Increasing knowledge and changing views in cardiac resynchronization therapy

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The introduction of cardiac resynchronization therapy (CRT) has changed the modern treatment of heart failure [1–4] and become a fruitful new area of research, especially imaging research [5, 6] and the development of “smarter” pacemaker technology [7–9].

One of the most important recent changes in perspective is the recognition that CRT may be an effective treatment for patients with substantial ventricular dysfunction whether or not their symptoms are severe. Several subanalyses of the first RCT's hinted that CRT was effective even in patients with mild symptoms [10–12]. Now, we have convincing evidence based on the REVERSE [13, 14], MADIT-CRT trials [15], and most recently the RAFT trial [16]. These trials show not only that CRT can retard or reverse the development of symptoms but also modify the progression of the underlying cardiac disease [14]. Indeed, implantation of devices in patients with substantial left ventricular dysfunction but only mild symptoms may have a greater overall impact on patients' well-being and longevity [1, 2, 12–14]. Recently updated European and North American guidelines have widened the recommendation for CRT to patients with mild symptoms [17, 18]. However, the story is not yet complete. Registries suggest that about half of patients who die from progressive heart failure within 2 years after ICD implantation have a QRS duration of less than 120 ms at the time of implant [19]. Observational studies also reported that younger patients with less

advanced heart failure (including less enlarged ventricular volumes and narrower QRS) may gain more benefit from CRT in the long run than more advanced cases [20–26]. These findings may shift attention onto the importance of the timing of CRT implantation in early-stage heart failure.

Less progress has been made regarding the prediction of which patients benefit and by how much and how to optimize CRT. The use of the terms “responder” and “non-responder” oversimplifies the situation and is unhelpful as a concept or in clinical practice and in any case what is usually reported is outcome rather than response. The concept of response is heavily confused with the concept of outcome but they are very different things [27]. The best outcomes with CRT occur in patients who did not need CRT and had no response—in other words patients who were too well ever to benefit! Patients who are very sick may respond well to CRT with improved symptoms and survival but, nonetheless, are at higher risk of a poor outcome over the subsequent year [27]. Outcomes to CRT are variable amongst individuals, spanning a spectrum from so-called super-responders to patients who appear to have no benefit in terms of cardiac function, symptoms or survival. Outcome is highly dependent on the substrate being treated (i.e. the patients and their heart), and only part of any outcome will be anything to do with the intervention. Response, as well as outcome, depends on multiple factors including the patients' age, sex, aetiology and stage of heart failure, other cardiac, and non-cardiac comorbidities, success of the CRT implantation procedure and programming, and the quality of general management. Due to the fluctuating importance of these contributing factors, the relation between response to CRT and heart failure outcome is also heterogeneous. In addition, the suggested response markers show substantial disagreement [28].

Randomized controlled trials are the only reliable way of determining whether outcome and response to therapy

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are concordant or discordant. Observational studies, although superficially attractive, can only really assess outcome. Propensity-matched cohorts are a second-best solution compared with the randomized trial. Markers that have been suggested for selecting patients for CRT may identify patients with a better outcome but may do so by denying sick people who might have had a substantial response access to treatment and promoting implantation in patients with good outcomes but who had little or no response to treatment.

Heart failure tends to progress, and its characteristics will change over the course of the disease; QRS progressively increases, whilst symptoms deteriorate [19, 29]. Application of a rigid selection system leaves little opportunity for borderline cases [30]. By the time, the subject is eligible according to guidelines the optimal time for intervention may have been missed. So, for instance, a patient with LVSD who requires an ICD may not fulfil criteria for a CRT on the day of implant but may do so within 2–3 years. This patient should take the small additional risk of having a CRT-D device implanted, that may be programmed to deliver CRT or not, or run the risk of requiring a second procedure in a few years time [31]. Recently, data from large cohort studies in Western Europe and North America report significant “off-label” use of CRT [32–34] (Table 1). These off-label procedures may represent borderline cases where the experts made an intelligent choice to implant a device informed by trial evidence and the guidelines that they know are likely to change in the future.

Currently, the response to CRT cannot be reliably predicted due, in part, to incomplete understanding about how CRT works [35]. It seems certain that mechanical ventricular dyssynchrony is not the only target for CRT and, indeed, it may only be a minor factor for most patients [5, 36, 37]. Further developments in imaging technology may provide additional measurements—based on displacement imaging (Speckle Tracking) [38–41], viability and scar assessment [22, 23], exercise-induced left ventricular dyssynchrony and assessment for dynamic mitral regurgitation [42, 43]—that help improve current selection methodology. However, the whole exercise of trying to predict

response may be futile and a flawed concept. Perhaps, the clinician with bed-side clinical skills and an ECG is best able to judge who should have CRT [17, 18, 44–51].

Rather than fretting about whether a patient who is indicated for a CRT will respond or not, more effort should be made to ensure that each patient has optimal management after the procedure [52–54]. However, the clinical value of trying to programme devices optimally is unclear and well-designed trials have been unable to show the benefit of individually tailored programming versus standard factory settings. It is possible that for most patients, the factory settings cannot be improved on but this does not preclude the possibility of benefit in some individuals that clinical trials, which investigate the average effect in a population or subpopulation, may not be able to detect. Device-integrated optimization methods provide alternatives to ones based on echocardiography, which are time-consuming and require considerable expertise. However, recently published RCTs using intracardiac ECG-based optimization methods have failed to show a benefit for regular optimization compared with routine clinical practice (using fixed AV delay at 120 ms) [55, 56]. In contrast, an implanted contractility sensor-based optimization method might improve the response to CRT [57]. The introduction of multipolar left ventricular leads will offer the possibility of choosing different left ventricular pacing sites or multisite pacing. For the moment, it appears that the conventional atrio- and interventricular delay settings are sufficient for most patients, but CRT optimization could be important for those with a suboptimal response to CRT.

Remote monitoring provides a new dimension to the management of heart failure. New technologies monitor not only device function but also patient physiology including heart rate and rhythm, heart rate variability, activity and thoracic bioimpedance that may help improve the management of heart failure [58–65]. Monitoring of the device function has already been shown to have benefits in terms of early warning of device failure. Whether and how physiological information can be used to improve patients' outcomes is the subject of intensive research.

Many other issues remain for future research. Patients with heart failure commonly have atrial fibrillation. If the

Table 1 Off-licence CRT implantation

Database	Total number	LVEF >35%	QRS <120 ms	RBBB	NYHA I–II ^d
GWTC programme ^a	811 ^c	9.6%	NA	NA	NA
European CRT survey ^b	2,438	17%	9%	6%	2 + 20%
NCDR ^c	45,392	1.3%	12%	NA	13.1%

NA, not available; LVEF, left ventricular ejection fraction; RBBB, right bundle branch block; NYHA I–II, New York Heart Association class I–II

^a American Heart Association's Get With The Guidelines-Heart Failure programme, ^b the European Cardiac Resynchronization Therapy Survey, ^c the National Cardiovascular Data Registry Implantable Cardiac-Defibrillator Registry (US), ^d Before updating the guidelines in 2010, ^c only new CRT implantation, overall study population included 33,898 heart failure patients

main mechanism of benefit from CRT is delivered by atrioventricular resynchronization, this group of patients would not be expected to benefit from CRT. A recent meta-analysis of available evidence reported a similar improvement in ejection fraction but less symptomatic benefit for patients with atrial fibrillation compared with subjects in sinus rhythm after CRT [66]. The RAFT trial suggested that, compared to ICD, CRT-D did not reduce morbidity or mortality in patients with atrial fibrillation [16]. Bradyarrhythmias may be an important cause of sudden death in patients with heart failure [67], and this may be one of the reasons why CRT, even without a defibrillator function, can reduce the risk of sudden death [68, 69]. Whether CRT-D is superior to CRT alone is uncertain. Better prediction of sudden death due to tachyarrhythmias might help target patients who need CRT-D rather than using it as a default option. CRT implantation technology is also improving that will enable better pacing site selection [70–72]. Implantation-related complications remain a problem [14, 73, 74] that future developments in lead technology and wireless electrodes may help overcome [75].

The present supplement offers a selection of review articles covering a broad range of subjects from bench to bedside in CRT. Topics have been selected either because there have been rapid advances or because there is a great deal of controversy and confusion surrounding them. Finally, we would like to express our sincere thanks to the dedicated authors who have contributed to this supplement and wish you enjoyable reading.

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