EDITORIAL

New guidelines for cardiac resynchronisation therapy: simplicity or complexity for the doctor?

C Leclercq

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The National Institute for Health and Clinical Excellence (NICE) published recently the guidance for cardiac resynchronisation therapy (CRT) for the treatment of heart failure which represents the view of this institute.[1] The guidance has to be taken into account by the healthcare professionals when practising. A summary of the guidance and the process of its development appears in this issue of *Heart* (***see article on page 1134***).[2]

The writing of guidelines is always a difficult task for several reasons: first, analysis of the evidence-based data is complex and the interpretation may sometimes differ slightly between two readers. Second, there is often a delay between the writing of the guidelines and their publication with the risk that data from the most recent trials are not implemented in the guidelines. Third, new guidelines may not always be exactly concordant with current published guidelines by other task forces and so may some times induce some ''dyssynchrony''.

At the present time, different guidelines for the recommended use of CRT have already been published.[3–6] These guidelines are based on the results and inclusion criteria of the different trials which validated the treatment.[7–10]

The European guidelines for the diagnosis and treatment of chronic heart failure were updated in 2005, just after the publication of the CARE-HF trial.[3] These guidelines implemented CRT using biventricular pacing with a high level of recommendation for improving symptoms as well as hospitalisations (class of recommendation I, level of evidence A) and survival (class of recommendation I, level of evidence B). CRT was recommended for patients with ''reduced'' ejection fraction and ventricular dyssynchrony (QRS width $\geqslant$120 ms) and who remain symptomatic (New York Heart Association (NYHA) III–IV) despite optimal drug treatment. There were no specific recommendations on the underlying atrial rhythm and no specific cut-off value of left ventricular ejection fraction (LVEF) to define a ''reduced'' ejection fraction. In the same guidelines, implantation of an implantable cardioverter-defibrillator (ICD) in combination with biventricular pacing can be considered in patients who remain symptomatic with severe heart failure NYHA class III–IV with LVEF $\leqslant$35% and QRS duration $\geqslant$120 ms to improve mortality or morbidity (class of recommendation IIa, level of evidence B).

The same year, an update of the ACC/AHA guidelines for the diagnosis and management of chronic heart failure in adults recommended biventricular pacing for patients with almost the same characteristics as those of the European guidelines.[4] Interestingly, the AHA/ACC guidelines considered only patients in sinus rhythm, so effectively excluding patients in atrial fibrillation. These guidelines defined a cut-off value of 35% for LVEF. Moreover, the NYHA class IV patients were considered for CRT only if the were ''ambulatory'' class IV patients and so excluded patients with very severe disease requiring inotropic support.

In 2006, the ACC/AHA/ESC guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death considered, with a class of recommendation IIa and a level of evidence B, that ICD treatment combined with biventricular pacing can be effective for primary prevention to reduce total mortality by a reduction in sudden cardiac death in patients with NYHA functional class III or IV despite optimal medical treatment, in sinus rhythm with a QRS complex of at least 120 ms, and who have reasonable expectation of survival with a good functional status for more than 1 year.[5] There was no specific comment about the value of the LVEF as an inclusion criterion. These guidelines considered also, with the same level of recommendation and evidence, that biventricular pacing in the absence of ICD treatment is reasonable for the prevention of sudden cardiac death in patients with NYHA functional class III or IV, an LVEF $\leqslant$35%, and a QRS complex $\geqslant$160 ms (or at least 120 ms in the presence of other evidence of mechanical dyssynchrony) despite optimal medical treatment and who have reasonable expectation of survival with a good functional status for more than 1 year.

The NICE guidance for CRT recommends a CRT with a pacemaker (CRT-P) for patients with heart failure in sinus rhythm and in NYHA class III or IV despite optimal medical treatment, an LVEF of $\leqslant$35% and ventricular dyssynchrony.[1] Ventricular dyssynchrony is based on the QRS duration with two distinct groups: patients with QRS duration $\geqslant$150 ms on surface ECG or patients with QRS duration of 120–149 ms and evidence of mechanical dyssynchrony based on echocardiographic criteria. Devices combining CRT and ICD (CRT-D) are recommended in the NICE guidance for

Correspondence to: Professor C Leclercq, Département de Cardiologie et Maladies Vasculaires, Centre Cardio-Pneumologique, Hôpital Pontchaillou, rue Henri Le Guilloux, 35033 Rennes Cedex 09, France; christophe.leclercq@chu-rennes.fr

Abbreviations: CRT, cardiac resynchronisation therapy; CRT-D, cardiac resynchronisation therapy with a defibrillator device; CRT-P, cardiac resynchronisation therapy with a pacing device; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association

patients fulfilling criteria for a CRT-P device and the use of ICD as recommended in NICE technology appraisal guidance,[1] considering for ICD implantation only patients with ischaemic cardiomyopathy and low LVEF and not at all patients with a non-ischaemic cardiomyopathy, and so ignoring the results of the SCD-HeFT trial.[11]

The NICE guidance is based on the results of the clinical trials which validated this treatment, with particular attention to the two landmark trials, COMPANION and CARE-HF.[6–10] These two trials were specifically designed to assess the efficacy of CRT on morbidity and mortality.[9 10] Usually, the guidelines select the target population on the basis of the inclusion criteria of the clinical trials and not on the patients really included in the trials. For example, most of the clinical trials included only patients in class III or IV, except the MIRACLE ICD and the CONTAK-CD trials, which included also NYHA class II patients.[12 13] The analysis of the patients really included in the trials showed that the proportion of NYHA class III and IV patients was different: in the CARE-HF trials only 9% of the included patients were in NYHA class IV and 18% in the COMPANION trial.[9 10] A recent subanalysis of the NYHA class IV patients of the COMPANION trial showed that CRT-D tended to reduce mortality but without statistical significance, whereas CRT-D significantly reduced mortality as compared with optimal drug treatment in the overall population including NYHA class III and IV patients.[14]

All patients included in the clinical trials had an LVEF <35%. However, the mean or median value of LVEF in the included patients was low, around 25%, raising the important question of efficacy of CRT according the value of baseline LVEF.[6–10]

The definition of ventricular dyssynchrony is still a matter of debate. All trials except the CARE-HF trials included patients only on the basis of the QRS duration.[10] The cut-off value of QRS duration to include patients in the CRT trials decreased progressively over time from 150 ms in the MUSTIC trial[6] to 130 ms in the MIRACLE trial[8] to 120 ms in the COMPANION and CARE-HF trials.[9 10] In the two last trials the median value of the QRS duration was 160 ms.[9 10] The CARE-HF trials added for the first time some conventional echocardiographic criteria of mechanical left ventricular dyssynchrony for patients with an ''intermediate'' QRS duration of 120–149 ms (prolonged left ventricular pre-ejection delay >140 ms, interventricular delay >40 ms and evidence of an overlap between systole and diastole).[10] Unfortunately, only 8% of the overall population of the CARE-HF trial had a QRS duration of 120–149 ms, which represents fewer than 100 patients and does limit dramatically the subanalysis of this specific population.[10]

Several reports have suggested that echocardiographic criteria would be more accurate to select CRT patients than ECG criteria.[15–18] However, none of these echocardiographic criteria have been validated so far by specifically designed prospective trials. The results of the PROSPECT trial aimed at evaluating the value of different echocardiographic variables to predict clinical outcome as well as left ventricular remodelling will probably give some interesting results.[19] The current NICE guidance suggests that only patients with moderately prolonged QRS and evidence of mechanical dyssynchrony according to echocardiographic measures seem attractive, but this is not yet supported by evidence. The NICE guidance did not define precisely which criteria can be used to assess mechanical dyssynchrony. At the present time, there are many criteria using either conventional echocardiography or more sophisticated parameters to define mechanical dyssynchrony, but the most powerful measure to define cardiac dyssynchrony has not been yet established. The NICE guidance underlines that only one trial, the COMPANION trial, provided the basis for a direct comparison between CRT-P and CRT-D but that it was not powered to detect differences for this comparison, even if only CRT-D yielded a significant reduction in mortality.[10] This crucial question risks being unanswered because a trial specifically designed probably will not be performed in the future owing to methodological considerations and sponsoring.[9]

Interestingly, the NICE guidance discussed the cost effectiveness of CRT with a cost per quality-adjusted life year (QALY) at about £16 000 and £23 000 for CRT-P and CRT-D, respectively. The guidance pointed out that implanting a CRT-D rather than a CRT-D device would have a cost per QALY of about £40 000. These finding suggest that the use of CRT-D, as least as far as cost effectiveness is concerned, should consider clinical baseline characteristics such as the age as shown by the cost-effectiveness analysis of the care-HF trial.[20]

In conclusion, the NICE guidance recommends CRT in a ''classical'' population except for the inclusion of echocardiographic criteria for patients with a moderate QRS width prolongation. This seems logical but is not yet clearly supported by the results of the clinical trials. The implementation of echocardiographic criteria in CRT indications should follow the same route as the other criteria with specifically designed trials. Although it may seem logical to recommend the use of echocardiographic measures, this seem to be too premature. Moreover, we can hypothesise that in the future other patients will be considered for CRT—for example, NYHA class II patients, patients with permanent atrial fibrillation, patients already implanted with a pacemaker or ICD and, finally, patients who are candidates for a conventional pacemaker or ICD. However, all these potential indications have to be validated definitively. Echocardiography is an attractive tool for selecting and, especially, for optimising the selection of patients as candidates for CRT, but it has also to be validated.

Conflict of interest: None declared.

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IMAGES IN CARDIOLOGY

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Late adverse ventricular remodelling as a consequence of acute left main coronary artery occlusion

A 40-year-old man presented with severe chest pain. The electrocardiogram showed extensive anterolateral ST elevation. His blood pressure was 110/90 mm Hg. Emergency coronary angiography demonstrated a severe right coronary artery (RCA) stenosis and left main (LM) stem occlusion (panels A and B). After the first balloon inflation (59 minutes from pain onset), abciximab and intra-aortic balloon counterpulsation (IABP), a 4.0×16 mm Taxus stent was implanted in the LM stem. There was impaired antegrade flow despite a good angiographic result. IABP and inotropic support continued for 72 hours.

Coronary angiography 1 week later demonstrated a good result of LM stenting. Using a FilterWire EZ, the RCA lesion was directly stented with a 4.5×16 mm Taxus stent (panels C and D). Left ventriculography showed mildly impaired left ventricular (LV) dysfunction with an LV ejection fraction (LVEF) of 39% and LV end diastolic pressure (LVEDP) of 16 mm Hg.

The patient had repeated admissions with breathlessness; however, hypotension limited treatment to rampril 2.5 mg and bisoprolol 2.5 mg. Nine months later the patient continued to complain of exertional dyspnoea. Repeat angiography demonstrated severe LV dysfunction with an LVEF of 19% and LVEDP of 38 mm Hg (panels E and F). Referral for heart transplantation was made.

Emergency restoration of coronary flow probably saved this patient's life. However, the consequence of such extensive global ischaemia was severe LV hypotension, restricting prescription of ACE inhibitors and β blockers. Subsequent adverse LV remodelling resulted in further deterioration of LV performance. This case illustrates a potential future role for catheter implantable LV assistance devices which might facilitate early revascularisation and maintain circulation in the weeks after major myocardial infarction.

W J van Gaal, B R Jennings, A P Banning
william@vangaal.org