



Current practice of cardiac resynchronization therapy (CRT) in the real world: insights from the European CRT survey

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This commentary refers to ‘The European cardiac resynchronization therapy survey’, by K. Dickstein et al. doi:10.1093/eurheartj/ehp359

Large randomized controlled trials have demonstrated that cardiac resynchronization therapy (CRT) improves morbidity and mortality in patients with moderate to severe heart failure [New York Heart Association (NYHA) functional class III–IV], reduced left ventricular ejection fraction (LVEF $\leq 35\%$), and a broad QRS complex > 120 ms on optimal medical therapy.^{1–3} As a result, the impressive survival benefit as well as the improvement in heart failure symptoms and quality of life observed in these trials have spurred interest in extending resynchronization therapy to a larger number of heart failure patients. Indeed, several lines of evidence indicate that currently employed guidelines (mainly based on the selection criteria used in the aforementioned pivotal trials) may not be perfect at identifying patients most likely to benefit from CRT, with a significant proportion of patients being ‘non-responders’ based on clinical outcomes or echocardiographic remodelling.⁴ Conversely, results from various small studies imply that certain patient populations may benefit from CRT despite the fact that they do not fulfil the criteria of current CRT guidelines.^{5–7} In the absence of randomized trials, data from large-scale ‘real world’ surveys provide a unique opportunity to study both the current practice regarding the employment of a novel type of therapy as well as its efficacy and safety, including ‘off-label’ indications.

The European CRT Survey, a joint initiative by the Heart Failure Association (HFA) and the European Heart Rhythm Association (EHRA) of the European Society of Cardiology (ESC), reports on the current European practice in the use of CRT.⁸ In order to provide this information, 2438 patients from 141 centres in 13 European countries who underwent successful implantation of a CRT device were followed from November 2008 until June 2009. In addition to providing a detailed description of patient demographics, selection criteria, and periprocedural outcomes, the survey’s data were further dissected according to the implanted device and age

of the recipients. The authors found that patients receiving CRT-P [i.e. a biventricular pacing device without implantable cardioverter–defibrillator (ICD) function] were older, less likely to present with co-morbidities including ischaemic heart disease or diabetes mellitus, and had better left ventricular function as compared with those receiving a CRT-D (i.e. CRT + ICD) device. Furthermore, the data demonstrate that patients older than 75 years more frequently had atrial fibrillation, a longer QRS duration, or concomitant co-morbidities (as reflected by higher serum creatinine and B-type natriuretic peptide (BNP) levels) as compared with those younger than 75 years. Probably as a result of the latter (and possibly for socioeconomic reasons), older patients were more likely to receive CRT-P devices.

While most of these associations do not necessarily come as a surprise and are in good agreement with previous trials and clinical experience, the survey does also show some interesting aspects of cardiac resynchronization practice across Europe which deserve further attention. Most interestingly, a substantial number of patients received CRT devices for ‘off-label’ indications, including 9% of patients with a narrow QRS complex (< 120 ms) as well as 10% with a QRS duration between 120 and 129 ms. Currently available data regarding the benefit of CRT in heart failure patients with a narrow QRS complex are conflicting. Using echocardiography-based dyssynchrony criteria, several small single-centre studies were able to identify patients with a narrow QRS who responded favourably to CRT.^{5,6,9} In contrast, the results of two recent randomized pilot studies (RethinQ¹⁰ and ESTEEM-CRT) remained elusive due to several inherent limitations.¹¹ Eventually, the answer to whether CRT improves morbidity and mortality in this particular patient group can only be provided by an adequately powered, endpoint-driven randomized clinical trial, which is currently underway (Echocardiography Guided Cardiac Resynchronization Therapy—EchoCRT; NCT00683696, www.clinicaltrials.gov).¹¹ Before the results of this trial become available, it will be of interest to observe the direction in which the expected 1 year data from the survey by Dickstein et al.⁸ will be pointing. Unfortunately, only qualitative assessment instead of quantitative (echocardiographic)

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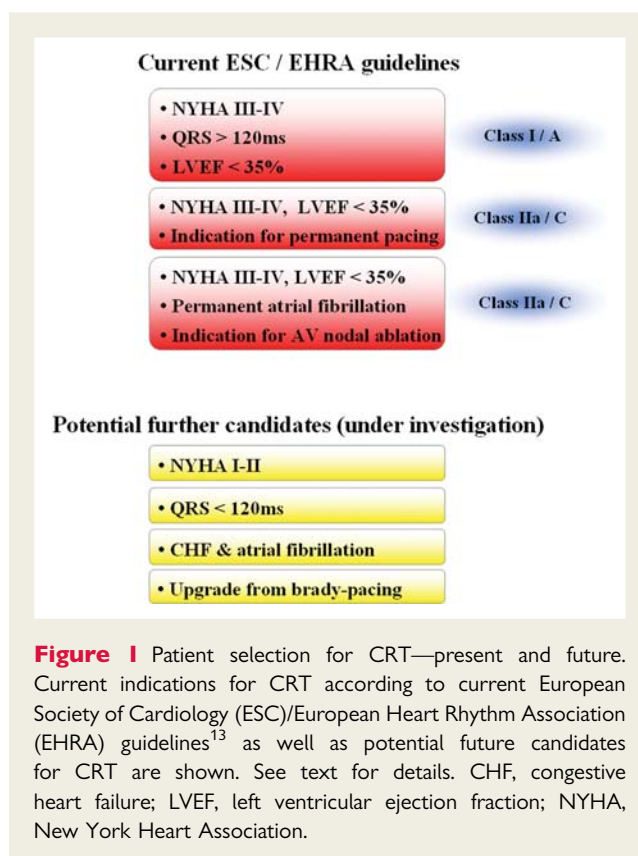
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parameters of left ventricular dyssynchrony were registered for these patients, which will make further comprehensive analysis of this subgroup's outcome difficult.

Previous small trials have, moreover, indicated that patients with atrial fibrillation may profit from CRT,⁷ but evidence from large trials is lacking as this particular patient group was generally excluded. Controversy currently exists, however, regarding the necessity of AV nodal ablation, of ablation of atrial fibrillation itself, concomitant rate- or rhythm-controlling medication, and optimal device programming. In the survey by Dickstein *et al.*,⁸ 23% of patients implanted were in atrial fibrillation. In view of the large proportion of heart failure patients with atrial fibrillation in clinical practice and the fact that data from large trials are scarce, further information on these parameters would have been desirable for this interesting subgroup. Nevertheless, outcome data after 1 year (possibly including this interesting information) will demonstrate to what extent these patients benefit in terms of clinical and echocardiographic improvement.

Evidence is emerging that patients with mildly symptomatic heart failure (i.e. NYHA class <III) may also benefit from CRT. Indeed, data from the REVERSE trial,¹² especially after 24 months of CRT (presented at the Annual meeting of the American College of Cardiology 2009 in Orlando) as well as preliminary results from MADIT-CRT (communicated by Boston Scientific in June 2009 and scheduled to be presented at the ESC 2009), indicate that CRT improves morbidity and mortality even in patients with NYHA class I–II heart failure. In the survey, 2 and 20% of the patients enrolled were indeed in NYHA functional class I and II, respectively. So far, however, the National Institute for Health and Clinical Excellence (NICE) has indicated that such patients may only be candidates for CRT if clinical deterioration has recently occurred. While in the overall survey population 57% of patients are reported to have been hospitalized for heart failure during the last year, no data are given regarding a recent deterioration in the subgroup of mildly symptomatic patients. Hence, a substantial proportion of these patients may have undergone CRT implantation on an off-label basis. In light of the above-mentioned recent study results, this intuitive expansion of an effective therapy above and beyond current guidelines seems to have been a very reasonable choice. Follow-up data of the survey will show whether a similar response rate will also be observed in this 'real world' population.

In addition to patient demographics and selection criteria, the authors also present periprocedural outcome data after implantation of CRT devices. In terms of efficacy, the majority of patients improved clinically, as demonstrated by a lower NYHA class after CRT implantation. Electrocardiographically, the average QRS duration decreased significantly with biventricular pacing; no acute changes in echocardiographic parameters are reported. From a safety point of view, the reported perioperative complication rate was low, which may reflect the implanting physicians' experience and skill over time. It may also be due to the fact, however, that only successful implantations were allowed to be enrolled in the survey; indeed, the numbers of CRT-eligible patients who failed or did not undergo implantation are not reported. The lack of stringent registration and subsequent analysis of all consecutively screened patients in whom CRT implantation was attempted



unfortunately reduces the survey's validity in assessing the safety of CRT implantation in the survey population.

All of this notwithstanding, the survey by Dickstein *et al.*⁸ gives a nice and robust overview of the current practice regarding CRT across a wide range of European centres. Planned assessment of survey patients after 1 year, including data on morbidity and mortality as well as echocardiographic remodelling and arrhythmias, will be eagerly awaited to evaluate the efficacy of CRT in this real world population. In view of the substantial number of patients treated with CRT for off-label indications, this will also be of interest from a socioeconomic point of view. From a scientific perspective, further information on less well studied subpopulations (including patients with atrial fibrillation, mildly symptomatic subjects, and patients with a narrow QRS complex, see Figure 1) as well as more in-depth information on technical subtleties such as left ventricular lead location, device programming, and optimization would be desirable. Importantly, consecutive patient enrolment and registration, as well as critical evaluation of unsuccessful CRT implantation will be crucial in order to assess the safety of CRT in the study population.

Conflicts of interest: none declared.

References

1. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–1549.
2. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–2150.

3. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**:1845–1853.
4. Kashani A, Barold SS. Significance of QRS complex duration in patients with heart failure. *J Am Coll Cardiol* 2005;**46**:2183–2192.
5. Yu CM, Chan YS, Zhang Q, Yip GW, Chan CK, Kum LC, Wu L, Lee AP, Lam YY, Fung JW. Benefits of cardiac resynchronization therapy for heart failure patients with narrow QRS complexes and coexisting systolic asynchrony by echocardiography. *J Am Coll Cardiol* 2006;**48**:2251–2257.
6. Jeevanantham V, Zareba W, Navaneethan S, Fitzgerald D, Yu CM, Achilli A, Bax J, Daubert J. Metaanalysis on effects of cardiac resynchronization therapy in heart failure patients with narrow QRS complex. *Cardiol J* 2008;**15**: 230–236.
7. Kamath GS, Steinberg JS. Cardiac resynchronization therapy and atrial fibrillation. *Cardiol J* 2009;**16**:4–10.
8. Dickstein K, Bogale N, Priori S, Auricchio A, Cleland JG, Gitt A, Limbourg T, Linde C, van Veldhuisen DJ, Brugada J. The European cardiac resynchronization therapy survey. *Eur Heart J*; doi:10.1093/eurheartj/ehp359
9. Bleeker GB, Holman ER, Steendijk P, Boersma E, van der Wall EE, Schalij MJ, Bax JJ. Cardiac resynchronization therapy in patients with a narrow QRS complex. *J Am Coll Cardiol* 2006;**48**:2243–2250.
10. Beshai JF, Grimm RA, Nagueh SF, Baker JH 2nd, Beau SL, Greenberg SM, Pires LA, Tchou PJ. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med* 2007;**357**:2461–2471.
11. Holzmeister J, Hurlimann D, Steffel J, Ruschitzka F. Cardiac resynchronization therapy in patients with a narrow QRS. *Curr Heart Fail Rep* 2009;**6**:49–56.
12. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C. 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**:1834–1843.
13. Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H, Gasparini M, Linde C, Morgado FB, Oto A, Sutton R, Trusz-Gluzka M; European Society of Cardiology; European Heart Rhythm Association. Guidelines for cardiac pacing and cardiac resynchronization therapy: the Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. *Eur Heart J* 2007;**28**:2256–2295.