, whatever the optimization method used.

Methods

Patient population and cardiac resynchronization therapy programming optimization

Methodology and results of the CLEAR trial have been previously published.[16] In brief, CLEAR was a prospective, multi-centre, single-blind, parallel-design, randomized treatment groups (SonR™-based optimization vs. optimization according to standard procedures) trial. The investigational trial, which complied with the Declaration of Helsinki was reviewed and approved by all local ethics committees of each participating institutions. All patients gave their written informed consent. Eligible patients were in New York Heart Association (NYHA) class III/IV despite optimal management, together with LV ejection fraction (LVEF) $<35\%$, LV end-diastolic diameter (LVEDD) ≥ 30 mm/m^2, QRS interval >150 ms or 120 ms $<$ QRS $<$ 150 ms with ≥ 2 echocardiographic indications of mechanical dyssynchrony. Patients were excluded if they were candidates for the implantation of a cardioverter defibrillator, had a history of atrial fibrillation, had experienced a myocardial infarction, undergone or were scheduled to undergo cardiac surgery or a coronary revascularization procedure within 3 months. A total of 268 patients were enrolled at 51 centres in 8 countries between November 2005 and February 2008, and the study ended in March 2009. Patients assigned to CRT-pacemaker (CRT-P) according to guidelines contemporary with the study start[17] received a NewLiving CHF® system (Sorin Biomedica, Saluggia, Italy), with MiniBest® (Sorin Biomedica, Saluggia, Italy) or Micro-Best ACT® Right Ventricular leads (Sorin Biomedica, Saluggia, Italy) (with the SonR™ sensor integrated into the lead). Right atrial and LV leads' choices were left to the investigators' preferences. The rate of successful implantations was 91.4%.[16] All patients followed the same visit schedule in a single-blinded way. Patients underwent clinical evaluations at post-implant, 1, 3, 6 and 12 months follow-up visits. Device optimization was performed only at scheduled optimization visits: post-implant, 3 and 6 months follow-up visits.

For this *post hoc* analysis, two groups were retrospectively formed from the CLEAR Intent-To-Treat (ITT) population ($n = 199$). Patients in Group 1 ($n = 66$) were selected as being 'systematically' optimized at each scheduled optimization visit. Group 2 was composed of all other patients in the ITT population ($n = 133$), consequently 'non-systematically' optimized at each scheduled optimization visit. These groups were formed independently from the method used to optimize AVD and VVD either automatically by the SonR™-based algorithm or manually by standard methods at investigators' discretion.

Study endpoints and follow-up

The primary endpoint was the percentage of clinically improved patients at 1 year based on a composite endpoint composed, in a hierarchical order of rates of death from any cause, hospitalization for HF management (HFH), NYHA functional class, and EuroQol-Visual Analogue Scale (EQ-VAS QoL) scores. Patients were classified as 'improved' if they were free from death and HFH, and if their NYHA functional class decreased by ≥ 1 point or their EQ-VAS QoL score increased by $\geq 10\%$, at 1 year.

The secondary endpoints of the analysis were all-cause mortality and hospitalizations for management of HF combined and taken separately. Other data collected included AVD and VVD at implant (M0), M3 (3 months after implant), and M6 and echocardiographic parameters [LVEF, LVEDD, and LV end-systolic diameter (LVESD)] at baseline and 1 year.

In case of death, every effort was made to determine the cause. Whenever possible, the pacemaker (Newliving CHF) was interrogated. If applicable, autopsy report was provided to the Sponsor.

Investigators reported both objective (death, hospitalizations) and subjective (NYHA class, EQ-VAS QoL scores) changes in clinical status in the CRF. The EQ-VAS QoL questionnaire was firstly completed by the patient and consisted in a single-item visual analogue score from 0 'worst imaginable health state' to 100 'best imaginable health state', in mm.[18]

Recorded echocardiographic parameters were analyzed by a central core lab (Dr G. Jauvert, Bizet Clinic, Paris, France) in a double-blinded fashion.

Data analysis and statistics

Case report forms (CRF) and electronic data were centrally collected and checked for consistency and completeness. Inconsistent or incomplete data were clarified by the study centre by a query process.

The statistical analyses were performed on the locked database in the biometry department of the Sponsor. The CLEAR ITT population was considered for the analysis. Data are expressed as percentages or mean ± standard deviation, as appropriate.

Demographic and clinical patients' characteristics (including aetiology, comorbidities, echocardiographic parameters, and medications) were compared between the treatment groups.

An analysis of variance was performed to compare AVD and VVD values between groups over the whole follow-up period. Within-group comparisons over periods of time ([M0–M3], [M3–M6] and [M6–M12]) were carried out with paired sign test.

In case of missing data for the NYHA functional class and EQ-VAS QoL score for the composite endpoint calculations, missing values were imputed using a 'Last Observation Carried Forward' approach.

In the univariate analysis, categorical variables were compared by χ^2 test or Fisher's exact or a two-tailed Student's *t*-test, as appropriate. For continuous variables with normal distribution, comparisons of change between groups from baseline to last follow-up were assessed using Student's *t*-test. For other continuous variables, a non-parametric Kruskall–Wallis test was applied. Only patients with available data at both enrolment and 1-year follow-up were included in the endpoint analysis. Analyses of changes for variables were made using paired tests: if the variables followed a normal distribution, a paired *t*-test was used; otherwise a sign-paired test was applied.

Kaplan–Meier estimates for mortality and HF-related hospitalizations were calculated; and differences between groups assessed using a log-rank test.

As a supportive analysis, a logistic multivariate model was applied on the composite endpoint for measuring the effect of CRT optimization frequency adjusted for the optimization method used.

The statistical analyses were conducted using SAS® software, version 9.2 (SAS Institute, Inc., Cary, NC) at a 0.05 level of significance (two-sided test).

Results

Study population and follow-up

The baseline demographic, clinical, and ECG characteristics of the two study groups were clinically similar (*Table 1*). The average follow-up duration was 367 ± 50 days ($n = 66$) in Group 1 and 354 ± 96 days ($n = 133$) in Group 2. No difference in the total number of visits post-implant was observed between Group 1 (median: 5, min/lower quartile/upper quartile/max: 3/5/5/8) and Group 2 (median: 5, min/lower quartile/upper quartile/max: 1/5/5/7; $P = 0.10$).

Atrioventricular and interventricular delays optimization

In Group 1, systematic AVD and VVD optimization was performed with SonR™ in 57 patients (86%) and with standard methods in nine patients (14%).

In Group 2, heterogeneous optimization frequency was observed: 64 patients (48%) had never been optimized at any time point in the study, 38 patients (29%) had been optimized once, and 31 patients (23%) had been optimized twice during the study. A total of 43 patients (32%) in this group were optimized using SonR™ and 90 patients (68%) were optimized with standard procedures.

Average AVD remained significantly shorter in Group 1 (systematically optimized patients) compared with Group 2 throughout the study ($P = 0.006$) (*Table 2*); mean absolute AVD change between last follow-up and baseline was 20.6 ± 16 ms in Group 1 vs. 14.4 ± 14 ms in Group 2 ($P = 0.001$). In Group 1, optimal AVD remained unchanged in 11%, shortened in 51% and lengthened in 38% of patients, while in Group 2, 38% of patients had unchanged AVD, 46% shortened and 16% lengthened.

The mean VVD values did not differ markedly throughout the study; VVD average values were −13 ± 31 ms in Group 1 vs. −12 ± 25 ms in Group 2 ($P = 0.971$) during the second semester (*Table 2*).

Clinical outcomes

Based on the primary composite endpoint, systematic optimization (Group 1) was associated with a higher rate of improved patients, at 1 year (85% in Group 1 vs. 61% in Group 2; $P < 0.001$, *Table 3*). Within Group 2 patients, the rate of improved patients was similar between patients never optimized (61%) and those optimized once or twice (61%).

Secondary endpoints' analysis showed an association between systematic optimization and fewer combined rates of deaths and hospitalizations, at 1 year (9% in Group 1 vs. 29% in Group 2; $P = 0.002$; *Table 3*).

The 1-year probability of being free from events (all-cause mortality and HFH) was higher in systematically optimized patients (91%) than in non-systematically optimized patients (71%) (hazard ratio 0.456, 95% confidence limits, CI = 0.212–0.980) and according to the log-rank test, this difference was statistically significant ($P = 0.039$) (*Figure 1*).

Additionally, systematic optimization was associated with fewer deaths (3% in Group 1 vs. 14% in Group 2, $P = 0.014$), fewer hospitalization (8% in Group 1 vs. 23% in Group 2, $P = 0.007$) (*Table 3*) and with a lower NYHA functional class (1.9 ± 0.6 in Group 1 vs. 2.2 ± 0.7 in Group 2, $P = 0.018$), at 1 year (*Table 3*).

A significant increase in EQ-VAS QoL scores were observed in each group ($P < 0.001$) at 1 year vs. baseline, without any significant difference between groups, as observed for hemodynamic parameters (LVEF, LVEDD, and LVESD) (*Table 3*).

The multivariate analysis showed that standard methods were associated with improved patient rates from 60%

Table 1 Baseline characteristics of the included ($n = 268$) population and the systematically optimized group (Group 1) and the non-systematically optimized group (Group 2)

	Overall population	Analyzed population ($n = 199$)		P^a
	All patients ($n = 268$)	Group 1 ($n = 66$)	Group 2 ($n = 133$)	
Demographics				
Age, years	73.1 ± 9.9	71.7 ± 9.5	74.1 ± 9.8	NS
Men, *n* (%)	168 (63%)	38 (59%)	86 (65%)	NS
Women, *n* (%)	98 (37%)	26 (41%)	47 (35%)	NS
Body mass index (kg/m^2)	26.3 ± 4.6	25.9 ± 4.4	26.4 ± 4.7	NS
Heart failure aetiology, *n* (%)				
Idiopathic	122 (46%)	33 (50%)	60 (45%)	NS
Ischaemic	105 (39%)	21 (32%)	56 (42%)	NS
Valvular	21 (8%)	8 (12%)	8 (6%)	NS
Secondary prevention	21 (8%)	4 (6%)	13 (10%)	NS
Characteristics				
NYHA functional class	3.0 ± 0.3	3.0 ± 0.2	3.1 ± 0.3	NS
QRS duration (ms)	160 ± 22	166 ± 20	159 ± 24	NS
LVEF (%)	27 ± 8	27 ± 8	27 ± 8	NS
LVESD (mm)	56 ± 10	56 ± 8	59 ± 9	NS
LVEDD (mm)	66 ± 10	65 ± 10	67 ± 10	NS
EQ-VAS QoL score (mm)	51 ± 19	48 ± 18	50 ± 19	NS
Comorbidities, *n* (%)				
Hypertension	126 (47%)	37 (56%)	78 (59%)	NS
Diabetes	66 (25%)	12 (18%)	37 (28%)	NS
Other associated condition(s)	105 (39%)	27 (41%)	54 (41%)	NS
Arrhythmia	69 (26%)	17 (26%)	33 (25%)	NS
Previous surgery	84 (31%)	17 (26%)	42 (32%)	NS
Medications, *n* (%)				
ACE inhibitor	184 (69%)	47 (71%)	93 (70%)	NS
ACE inhibitor substitutes	31 (12%)	6 (9%)	16 (12%)	NS
Beta-adrenergic blocker	194 (72%)	50 (76%)	99 (74%)	NS
Diuretic	214 (80%)	52 (79%)	108 (81%)	NS
Spironolactone	122 (46%)	32 (48%)	60 (45%)	NS
Laboratory data				
BNP (pg/ml)	619 ± 730	502 ± 628	720 ± 826	NS

Group 1, systematically optimized group; Group 2, non-systematically optimized group.
[a]Difference between groups.
Values are given as number (%) or mean (± standard deviation).
ACE, angiotensin-converting enzyme; NS, not significant.

(non-systematically optimized, $n = 90$) to 78% (systematically optimized, $n = 9$) and SonR^{TM}-based optimization was associated with improved patients' rates from 63% (non-systematically optimized, $n = 27$) to 86% (systematically optimized, $n = 49$). This supportive multivariate analysis further suggests that long-term clinical outcomes were associated with the optimization frequency ($P = 0.004$), not with the optimization method used ($P = 0.607$).

Discussion

Findings

Our results showed an association between frequent AVD and VVD optimizations and an improved therapeutic response at 1 year based on a number of variables: the composite primary endpoint, death, and hospitalization in combination and taken separately and the NYHA functional class. These associations appeared to be related to the optimization frequency ($P = 0.004$), regardless of the optimization method used ($P = 0.607$).

Results in context

As stated previously, up to one-third of patients with advanced HF do not exhibit a positive response to CRT. It has been previously published by Mullens *et al.*[19] that among the different reasons of non-response, suboptimal AV timing accounts for CRT suboptimal response in a significant proportion of patients. This *post hoc* analysis further supports these results.

Table 2 Atrioventricular and interventricular delays in the systematically optimized (Group 1) vs. the non-systematically optimized (Group 2) groups

		M0–M3	M3–M6	M6–M12
AV Delay (ms)[a]	Sys. opt. (Group 1), $n = 66$	100 ± 24	101 ± 25	95 ± 22
	Non-sys. opt. (Group 2), $n = 133$	107 ± 20	107 ± 24	106 ± 23
	P value	0.029	0.121	<0.001
VV Delay (ms)[b,c]	Sys. opt. (Group 1), $n = 66$	−12 ± 32	−11 ± 31	−13 ± 31
	Non-sys. opt. (Group 2), $n = 133$	−15 ± 30	−11 ± 24	−12 ± 25
	P value	0.360	0.956	0.971

Values are expressed as mean ± standard deviation.
[a]$P = 0.006$ for difference between groups over the 3 follow-up visits (analysis of variance).
[b]Negative values indicate LV pre-activation; positive values indicate RV pre-activation.
[c]P = NS for difference between study groups over the 3 study visits (analysis of variance).

Table 3 Primary and secondary endpoints and echocardiographic parameters in the systematically optimized group (Group 1) and the non-systematically optimized group (Group 2)

	Group 1, sys. opt. ($n = 66$)		Group 2, non-sys. opt. ($n = 133$)		P^c
Composite criterion[a] improved, *n* (%)	56/66 (85%)		81/133 (61%)		<0.001
Free from deaths and HFH, *n* (%)	60/66 (91%)		95/133 (71%)		0.002
Free from death, *n* (%)	64/66 (97%)		114/133 (86%)		0.014
Free from hospitalizations, *n* (%)	61/66 (92%)		102/133 (77%)		0.007
NYHA functional class					
Baseline	3.0 ± 0.2, $n = 66$		3.1 ± 0.3, $n = 131$		
Last follow-up	1.9 ± 0.6, $n = 63$	<0.001[b]	2.2 ± 0.7, $n = 109$	<0.001[b]	0.018
EQ-VAS QoL scores					
Baseline	49 ± 19, $n = 58$		49 ± 19, $n = 99$		
Last follow-up	67 ± 18, $n = 58$	<0.001[b]	65 ± 19, $n = 99$	<0.001[b]	0.479
LVEF (%)					
Baseline	27 ± 8, $n = 61$		27 ± 8, $n = 118$		
Last follow-up	38 ± 13, $n = 57$	<0.001[b]	38 ± 14, $n = 97$	<0.001[b]	0.749
LVEDD (mm)					
Baseline	65 ± 9, $n = 54$		68 ± 10, $n = 88$		
Last follow-up	61 ± 11, $n = 54$	0.003[b]	60 ± 11, $n = 88$	<0.001[b]	0.911
LVESD (mm)					
Baseline	55 ± 10, $n = 55$		57 ± 11, $n = 82$		
Last follow-up	49 ± 13, $n = 55$	<0.001[b]	48 ± 13, $n = 82$	<0.001[b]	0.981

Values are expressed in % (numbers) or mean ± standard deviation.
[a]Composite of parameters including deaths from any cause, HF-related hospitalizations, NYHA class and QoL.
[b]Test at 1 year from baseline in each group.
[c]Test at 1 year between groups.

Concerning AVD, it is widely accepted today that optimal AVD may change significantly over time. In a study presented by Zhang *et al.*, the optimal AVD remained unchanged in only 44% of the patients over a 16-month follow-up; it was shortened in 38% and lengthened in 18% of the patients.[20] O'Donnel *et al.*[10] reported that optimal AVD and VVD vary over time and could not be predicted in individual patients. Finally, Ritter *et al.* also confirmed a large variability in optimized AVD and VVD, individually and over time.[16] All these studies suggest the need for individual and periodic device optimization. Our results are aligned with these findings: in the group of patients systematically optimized, optimal AVD remained unchanged in only 11%, 51% of the patients presenting shortened AVD and 38% lengthened AVD. A large variability of optimal AVD was observed over time, with an average absolute variation of 20.6 ± 16 ms. Moreover, Brenyo *et al.*[21] reported short values for optimal AVD (<100 ms) that were associated

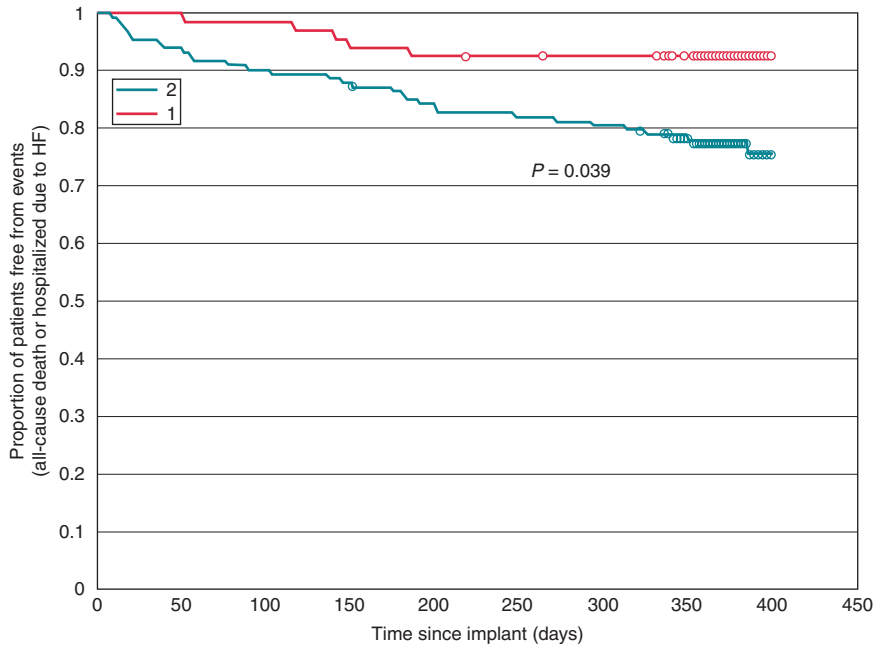

Figure 1 Kaplan–Meier representation of time to first event for the combined secondary endpoint of death for all cause or hospitalization for heart failure in the systematically optimized Group 1 and the non-systematically optimized Group 2.

with a greater reduction in LV end-systolic volume (LVESV). These results are further supported by the analysis presented: mean AVD values in the systematically optimized group were shortened up to <100 ms and remained significantly shorter than those of the non-systematically optimized patients.

Concerning clinical outcomes, our results are in contrast to those reported in landmark trials such as FREEDOM and SMART-AV. The FREEDOM trial did not show any significant improvements in response rates when CRT was optimized based on AVD and VVD.[14] The SMART-AV trial found no differences in HF-related events and LVESV between systematic AVD optimization with an automatic algorithm and AVD optimization using echocardiography or a fixed AVD of 120 ms.[15] The reasons why our results differ remain speculative. However, in the SMART-AV trial the primary endpoint was not based on a clinical composite criterion, the study lasted only 6 months and no VVD optimization was performed. In the CLEAR and the FREEDOM trials, the composite endpoint was slightly different, i.e. a composite of all-cause death, HF hospitalization, NYHA functional class and QoL score in the CLEAR study and a composite of all-cause death, HF hospitalization and NYHA functional Class in the FREEDOM trial. Moreover, the algorithms employed differ markedly between the three studies, as well as the optimization methods. Importantly, in this CLEAR post-hoc analysis the benefit of CRT optimization could be observed only when the optimization was performed systematically at each follow-up. A lower rate of optimization in SMART-AV and FREEDOM studies could explain the differences observed. Finally, SMART-AV and FREEDOM included patients indicated for CRT devices with defibrillator compared with this study which included patients indicated for CRT with pacemaker.

Because no large-scale randomized clinical trials have yet proven sufficient evidences, no recommendations on long-term CRT management and specifically on AVD and VVD optimizations are officially given to date. However, even though the modest sample size advocates caution when interpreting the data, this *post hoc* analysis supports the need for greater efforts to frequently optimize CRT programming in clinical practice, and this whatever the method chosen (echo-based or with SonR^{TM}).

Optimization methods and clinical implications

In this context, an automated device-based CRT optimization has several advantages over the usual echocardiographic methods. They obviate the need for a complicated initial optimization procedure, as well as for recurrent optimizations at clinical follow-up visits. They further fine-tune the performance of the device according to changing patient needs, in a way not possible without impractically frequent patient visits. Several studies show how poorly patients are optimized through echocardiographic methods and even not optimized at all in clinical practice.[11] The encouraging results presented allow considering SonR^{TM} as a viable option for systematic optimization, since in this analysis 86% of patients were optimized by this hemodynamic sensor.

Nevertheless, long-term clinical benefits of AVD and VVD optimization and the efficiency of the automated devices remain to be further demonstrated, together with the underlying mechanisms involved in CRT optimization elucidated. A large scale trial

(RESPOND CRT, Clinicaltrial.gov: NCT01534234) has started and is planned to include up to 1000 patients to further investigate this rapidly evolving technology.

Study limitations

This *post hoc* analysis has its associated caveats. This was a non-randomized analysis from a randomized trial. Another limitation to be considered is the unblinded assessment of NYHA functional class.

A trend towards more ischaemic and diabetic patients was observed in Group 2 compared with Group 1, but without any clinical (and statistical) difference. Therefore, it is unlikely that these baseline trends played a role in the study findings.

Finally, no differences in markers of remodelling could be highlighted between frequent and non-frequent optimization; several other studies have shown similar weak correlations between echocardiographic and clinical responses to CRT.[22,23]

Conclusions

This *post hoc* analysis from the CLEAR pilot study data further suggests the clinical value of frequent CRT optimization on the long term in severe chronic heart failure patients. Even though the modest sample size advocate caution when interpreting the data, results support the interest for greater efforts towards frequent CRT optimization programming in clinical practice.

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Appendices

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