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# **Current Practice of Cardiac Resynchronization Therapy in the Real World: Insights from the European CRT Survey**

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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 remodeling.(4) Conversely, results from various small studies imply that certain patient populations may benefit from CRT despite the fact that they do not fulfill 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.

In this issue of the Journal, 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 cardiac resynchronization therapy. In order to provide these information, 2438 patients from 141 centers 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., biventricular pacing device without ICD function) were older, less likely to present with comorbidities including ischemic heart disease or diabetes mellitus, and had better left ventricular function as compared to 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 comorbidities (as reflected by higher serum creatinine and BNP levels) as compared to 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 deserves 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 (<120ms) as well as 10% with a QRS duration between 120ms and 129ms. 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 center studies were able to identify patients with narrow QRS who responded favorably to CRT.(5, 6, 8) In contrast, the results of two recent randomized pilot studies (RethinQ(9) and ESTEEM-CRT) remained elusive due to several inherent limitations.(10) Eventually, the answer to whether CRT improves morbidity and mortality in this particular patient group can only be provided by an adequately powered, end-point driven randomized clinical trial, which is currently underway (Echocardiography Guided Cardiac Resynchronization Therapy – EchoCRT; NCT00683696, [www.clinicaltrials.gov](http://www.clinicaltrials.gov)).(10) Before the results of this trial will be available, it will be of interest to observe the direction in which the expected one year data from the current survey will be pointing. Unfortunately, only qualitative assessment instead of quantitative (echocardiographic) parameters of LV 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 cardiac resynchronization therapy,(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 present survey, 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 one 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 also patients with mildly symptomatic heart failure (i.e., NYHA class < III) may benefit from CRT. Indeed, data from the REVERSE trial,(11) 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 of 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, numbers on 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 present survey gives a nice and robust overview of the current practice regarding cardiac resynchronization therapy across a wide range of European centers. Planned assessment of survey patients after 1 year, including data on morbidity and mortality as well as echocardiographic remodeling and arrhythmias, will eagerly be 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) 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**

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## Figure: Patient selection for CRT – Present and Future

Current indications for CRT according to current European Society of Cardiology (ESC) / European Heart Rhythm Association (EHRA) guidelines (12) as well as potential future candidates for CRT are shown. See text for details.

A Fib: Atrial fibrillation; CHF: Congestive heart failure; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association.

### Current ESC / EHRA guidelines

<ul style="list-style-type: none"><li>• NYHA III-IV</li><li>• QRS &gt; 120ms</li><li>• LVEF &lt; 35%</li></ul>	Class I / A
<ul style="list-style-type: none"><li>• NYHA III-IV, LVEF &lt; 35%</li><li>• Indication for permanent pacing</li></ul>	Class IIa / C
<ul style="list-style-type: none"><li>• NYHA III-IV, LVEF &lt; 35%</li><li>• Permanent atrial fibrillation</li><li>• Indication for AV nodal ablation</li></ul>	Class IIa / C

### Potential further candidates (under investigation)

<ul style="list-style-type: none"><li>• NYHA I-II</li></ul>
<ul style="list-style-type: none"><li>• QRS &lt; 120ms</li></ul>
<ul style="list-style-type: none"><li>• CHF &amp; atrial fibrillation</li></ul>
<ul style="list-style-type: none"><li>• Upgrade from brady-pacing</li></ul>