Automatic Optimization of Cardiac Resynchronization Therapy Using SonR—Rationale and Design of the Clinical Trial of the SonRtip Lead and Automatic AV-VV Optimization Algorithm in the Paradym RF SonR CRT-D (RESPOND CRT) Trial

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Although cardiac resynchronization therapy (CRT) is effective in most patients with heart failure (HF) and ventricular dyssynchrony, a significant minority of patients (approximately 30%) are non-responders. Optimal atrioventricular and interventricular delays often change over time and reprogramming these intervals might increase CRT effectiveness. The SonR algorithm automatically optimizes atrioventricular and interventricular intervals each week using an accelerometer to measure change in the SonR signal, which was shown previously to correlate with hemodynamic improvement (left ventricular [LV] dP/dt_{max}). The RESPOND CRT trial will evaluate the effectiveness and safety of the SonR optimization system in patients with HF New York Heart Association class III or ambulatory IV eligible for a CRT-D device. Enrolled patients will be randomized in a 2:1 ratio to either SonR CRT optimization or to a control arm employing echocardiographic optimization. All patients will be followed for at least 24 months in a double-blinded fashion. The primary effectiveness end point will be evaluated for non-inferiority, with a nested test of superiority, based on the proportion of responders (defined as alive, free from HF-related events, with improvements in New York Heart Association class or improvement in Kansas City Cardiomyopathy Questionnaire quality of life score) at 12 months. The required sample size is 876 patients. The two primary safety end points are acute and chronic SonR lead-related complication rates, respectively. Secondary end points include proportion of patients free from death or HF hospitalization, proportion of patients worsened, and lead electrical performance, assessed at 12 months. The RESPOND CRT trial will also examine associated reverse remodeling at 1 year. (Am Heart J 2014;167:429-36.)

Cardiac resynchronization therapy (CRT) is efficacious and well-established for patients with heart failure (HF) and ventricular dyssynchrony.[1-3] However, despite various efforts to improve the effectiveness of CRT delivery, thirty percent non-responder rates have persisted.[4-7]

For several years it has been recognized that optimal atrioventricular (AV) and interventricular (VV) delays often change over time and that reprogramming these intervals might be useful to improve CRT effectiveness. Hemodynamic improvements with optimized device programming have been reported,[8-11] but the long-term clinical benefit of systematic optimization of CRT remains to be confirmed in large-scale studies.

In the CLEAR pilot study using the SonR system integrated into a CRT-P device, Ritter et al demonstrated significant improvements in New York Heart Association (NYHA) class when CRT was systematically optimized with SonR compared with a control group where optimization was left to physicians' standard procedure.[15] To confirm these results in a larger CRT-D population, a prospective study has been designed.

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This paper describes the design of RESPOND CRT. The objective of RESPOND CRT is to evaluate the effectiveness and safety of the SonR optimization algorithm compared with echocardiographic optimization in patients with HF receiving a CRT-D device.

System background

The SonR system uses an accelerometer sealed in a right atrial lead (the SonRtip lead, Sorin Group Italia, Saluggia, Italy) to measure the SonR signal. The SonR sensor is based on the measurement of vibrations generated by the heart cycle. The peak-to-peak amplitude of the myocardial vibrations generated during the isovolumetric contraction phase (SonR signal) is correlated to the first heart sound amplitude, itself correlated to cardiac contractility. Previous studies demonstrated that changes in the SonR signal amplitude correlate closely with changes in invasive LV $dP/dt_{max.}$[12] A SonR-based algorithm has been developed in order to identify the optimal AV and VV delays at weekly intervals[13,14] The SonRtip lead is a straight, bipolar right atrial pacing lead with active fixation. The SonR system uses the hemodynamic SonR sensor[14,20-22] embedded in the tip of the SonRtip bipolar atrial lead. The first component of the SonR signal, recorded during the isovolumetric contraction phase of the cardiac cycle, has been demonstrated to correlate with LV contractility (expressed as LV dP/dt_{max}), which itself is modulated by the degree of LV filling.

CRT optimization using the SonR algorithm can be performed in the clinic using the device programmer, or can be programmed to perform optimization automatically, updating AV and VV intervals weekly. The SonR optimization algorithm is comprised of two successive steps:

- The device first tests seven VV configurations (VV sequence = left before right with VV delays = 48, 32, 16, 0 ms; VV sequence = right before left with VV delays = 16, 32, 48 ms): for each VV configuration the device measures the SonR signal amplitude at several AV delays, identifying the optimal VV configuration as the one with the highest average SonR measurement.[13]
- Using this optimal VV configuration, the algorithm determines the optimal sensed and paced AV delays by measuring the SonR amplitudes at 11 AV delays shorter than patient's PR and/or AR intervals. According to the patient's conditions, the system will determine and apply both sensed and/or paced optimal atrioventricular intervals. When the AV-VV Auto Optimization function is enabled, the device will also perform an exercise AV delay optimization while the patient is exercising. The optimal AV delay is then linearly adjusted according to patient heart rate.

RESPOND CRT study design

Design and centers

RESPOND CRT (clinicaltrials.gov identification NCT01534234) is a multi-center, randomized, two-arm, double-blinded, prospective trial. It is planned to enroll 1032 patients, in Europe, North America and Australia. The study will be conducted in compliance with Good Clinical Practice guidelines, consistent with the most recent version of the Declaration of Helsinki and with the approval of all appropriate national and local ethics committees.

Randomization, blinding and follow-up

Enrolled patients will be randomized to either the treatment (weekly AV and VV delay optimization using SonR) or the control arm (echocardiographic optimization, with SonR programmed off) utilizing a 2:1 ratio stratified by clinical site using SAS 9.2 before the study onset. Randomization occurs within 14 days after successful implant.

All patients will be blinded to their randomization assignment. In addition, staff members assigned to assess the patient's clinical status (heart failure/cardiologist staff who manage patient's heart failure, administer quality of life questionnaires, assess NYHA functional class and perform a physical examination) are blinded to the subject's randomization assignment. Blinding will be maintained by ensuring that blinded individuals do not have access to the patient data book, CRFs, programmer screens, or documentation in the subject chart that refers to randomization assignment, including echocardiograms. Unblinded personnel (electrophysiologists, echocardiography staff) will perform device interrogation, optimization and programming.

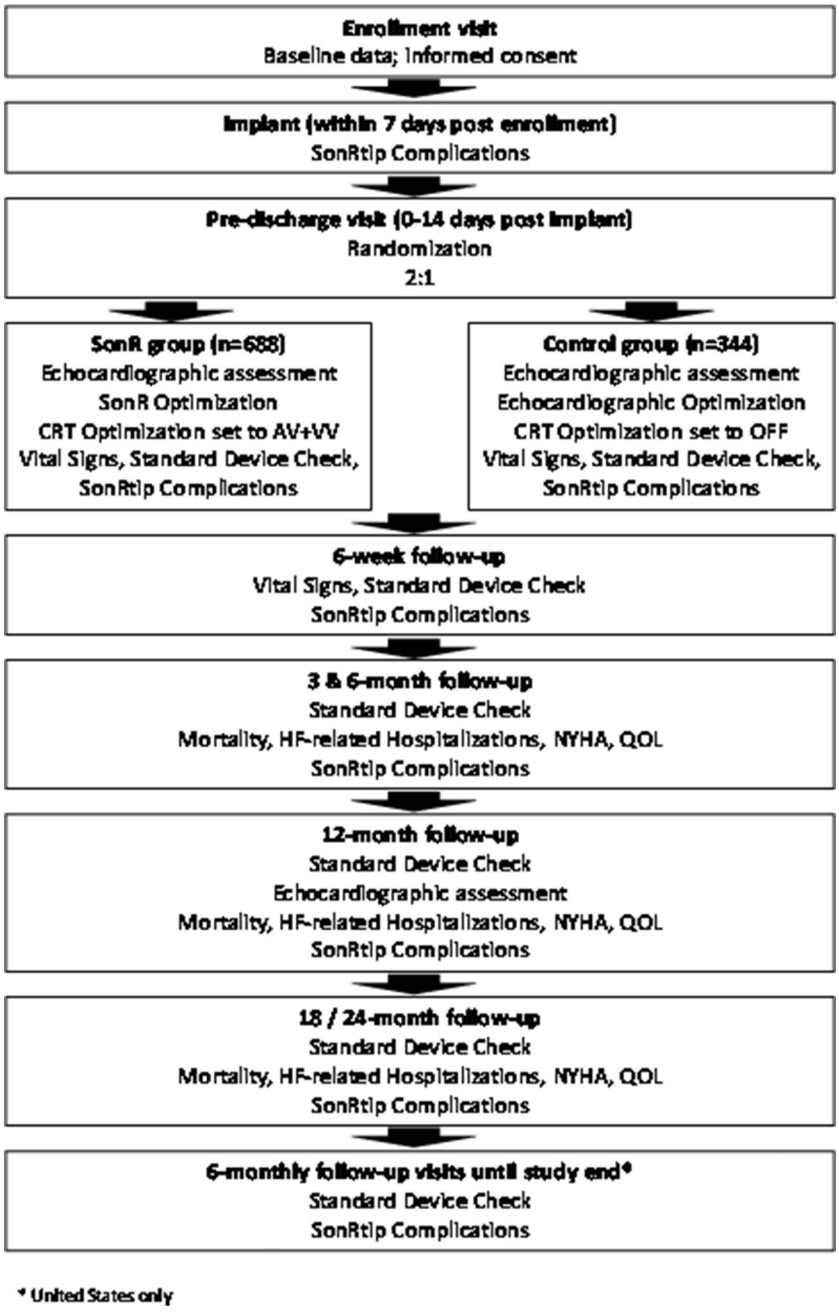
All patients will be evaluated at baseline, pre-discharge, 6 weeks post-implant, 3 months post-implant and every 6 months after implant up to 24 months (Figure 1). The primary and secondary effectiveness end points will be evaluated after 12 months of follow-up, while the primary safety end points will be evaluated after 3 and 12 months of follow up. Long-term effectiveness will be assessed at 18 and 24 months.

Patients in the United States will continue to be followed after 24 months until the device receives federal approval in a non-randomized, observational way in order to determine the patient's vital signs and to check device and leads functioning (standard device check).

Patients and study therapies

Patients will be enrolled in RESPOND CRT if they have moderate-to-severe HF NYHA functional class III or ambulatory IV despite optimal pharmacological

Figure 1



RESPOND CRT study flow chart.

treatment and meet the eligibility criteria for implantation of a CRT-D device enumerated in current guidelines as level of evidence class I and IIA,[16-19] namely depressed LVEF (≤35%), and wide QRS (>120 ms in LBBB; QRS >150 ms in non-LBBB). The main exclusion criteria are: any ventricular tachyarrhythmia of transient or reversible causes; incessant ventricular tachyarrhythmia; unstable angina, acute myocardial infarction, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty within the past 4 weeks; correctable valvular disease that is the primary cause of heart failure; a cerebrovascular event or transient ischemic attack within the previous 3 months; persistent or permanent atrial arrhythmias (or cardioversion for atrial fibrillation within

the past month); post heart transplant; renal failure requiring dialysis; previous CRT-P or CRT-D implant; life expectancy <1 year.

All patients will be implanted with the Paradym RF SonR (Sorin CRM SAS, Clamart, France) triple chamber CRT-D device (model 9770) and the SonRtip atrial lead. The choice of right ventricular (RV) and LV leads is at the investigators' discretion. In Europe only, CE marked devices, locally approved and commercially available, will be used. In the United States, the SonR CRT-D and SonRtip atrial lead are evaluated under an Investigational Device Exemption.

SonR optimization will be initiated in clinic within 14 days post-implant for patients assigned to the SonR group, with weekly AV and VV automatic optimization at rest, and weekly exercise AV delay optimization during daily activities.

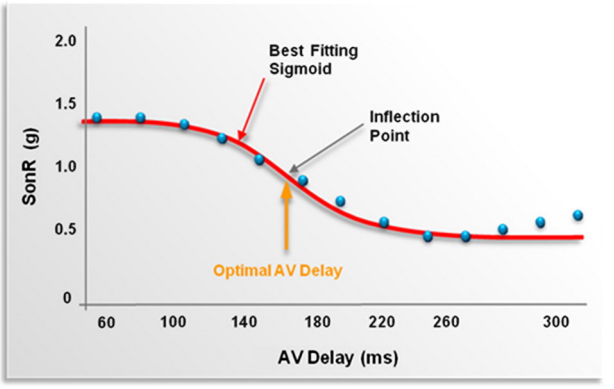
In the control group, echo-based optimization will be performed within 14 days post-implant. The decision to conduct repeat optimizations during follow-up is left to the blinded clinician(s) assessing symptoms. In this group, optimization will be performed using the iterative method with Doppler echocardiography. AV delay will be optimized by identifying the longest LV filling time without any truncation of the A wave. The VV interval will be optimized using aortic velocity time integral (AoVTI) as a surrogate for stroke volume, at the same 7 VV delays used in the SonR algorithm.

End points

The primary objective of RESPOND CRT is to assess the effectiveness and safety of the SonR system. The primary effectiveness end point is the proportion of responders at the 12-month follow-up visit. The proportion of responders in the SonR group will be compared for non-inferiority to the control group with a non-inferiority margin of 10%, with a nested test of superiority. Response will be assessed based on a hierarchical clinical composite endpoint[23] including all-cause death, HF-related events (unplanned HF hospitalization, invasive intervention or initiation of any intravenous drug treatment for HF), NYHA functional class and quality of life, as determined by the Kansas City Cardiomyopathy Questionnaire (KCCQ).[24,25] Quality of life questionnaires will be administered by blinded personnel (heart failure/cardiologist staff) who will also carry out NYHA functional classifications, physical examinations and adverse event reporting.

A patient will be considered improved if he/she is alive without experiencing an HF-related event and shows improvement of more than 1 NYHA class or, if NYHA class is stable, an improvement of more than 5 points in overall KCCQ quality of life score (Figure 2). Patients will be considered worsened if they: (a) die, or (b) experience an HF-related event, or (c) show worsening of at least 1 NYHA class, or (d) show a stable NYHA with a worsening of more than 5 in overall KCCQ quality of life score. Patients will be considered stable if neither improved nor worsened. Only patients improved will be considered as responders. (See Fig. 3.)

Figure 2



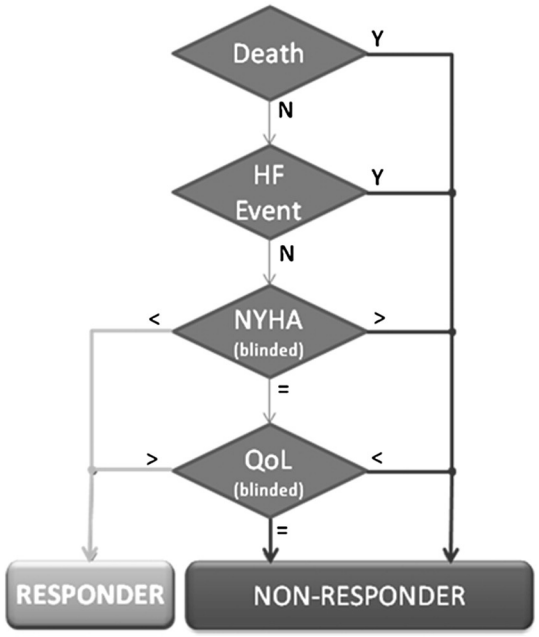
SonR amplitude (g) plotted against AV delays (ms) for the optimal VV configuration. The optimal atrioventricular delays value is that corresponding to the point of inflexion of this sigmoid curve.

Primary safety end points are rates of freedom from acute and chronic SonRtip lead-related complications. The acute end point is defined as the proportion of patients not experiencing any complication related to the SonRtip lead within 3 months post-implant; chronic SonRtip lead-related complications are those occurring between 3 and 12 months post-implant. Lead-related complications are those that require surgery or external defibrillation and that cannot be resolved by reprogramming or change in medication.

Secondary endpoints will be a composite of mortality or HF hospitalization at 12 months, the proportion of patients worsened at 12 months, and lead performance throughout 12 months of follow-up (appropriate atrial sensing amplitudes, pacing thresholds, and pacing impedance). The individual components of the effectiveness end point and changes in echocardiographic parameters (left ventricular end diastolic volume, left ventricular end systolic volume, left ventricular ejection fraction, left atrial area in systole, area of the mitral regurgitation jet, E/A ratio, E wave deceleration time, LV filling time, R-R interval, aortic pre-ejection time, excursions of the tricuspid annular plane, tricuspid flow velocity curve/pressure gradient, pulmonary flow velocity curve/pulmonary pre-ejection time) from baseline to month 12 will be subjects of ancillary analyses, as will the superiority of SonR-based optimization at the 18- and 24-month follow-up visits.

Adverse events will be collected throughout the study. A Data Safety Monitoring Board (DSMB), made of three

Figure 3



Decision algorithm for evaluation of the effectiveness end point.

independent physicians and a non-voting statistician, will review the study data to determine the progress of the study from a safety point of view and will recommend to the sponsor whether the available information would allow the sponsor to continue, modify, or terminate the study (Table). A Clinical Events Committee (CEC) consisting of three independent HF experts blinded to randomization assignment will adjudicate all putative HF-related events in the primary effectiveness end point and review all adverse events in order to ascertain the relation to the devices under investigation and study conduct (Table[26]). Finally, echocardiographic parameters will be assessed by an independent, blinded Core Laboratory (Table).

Study success is defined as meeting all three primary endpoints: a finding of non-inferiority of treatment to control in the primary effectiveness outcome at 12 months post-implant, acute lead-related complication-free rate greater than 91%, and chronic lead-related complication-free rate greater than 94%. The secondary endpoints will only be evaluated if the primary endpoints are met.

Statistical considerations

Overall sample size calculations were based on the superiority analysis of the primary effectiveness endpoint. This superiority test is nested hierarchically within the non-inferiority comparison (superiority will be tested if non-inferiority is met) and is a closed-testing procedure, thus no alpha adjustment is required. The study power is set to 80% with a two-sided .05 α level. Assuming responder rates of 67% in the control group and 76% in the treatment group, with a 2:1 allocation of patients to SonR and control, respectively, the sample size required is 876 (584 treatment: 292 control) patients. With an assumed global attrition rate of 15% (including ~5% implant failure) the overall sample size is 1032 (688 treatment, 344 control, respectively). This sufficiently powers all primary and secondary objectives.

Up to one third of this population is expected to be attributed to US patients.

The primary analysis population will consist of all patients successfully implanted with the CRT-D system and for whom evaluable end point data are available, defined as not lost to follow-up at 12 months and with NYHA and KCCQ recorded at least once during follow-up. The distribution of missing end point data will be assessed.

In addition, the following populations will be analyzed: the intention-to-treat population, consisting of all randomized patients; the as-treated population,[27] in which patients will be analyzed according to the treatment received from the start of the study; and the per-protocol population, consisting of all patients without major protocol deviations and attending all scheduled follow-up visits.

For lead safety endpoints, all patients implanted with a SonRtip lead (irrespective of whether a full CRT system was implanted) will be included in the primary analysis population.

Sensitivity analyses will be performed on each of the primary endpoints (effectiveness and safety) to assess the effect of missing data on the endpoints in the intention-to-treat population. The multiple imputation analyses will be carried out with SAS PROC MI/PROC MIANALYZE, or another validated imputation software package. These analyses will be performed to each endpoint separately, and for the effectiveness endpoint to the two randomization arms, in order to obtain imputed values that appropriately characterize variability to the imputation.

The potential for a difference in the study outcomes by geography (outside of the USA compared to USA), clinical sites and population sub-groups will be examined using standard poolability analyses (significance level at .15). Subgroups will be evaluated based on baseline factors that might influence response to CRT.

Timelines

As of November 20, 2013, 608 patients have been enrolled in the RESPOND CRT study. The final results are expected by the end of 2016.

Role of the sponsor

All statistical analyses will be performed by Sorin CRM SAS (Clamart, France) on SAS software, version 9.2 (SAS

Table. Steering Committee, Core Laboratory, CEC and DSMB of the RESPOND CRT trial

Steering Committee
Pr Josep Brugada (chairman), University of Barcelona, Spain
Pr Johannes Brachmann, Coburg Hospital, Germany
Dr Peter Paul Delnoy, Isala Kliniken, The Netherlands
Pr Luigi Padeletti, Careggi University Hospital, Italy
Dr Dwight Reynolds, University of Oklahoma, USA
Dr Philippe Ritter, Bordeaux, France
Dr Jagmeet P. Singh, Massachusetts General Hospital, USA
DSMB
Dr Ignacio Garcia-Bolao, Navarra University Clinic, Pamplona, Spain
Dr Suneet Mittal, The Valley Hospital; Ridgewood, NJ, USA
Dr Mark Sopher, Royal Bournemouth Hospital, Bournemouth, UK
CEC
Dr Alan Bank, St. Paul Heart Clinic; St. Paul, MN, USA
Dr Edoardo Gronda, IRCCS MultiMedica; Sesto S. Giovanni (MI), Italy
Dr Mario M. Oliveira, Santa Marta Hospital; Lisbon, Portugal
Core Laboratory
Dr Stefano Ghio, IRCCS Policlinico San Matteo; Pavia

Institute, Cary, NC). The sponsor will also provide assistance with study management: it will provide resources for study development on sites, data monitoring, data entry and data analysis.

The Steering Committee is solely responsible for the study design and conduct, the drafting and editing of the paper and its final content.

Discussion

Despite major efforts to identify responders to CRT among HF patients,[4,28] non-responder rates have persisted at around 30% since its introduction. Thus, the potential to increase CRT performance with different optimization methods deserves further investigation. The use of weekly automated optimization of AV and VV based on SonR has not been previously evaluated in a long-term, large-scale study. The CLEAR pilot study on SonR in CRT-P patients showed promising results in improving the rate of responders to CRT based on a composite endpoint.[15] If those results can be confirmed in a larger population of CRT-D patients in RESPOND CRT, this will provide the first solid evidence for the potential to improve responder rates with an automatic optimization system.

The main rationale for frequent optimization of AV and VV delays is the dynamic nature of hemodynamic performance. In particular, CRT tends to influence the optimal AV delay in HF patients.[29,30] However, although several reports have indicated that AV and VV delay optimization leads to acute hemodynamic improvements,[8-11,31-33] it has been difficult to demonstrate clinical benefits in large-scale randomized outcomes trials. The scientific community was reminded recently of this difficulty with the presentation of the neutral results from three large prospective trials, SMART-AV,[5] FREEDOM,[7] and the aCRT trials.[34]

SMART-AV reported no benefits from AV optimization based on sensed and paced AV delays derived from the intracardiac electrogram and modified based on the QRS duration on the surface electrocardiogram. The primary end point was improvement in LV end-systolic volume at 6 months. However, it has been suggested that the definition of response was too strict and that the study may have been underpowered.[35] The FREEDOM study also assessed a CRT optimization algorithm derived from intracardiac electrogram and showed inconclusive long-term results. The accuracy of the QuickOpt algorithm has been suggested as a possible reason for the lack of benefits.[36]

The most recent trial aCRT studied an algorithm that provides RV-synchronized LV pacing in presence of intact AV conduction and biventricular pacing otherwise, adjusting AV and VV delays on the basis of periodic, automatic evaluation of intrinsic conduction intervals. On the primary end point, clinical composite score at 6 months follow-up, the trial showed non-inferiority of the aCRT algorithm compared with biventricular pacing with comprehensive echocardiography optimization. However, a pre-specified test for superiority failed to demonstrate clinical benefits with the optimization algorithm over those from conventional optimization.[34]

Finally, in the SMART-AV, FREEDOM, and aCRT studies, these electrical-based algorithms do not adjust based on measurements specific to exercise conditions, whereas it has been proposed that the most efficacious method would be to apply optimization during exercise.[37] The SonR optimization will be performed automatically both at rest and during exercise with a hemodynamic sensor.

Results from a sub-analysis from CLEAR[38] showed that, compared with no optimization, frequent optimization *per se* is associated with clinically meaningful improvements. In actual clinical practice, echocardiographic optimization is very rarely performed, because of the time and resources involved.[39-41] The SonR system may or may not provide superior optimization to that available with echocardiographic methods when performed with the same frequency. However, while the protocol allows for repeat echocardiographic optimization at the discretion of the treating physicians, the SonR group in RESPOND CRT will be optimized automatically on a weekly basis, which is highly unlikely to be the case in the control group.

The question of what constitutes 'response' to CRT remains a subject of controversy.[42,43] The 26 most cited publications on predicting response use 17 different criteria to define the term.[44] It is clear that no single end point provides a reliable, sensitive, and reproducible measure of clinical response to treatment.[45] In RESPOND CRT the definition of response is based on improvements in NYHA functional class or quality of life and responders must remain free of HF-related events. The decision algorithm used to evaluate response to treatment follows

that developed by Packer[23] which has been used in a large number of trials evaluating the efficacy of CRT.[2,4,7,33,46,47] As noted by Packer, the clinical composite score does not attempt to combine efficacy measures of unequal weight (e.g., death and quality of life) into a single score. A patient with improved symptoms at month 12 will not be classified as a responder if the patient has experienced HF-related events during follow-up.

If RESPOND CRT shows that automatic device-optimization of CRT leads to a higher clinical response rate in a randomized population, this will reinforce the need for better and individualized delivery of resynchronization therapy.

Acknowledgements

Conflicts of interest

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References

1. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873-80.
2. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845-53.
3. Cleland JGF, Daubert J-C, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-49.
4. Chung ES, Leon AR, Tavazzi L, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. Circulation 2008;117:2608-16.
5. Ellenbogen KA, Gold MR, Meyer TE, et al. Primary results from the SmartDelay determined AV optimization: a comparison to other AV delay methods used in cardiac resynchronization therapy (SMART-AV) trial: a randomized trial comparing empirical, echocardiography-guided, and algorithmic atrioventricular delay programming in cardiac resynchronization therapy. Circulation 2010;122:2660-8.
6. Krum H, Lemke B, Birnie D, et al. A novel algorithm for individualized cardiac resynchronization therapy: rationale and design of the adaptive cardiac resynchronization therapy trial. Am Heart J 2012;163:747e1-52e1.
7. Abraham WT, Gras D, Yu CM, et al. Results from FREEDOM trial—assess the safety and efficacy of frequent optimization of cardiac resynchronization therapy. HRS 2010 Late-Breaking Clinical Trials. 2010.
8. Sheppard RC, Ren JF, Ross J, et al. Doppler echocardiographic assessment of the hemodynamic benefits of rate adaptive AV delay during exercise in paced patients with complete heart block. Pacing Clin Electrophysiol 1993;16:2157-67.
9. Auricchio A, Ding J, Spinelli JC, et al. Cardiac resynchronization therapy restores optimal atrioventricular mechanical timing in heart failure patients with ventricular conduction delay. J Am Coll Cardiol 2002;39:1163-9.
10. Inoue N, Ishikawa T, Sumita S, et al. Long-term follow-up of atrioventricular delay optimization in patients with biventricular pacing. Circ J 2005;69:201-4.
11. Gold MR, Niazi I, Giudici M, et al. A prospective comparison of AV delay programming methods for hemodynamic optimization during cardiac resynchronization therapy. J Cardiovasc Electrophysiol 2007;18:490-6.
12. Bordachar P, Labrousse L, Ploux S, et al. Validation of a new noninvasive device for the monitoring of peak endocardial acceleration in pigs: implications for optimization of pacing site and configuration. J Cardiovasc Electrophysiol 2008;19:725-9.
13. Delnoy PP, Marcelli E, Oudeluttikhuis H, et al. Validation of a peak endocardial acceleration-based algorithm to optimize cardiac resynchronization: early clinical results. Europace 2008;10:801-8.
14. Dupuis J-M, Kobeissi A, Vitali L, et al. Programming optimal atrioventricular delay in dual chamber pacing using peak endocardial acceleration: comparison with a standard echocardiographic procedure. Pacing Clin Electrophysiol 2003;26:210-3.
15. Ritter P, Delnoy PP, Padeletti L, et al. A randomized pilot study of optimization of cardiac resynchronization therapy in sinus rhythm patients using a peak endocardial acceleration sensor vs. standard methods. Europace 2012;14:1324-33.
16. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) Developed in Collaboration With the American Association for Thoracic Surgery and Society of Thoracic Surgeons. Journal of the American College of Cardiology 2008;51:e1-62.
17. Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 2009;53:e1-90.
18. McMurray JJV, Adamopoulos S, Anker SD, et al. 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. European Heart Journal 2012;33:1787-847.
19. Stevenson WG, Hernandez AF, Carson PE, et al. Indications for cardiac resynchronization therapy: 2011 update from the Heart Failure Society of America Guideline Committee. J Card Fail 2012;18:94-106.
20. Bordachar P, Garrigue S, Reuter S, et al. Hemodynamic assessment of right, left, and biventricular pacing by peak endocardial acceleration and echocardiography in patients with end-stage heart failure. Pacing Clin Electrophysiol 2000;23:1726-30.
21. Leung SK, Lau CP, Lam CT, et al. Automatic optimization of resting and exercise atrioventricular interval using a peak endocardial acceleration sensor: validation with Doppler echocardiography and direct cardiac output measurements. Pacing Clin Electrophysiol 2000;23:1762-6.

22. Padeletti L, Porciani MC, Ritter P, et al. Atrioventricular interval optimization in the right atrial appendage and interatrial septum pacing: a comparison between echo and peak endocardial acceleration measurements. Pacing Clin Electrophysiol 2000;23: 1618-22.
23. Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. J Card Fail 2001;7:176-82.
24. Green CP, Porter CB, Bresnahan DR, et al. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35: 1245-55.
25. Eurich DT, Johnson JA, Reid KJ, et al. Assessing responsiveness of generic and specific health related quality of life measures in heart failure. Health Qual Life Outcomes 2006;4:89.
26. Boehmer JP, Carlson MD, De Marco T, et al. Adjudication of mortality events in a heart failure-arrhythmia trial by a multiparameter descriptive method: comparison with methods used in heart failure trials and methods used in arrhythmia trials. J Interv Card Electrophysiol 2008;23:101-10.
27. Hernan MA, Hernandez-Diaz S. Beyond the intention-to-treat in comparative effectiveness research. Clinical Trials 2011;9:48-55.
28. Richardson M, Freemantle N, Calvert MJ, et al. Predictors and treatment response with cardiac resynchronization therapy in patients with heart failure characterized by dyssynchrony: a pre-defined analysis from the CARE-HF trial. European Heart Journal 2007;28:1827-34.
29. O'Donnell D, Nadurata V, Hamer A, et al. Long-term variations in optimal programming of cardiac resynchronization therapy devices. Pacing Clin Electrophysiol 2005;28(Suppl 1):S24-6.
30. Valzania C, Biffi M, Martignani C, et al. Cardiac resynchronization therapy: variations in echo-guided optimized atrioventricular and interventricular delays during follow-up. Echocardiography 2007; 24:933-9.
31. van Gelder BM, Bracke FA, Meijer A, et al. Effect of optimizing the VV interval on left ventricular contractility in cardiac resynchronization therapy. Am J Cardiol 2004;93:1500-3.
32. Sogaard P, Egeblad H, Pedersen AK, et al. Sequential versus simultaneous biventricular resynchronization for severe heart failure: evaluation by tissue Doppler imaging. Circulation 2002;106: 2078-84.
33. Bordachar P, Lafitte S, Reuter S, et al. Echocardiographic parameters of ventricular dyssynchrony validation in patients with heart failure using sequential biventricular pacing. J Am Coll Cardiol 2004;44: 2157-65.
34. Martin DO, Lemke B, Birnie D, et al. Investigation of a novel algorithm for synchronized left-ventricular pacing and ambulatory optimization of cardiac resynchronization therapy: results of the adaptive CRT trial. Heart Rhythm Published Online First: July 2012 2012, http: //dx.doi.org/10.1016/j.hrthm.2012.07.009.
35. Shanmugam N, Borgulya G, Anderson L. Letter by Shanmugam et al Regarding Article, 'Primary Results From the SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy (SMART-AV) Trial: A Randomized Trial Comparing Empirical, Echocardiography-Guided, and Algorithmic Atrioventricular Delay Programming in Cardiac Resynchronization Therapy'. Circulation 2011;124:e190.
36. Houthuizen P, Bracke F, Gelder BM. Atrioventricular and interventricular delay optimization in cardiac resynchronization therapy: physiological principles and overview of available methods. Heart Failure Reviews 2010;16:263-76.
37. Sun JP, Lee AP-W, Grimm RA, et al. Optimisation of atrioventricular delay during exercise improves cardiac output in patients stabilised with cardiac resynchronisation therapy. Heart 2012;98:54-9.
38. Gras D, Gupta MS, Boulogne E, et al. Optimization of AV and VV delays in the real-world CRT patient population: an international survey on current clinical practice. Pacing Clin Electrophysiol 2009; 32(Suppl 1):S236-9.
39. St John Sutton MG, Plappert T, Abraham WT, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation 2003;107:1985-90.
40. Bax JJ, Abraham T, Barold SS, et al. Cardiac resynchronization therapy: Part 2–issues during and after device implantation and unresolved questions. J Am Coll Cardiol 2005;46:2168-82.
41. Delnoy PP, Ritter P, Naegele H, et al. 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. Europace 2013; 15:1174-81.
42. Ghio S, Freemantle N, Scelsi L, et al. Long-term left ventricular reverse remodelling with cardiac resynchronization therapy: results from the CARE-HF trial. Eur J Heart Fail 2009;11:480-8.
43. Cleland JGF, Daubert J-C, Erdmann E, et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. Eur Heart J 2006;27:1928-32.
44. Foley PWX, Leyva F, Frenneaux MP. What is treatment success in cardiac resynchronization therapy? Europace 2009;11(Suppl 5): v58-65.
45. Fornwalt BK, Sprague WW, BeDell P, et al. Agreement is poor among current criteria used to define response to cardiac resynchronization therapy. Circulation 2010;121:1985-91.
46. Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA 2003; 289:2685-94.
47. Linde C, Abraham WT, Gold MR, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008;52:1834-43.