Predicting outcome in severe heart failure. Who will benefit from device therapy (CRT)?

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This editorial refers to ‘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’ by M. Richardson et al., on page 1827

Dyssynchronous ventricular contraction in severe heart failure contributes to low cardiac output, worsening symptoms, and poor prognosis. Recognition of the effect of dyssynchrony in heart failure, and the possibility of manipulating the sequence of electrical cardiac activation to improve the efficiency of mechanical events, led Cazeau et al. to attempt four-chamber pacing in 1994.¹ This early system could stimulate both atria and both ventricles extrinsically, and could dictate the temporal relationship between atrial systole and ventricular systole, and the ventriculo-ventricular relationship. Modern cardiac resynchronization therapy (CRT), involving pacing of the right and left ventricles, with right atrial pacing to optimize atrio-ventricular delay, has evolved rapidly from this beginning.

Left bundle branch block (LBBB) on the surface electrocardiogram (ECG) has been considered a marker of mechanical dyssynchrony as it represents a delay in conduction of depolarization to the left ventricle, with the greatest delay usually being in the lateral free wall. The presence of LBBB, seen in about one-third of patients with heart failure,² is associated with a poorer outcome than when LBBB is not present.³,⁴ Furthermore, the wider the QRS complex in LBBB, the worse the prognosis. The presence of a broad QRS complex with LBBB morphology has been an important entry criterion to most of the trials of CRT, which has now been evaluated in randomized clinical trials involving >4000 patients.⁵-⁹ The European Society of Cardiology has now incorporated recommendations for use in clinical practice guidelines.¹⁰ The patients for whom CRT is recommended in these guidelines are those who represent a similar group to those involved in the randomized controlled trials, where in most cases the objective evidence of dyssynchrony was a broad QRS complex on the 12-lead ECG.

The pharmacological and device-based therapies recommended in clinical practice guidelines for management of patients with chronic heart failure are soundly based on reliable evidence from large-scale randomized trials. Not all patients, however, benefit equally from any given form of therapy, and in the CRT trials 20–30% of patients have not shown significant improvement.¹¹,¹² This lack of benefit is even more important for device-based therapies than for pharmacological therapies because of the costs involved—the initial cost of the hardware, the resource cost involved in the implantation procedure, and the on-going cost of monitoring and programming the device. Despite operator experience and technological improvements, transvenous left ventricular lead implantation can still be challenging and time consuming, although implantation success rates are generally >90%. In addition, device therapy for heart failure carries all the usual risks of conventional pacemaker therapy, as well as some specific complications associated with left ventricular lead placement, such as coronary sinus dissection. When the costs and risks of device therapy are considered, it would clearly be very helpful to separate those patients unlikely to benefit from CRT from those who are likely to benefit, before implanting a device.

Non-response to CRT may be multifactorial, and include such factors as presence of extensive scar from prior myocardial infarction, inappropriate LV lead position (failure to find a suitable pacing site on the lateral or posterolateral wall), and suboptimal device programming post-implantation. Importantly, however, there may not be significant mechanical dyssynchrony. The presence of LBBB on the ECG is actually a relatively crude assessment of dyssynchrony, and it is well recognized that patients may not have significant mechanical dyssynchrony despite the presence of LBBB.

Recently, trials have reported that echocardiographic measures of both acute haemodynamic response and longer-term improvements in left ventricular remodelling predict long-term favourable clinical outcome with CRT. However, even if acute haemodynamic assessment could accurately identify responders and non-responders to CRT in the electrophysiology laboratory, ideally non-responders to this therapy should be identified before the patient...
even reaches the laboratory in order to avoid risk to the patient of implantation and unnecessary use of scarce subspecialist resources.

The report by Richardson et al. from the CARE-HF trial suggests that this aim may be achievable using simple, non-invasive clinical and echocardiographic assessments of mechanical dyssynchrony before device implantation. In the CARE-HF trial, the primary end-point of all-cause mortality or any unplanned hospitalization for any major cardiovascular event was reduced from 55% in the medically treated group to 39% in the CRT group after an average follow-up of 29 months. The current study reports the relationship between specific prospectively defined clinical, neurohormonal, and echocardiographic baseline variables and overall outcome and response to CRT in the trial. Ischaemic aetiology of heart failure, more severe mitral regurgitation, and higher N-terminal pro-brain natriuretic peptide (NT-proBNP) were independent predictors of death or unplanned cardiovascular hospitalization irrespective of CRT.

Only echocardiographically determined interventricular mechanical delay (IVMD) and systolic blood pressure (SBP) predicted response to CRT, with longer IVMD and lower SBP predicting response to therapy. IVMD was calculated as the time difference between the onset of forward flow in the left ventricular outflow tract (onset QRS to onset aortic flow) and the right ventricular outflow tract (onset QRS to onset pulmonary flow) using Doppler echocardiography. This represents a simplification of the usual tripartite description of dyssynchrony: AV dyssynchrony, interventricular dyssynchrony, and intraventricular (LV) dyssynchrony, and is usually easy to measure in the four-chamber view.

The risk modelling utilized by Richardson et al. demonstrates the absolute risk of events with and without CRT across patients with higher and lower values for IVMD and SBP. The benefits of CRT exist across the range of patients, but absolute risk of adverse events was higher and the magnitude of the treatment effect with CRT greater in those with worse IVMD and lower SBP. These data utilized Cox proportional hazards modelling of the relationship between the baseline parameters and response to therapy. When interpreting any model, it is essential that the findings be considered in the context not only of the patient group, but also the predictors that are used and other aspects of model construction. Individual hazard ratios and their significance must be interpreted in keeping with the unit of measurement and any transformation that has taken place. The current study creates hazard ratios for SBP per mmHg, IVMD per ms, and NT-proBNP per log, pg/mL. Leaving measurements in their natural continuous form maximizes the model fit for a specific group of predictors, but minimizes the clinical interpretation of the role of individual predictors. Furthermore, removing predictors from the model that are not independently significant helps simplicity; however, this can increase the significance of the predictors that remain.

Any modelling process is prone to creating a model that works well for the group of individuals used to create it, but does not hold when applied to what seems to be a similar group of different people. The authors have used a number of techniques to address this issue in their statistical approach; however, they rightly point out that the model’s validity needs to be tested on a new sample of people, external to the group used to construct the model. It should be noted that the significance of the interaction between CRT and SBP did not hold when creating the model after multiple imputation (to assess the impact of missing data), suggesting that slight variations in the measurements will indeed change the composition of the model. Thus, while it is useful to consider the change in absolute risk that may occur by modification of individual predictors, these figures should be considered as a guide and cannot be directly extrapolated to individual patients.

These data may help to define further specific areas of research regarding criteria for selection of patients for future trials of CRT, but at present the recommendations for the routine clinical use of CRT should remain based on the criteria for inclusion in trials such as CARE-HF. With this in mind, it is important to recognize that for patients to be considered eligible for the CARE-HF trial with QRS duration of 120–149 ms, two of three additional echocardiographic criteria of dyssynchrony were required before enrolment. It would appear reasonable to apply similar recommendations for patient selection for CRT in clinical practice, which would require some refinement of the recommendations as currently written in the ESC heart failure guidelines. The increased use of device-based therapies as part of the management of patients with severe heart failure requires a substantial increase in resource allocation and is already providing a major challenge to many health care services. Predicting which patients will optimally respond to CRT will allow targeted delivery of this therapy to appropriate patients, and the data provided from the CARE-HF trial in the paper by Richardson et al. go some way towards this end. Future trials and analyses will help to refine patient selection for this valuable therapy.

Conflict of interest: none declared.

References


Clinical vignette

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Unruptured left main coronary artery aneurysm presented with acute cerebral infarction

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A 72-year-old male with a history of chest pain presented to the ER with left-side motor weakness. Brain MRI revealed acute infarction of right anterior cerebral artery territory, and echocardiography showed normal ejection fraction and no visible thrombus. However, coronary angiography revealed left main coronary artery saccular aneurysm (8 × 10 mm²) originating at the distal segment of the left main between LAD and LCX. IVUS examination showed similar size and appearance of aneurysm at the left main bifurcation site without thrombus formation. For more precise anatomical details, we used a 16-channel MDCT with ECG gating, which showed the saccular aneurysm of the left main but not involving the LAD or LCX. The patient was conservatively managed with dual antiplatelets, including aspirin 100 mg and clopidogrel 75 mg, and with anticoagulation. At 6 months’ follow-up, coronary angiography showed no significant interval change in size and shape of the left main aneurysm without any complication or clinical event.

Left main aneurysm is rare and occur in ~0.1% of the population. Common causes of coronary aneurysm are coronary atherosclerosis, ectasia, Kawasaki disease, and arteritis. Although the management of coronary artery aneurysm is not well established yet owing to the rarity and unpredictable natural history, these dilated sections of coronary artery are not benign entities because they are subject to spasm, thrombosis, and spontaneous dissection and can be a potential cause of myocardial infarction. In the selective case of left main coronary artery aneurysm, adequate medical management including antiplatelets and/or anticoagulation may confer an optimal management without surgery with a careful periodic follow-up.

Panel A. Initial coronary angiography showed left main saccular coronary artery aneurysm.

Panel B. Intravascular ultrasound at LAD ostium (os) showed a huge aneurysm in the 5-to-9 o’clock direction in the left main bifurcation site at the index procedure.

Panel C. Three-dimensional coronary MDCT showed left main coronary artery aneurysm at the left main bifurcation site.

Panel D. Six month follow-up coronary angiography showed unruptured left main coronary artery aneurysm, and the size was not different compared with the index.

See online Supplementary material for a colour version of this figure available at European Heart Journal online.