Widening indications for CRT implants: not necessarily 'the more the merrier'?

Despite significant advances in pharmacological therapies, heart failure still leads to significant morbidity and mortality, with a prognosis comparable to that of many of the cancers. Cardiac resynchronization therapy (CRT) aims to improve systolic function through correction of the left ventricular dyssynchronous contraction which is seen in a significant proportion of patients with heart failure.

Landmark clinical trials have shown that CRT significantly improves morbidity (symptoms, exercise tolerance, hospitalizations), echocardiographic indices of left ventricular function and importantly also reduces mortality (Bristow et al, 2004; Cleland et al, 2005). CRT has thus become one of the cornerstones of heart failure therapy in suitable patients and incorporated into international guidelines.

In 2012 updated international guidelines for CRT implantation were published by the European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology (ACC/AHA) (McMurray et al, 2012; Tracy et al, 2012). The most momentous development in these guidelines has been the recommendation that patients with mild heart failure symptoms or even asymptomatic patients (New York Heart Association (NYHA) class I and II in ACC/AHA guidelines; NYHA class II in ESC guidelines) with other standard CRT indications are eligible for a CRT device. This is based on persuasive evidence from three randomized controlled trials (REVERSE, MADIT-CRT and RAFT) showing that CRT in these patients improves reverse remodelling of the left ventricle, thus slowing or even preventing heart failure deterioration and consequent hospitalizations (Linde et al, 2008; Moss et al, 2009; Tang et al, 2010).

In these trials, CRT led to echocardiographic changes suggesting improved left ventricular dimensions and function, and also benefits of slowing symptomatic progression particularly in patients with the widest QRS duration. In the RAFT study CRT even demonstrated mortality benefit among patients with NYHA class II symptoms and left ventricular ejection fraction ≤30%, but not in patients with NYHA class I symptoms (Tang et al, 2010).

The most notable change in both sets of guidelines was the extension of class I recommendation to include patients with NYHA class II symptoms (in addition to left bundle–branch block, QRS duration ≥150 ms and left ventricular ejection fraction of ≤35% in ACC/AHA guidelines; left bundle–branch block, QRS duration of ≥130 ms and left ventricular ejection fraction ≤30% in ESC guidelines). For the first time ever, the ACC/AHA guidelines recommend that CRT implantation may be considered (class IIb recommendation) in asymptomatic patients with heart failure (NYHA class I if left ventricular ejection fraction ≤30%, ischaemic aetiology of heart failure, sinus rhythm, QRS duration ≥150 ms) whereas the European guidelines have not included these patients.

Another significant change is the reservation of the strongest recommendation (class I) for heart failure patients with left bundle–branch block QRS morphology. This is based on robust evidence from trials such as MADIT-CRT, CARE-HF and RAFT showing that the highest response rate from CRT is among patients with left ventricular dyssynchrony caused by left bundle–branch block (Cleland et al, 2005; Moss et al, 2009; Tang et al, 2010), and suggesting that patients with right bundle–branch block respond poorly to CRT.

A meta-analysis of over 5300 patients from four randomized controlled trials showed a significant reduction in clinical events such as all-cause mortality and heart failure hospitalizations only among patients with left bundle–branch block QRS morphology (relative risk 0.64, 95% confidence interval (CI) 0.52–0.77, $P<0.001$) compared to the lack of significant benefit in patients with non-left bundle–branch block QRS morphologies (relative risk 0.97, 95% CI 0.82–1.15, $P=0.75$) (Sipahi et al, 2012). This was particularly so among patients with right bundle–branch block (relative risk 0.91, 95% CI 0.69–1.2, $P=0.49$) or non-specific intra-ventricular conduction delay (relative risk 1.19, 95% CI 0.87–1.63, $P=0.28$).

While electrical dyssynchrony, as predicted by prolonged QRS duration on surface electrocardiogram, is a crude, simplistic assessment for ventricular dyssynchrony, it remains the best option, as imaging studies for mechanical dyssynchrony have shown large variations in sensitivity and specificity. Similarly CRT has not been shown to have clinical benefit in the presence of mechanical dyssynchrony on its own despite other standard CRT indications, so both sets of guidelines do not recommend device implant in these patients.

While these guidelines have broadly similar recommendations for the most eligible patients, e.g. those with a combination of severe left ventricular dysfunction, moderate to severe heart failure symptoms or severe left ventricular dyssynchrony as well as left bundle–branch block, there are some subtle yet conspicuous differences between them. It seems that guidelines regarding suitability for CRT implant demonstrate regional variation depending on availability of health-care resources. This can partly be explained by the fact that, while early clinical studies identified clear categories of patients who might be expected to benefit, subsequent examination of subgroups and meta-analyses have allowed extrapolation of primary outcome results into other categories as a result of various factors, including different electrocardiogram and symptomatic criteria between study participants.

The ACC/AHA guidelines restrict the strongest 'recommended' category (class I) for cases in which the QRS is ≥150 ms although therapy can be considered in other cases where appropriate (Tracy et al, 2012). The European guidelines, however, use a cut-off QRS duration of ≥120 ms in patients with NYHA class III or ambulatory class IV symptoms and ≥130 ms in patients with NYHA class II symptoms for class I recommendation of CRT implant (McMurray et al, 2012). Dependent on the

entry criteria, clinical studies of CRT have defined 'electrical dyssynchrony' as a QRS complex of either >120 ms or >150 ms. However, a meta-analysis of five studies with around 6500 patients of all NYHA classes suggested that clinical benefit from CRT may be limited to patients with QRS duration ≥150 msec (Sipahi et al, 2011). There was a significant reduction in composite clinical end-points among patients with QRS duration >150 msec (relative risk 0.60, 95% CI 0.53–0.67, $P<0.001$), but a lack of benefit among patients with QRS duration 120–149 msec (relative risk 0.95, 95% CI 0.92–1.10, $P=0.49$).

How will these guidelines affect clinical practice?

The latest CRT guidelines from the National Institute for Health and Care Excellence were issued 6 years ago, so updated guidance is due to be issued later this year. It is foreseeable that these will also reflect the changes in the international guidelines for CRT therapy to include patients with mild heart failure symptoms.

These guidelines are likely to have a major impact on the proportion of patients who may not show a clinical response to a CRT implant ('non-responders'). Even when CRT implant is successful, about 30% of patients will not respond to therapy (Fox et al, 2005). Wider eligibility criteria could substantially increase the number of non-responders. While inclusion of patients with milder symptoms is a positive step towards achieving early cardiac resynchronization and possibly preventing deterioration in heart failure, this is likely to add to the already significant problem of non-response. It may also impose a further burden on health-care resources, with extra attendances for device optimization, investigations to assess the cause of non-response and additional procedures for lead repositioning.

There is an urgent need to identify measures to improve CRT response rate. These include incorporation of newer lead technology such as the quadripolar left ventricular lead, multi-site pacing and imaging technology to improve targeted lead placement by avoiding areas of myocardial scarring. A clearer definition of 'response' is needed, as demonstrating improved morbidity or reduction in mortality as a result of CRT would be challenging in patients with mild or no symptoms of heart failure.

A more judicious approach would be to use a combination of measures, e.g. reduced hospitalizations and improved left ventricular parameters, to give a broader definition of CRT response. It then becomes more important to explain in detail to eligible patients the potential risks *vs* benefits of CRT implant, to allow them to take a balanced decision based on expectations from therapy. While the latest guidelines reflect dynamic changes in heart failure device therapy, in a world with shrinking global boundaries the trans-Atlantic differences in QRS duration cut-off between the two sets of guidelines could lead to confusion and potentially medicolegal controversies both among health-care professionals and patients.

Device therapy is a dynamic field with rapid advances in therapy as well as steady accumulation of new evidence. Recent results from the BLOCK HF trial showed that CRT is superior to right ventricular pacing in patients with atrioventricular block requiring pacing, left ventricular ejection fraction <50% and NYHA class I–III symptoms. It is likely that the next update of the CRT guidelines will further expand eligibility criteria for implant (Curtis et al, 2013).

It is important to remember that patients in large randomized trials are carefully selected with their heart failure pharmacological therapies fully optimized and are also intensely followed up. The impressive outcomes seen in trials are also not always reproducible in the real world. Guidelines offer an overview and recommend a unifying approach, but they must be interpreted and adapted in the context of each individual patient. When interpreting guidelines based on landmark studies, decision making must to suit the needs and expectations of individual patients. BJHM

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KEY POINTS

- Recently updated international guidelines for cardiac resynchronization therapy implants recommend inclusion of heart failure patients with mild symptoms provided they fulfil echocardiographic and electrocardiogram criteria.
- This is a positive step as it aims to prevent heart failure progression at an early stage.
- However, this is also likely to increase the proportion of non-responders and thus underlines an urgent need to identify novel techniques to improve response to cardiac resynchronization therapy.