How many patients need cardiac resynchronization therapy?

John G.F. Cleland*, Kevin Goode, Olga Khaleva, and Nasrin Khan

Department of Cardiology, Castle Hill Hospital, University of Hull, Kingston upon Hull, UK

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This editorial refers to 'How many patients with heart failure are eligible for cardiac resynchronization? Insights from two prospective cohorts' by F.A. McAlister et al., on page 323

For patients with moderate or severe heart failure who have evidence of cardiac dyssynchrony there is overwhelming evidence that cardiac resynchronization therapy (CRT) improves symptoms substantially, reduces morbidity, and prolongs life.1 The CARE-HF programme demonstrated that CRT reduced all-cause mortality by 40% and cardiovascular mortality by about 45%.2 The COMPANION trial, which was stopped prematurely, and a meta-analysis of CRT trials including 3393 patients, are consistent with these data.3 In CARE-HF, the absolute reduction in mortality was 13.4%,4 which translates into a life saved for every 7.5 devices implanted over an average 3-year follow-up. The treatment appears cost-effective. In summary, there is no doubt that CRT is valuable in patients similar to those recruited in the clinical trials. Resources now have to be found to implement their results.

Effective planning requires some idea about the number of patients who need this treatment. McAlister et al.3 tried to address this question using two populations of patients from Ontario (population 12 million). The authors identified 9943 hospital admissions with a first-time diagnosis of heart failure over a 2-year period, a rate of 0.4/1000 population/year, which is three to four times lower than expected.4 The annual rate of first-time admissions for heart failure is about 12 000 in Scotland (population 5 million).5 The data from Ontario are therefore not consistent with that from Europe or the USA.4–6 Among the Ontario patients, only 2640 (27%) had left ventricular systolic dysfunction (LVSD), compared with 54% in the EuroHeart Failure Survey (EHFS) of hospital discharges.7 Only 73 patients (0.7%), 106 if atrial fibrillation was included, were considered to fulfil fairly broadly defined eligibility criteria for CRT. In contrast, amongst 309 patients attending a specialist clinic over a 6-month period, 263 (85%) had LVSD and of these 54 (21%) were considered CRT eligible, which is in broad agreement with the estimates of others.

Despite their conflicting data, the authors suggest that few patients in Ontario require CRT. Which of the data presented should we believe? In Ontario, in 2004, before there was convincing evidence that CRT was effective or cost-effective, manufacturers data indicate that there were 345 CRT or CRT-D implants or about 29 per million population. In western Europe implantation rates were 46 per million in 2004. Clearly, the rate of device use is already much higher than that implied by the data on first-time hospitalizations from Ontario (six per million) and much closer to an estimate derived from the specialist clinic cohort assuming that about 1% of the population have heart failure, that half of these have severe LVSD and that it will take about 5 years to reach a steady state where incidence matches implantation rate.8

In the hospital cohort, the authors confined their interest to patients with a first admission for a principle diagnosis of heart failure. The choice of this population was a mistake for three important reasons. First, many more patients leave hospital with a diagnosis of heart failure than are admitted with it. Secondly, patients with new onset heart failure may be the group least likely to have dysynchrony. The median duration of heart failure in COMPANION was 3.5 years and in CARE-HF 3.2 years (inter-quartile range 1.1–6.9 years). In patients with heart failure, QRS duration increases over time, presumably reflecting deteriorating LVSD, increasing dysynchrony, and a worse prognosis. Indeed, in EHFS, among 1493 patients with a recurrent admission for heart failure and LVSD, 45% had a QRS ≥120 ms compared with 36% among those with a first recorded admission.9 Finally, the authors do not justify the exclusion of patients in whom heart failure was a secondary diagnosis. These patients require treatment too. There is little evidence that a diagnosis of heart failure coded in the first or second position is meaningfully different.

Having selected the wrong population for study, the authors then proceed to discard large numbers of patients whom they assume, but do not show, are ineligible for CRT. As in Europe, about one-third of patients admitted to hospital have no record of an assessment of cardiac function.2 It is not safe to assume that these patients do not have LVSD. The authors exclude 10% of patients on the basis of a recent MI but there is no evidence that patients with IHD benefit less from CRT in terms of reduction in

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* Corresponding author. Tel: +44 1482 624 087; fax: +44 1482 624 085.
E-mail address: j.g.cleland@hull.ac.uk
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major morbidity or mortality than other patients. These patients could be eligible within weeks. The authors indicate that many patients were excluded because they were not in NYHA III/IV at the time of hospital assessment but do not provide numbers. Why were these patients in hospital if not for the management of severe symptoms? In the EHFS of patients with a first or recurrent admission with heart failure, 26% patients were in NYHA III/IV at 12 weeks after discharge. The data from the specialist clinic are potentially more relevant and suggest that a substantial proportion of patients were eligible for CRT but as the clinic only cared for 309 patients out of the estimated 120 000 patients with heart failure in Ontario these may not be representative of the population at risk. In our own clinic, of over 3000 patients with suspected heart failure reviewed from a population of 0.6 million, 1288 had LVSD, and of these, 451 (43%) had QRS \geq 120 ms. In summary, the authors provide neither relevant nor reliable data from either cohort.

The size of the benefit and consistency across subgroups in clinical trials of CRT must be considered. At least one-third of patients in the trials were aged \geq 70 years and similar benefits were observed among younger and older patients. Epidemiological data in Europe indicate that the average age of patients discharged from hospital with LVSD is 67 years and 71% will be men. Patients without LVSD are more likely to be women and to be older.\footnote{6}

All trials recruit a proportion of patients who do not strictly fulfil their inclusion criteria. In CARE-HF, \geq 20% of patients reported that they were in NYHA class I/II at baseline,\footnote{7} and in the control group, 40% reported they were in NYHA I/II by 3 months. Most patients in CARE-HF were taking the equivalent of \leq 40 mg of furosemide and 25% of patients in CARE-HF had plasma concentrations of N-terminal pro-brain natriuretic peptide < 100 pmol/L. In COMPANION, the subgroup of patients not taking diuretics obtained the largest benefit from CRT. The clinical community is divided into those who see clinical trials as a set of rigid rules and those who use them to guide the general principles of clinical practice. Trials are the science that inform the art of medicine, as trials covering every clinical scenario are not feasible. Clinical trialists do have an obligation to minimize exclusion criteria and this is an appropriate message from the Ontario paper. However, evidence-based medicine will have little impact on the well-being of patients without some extrapolation, although cautious, from clinical trials. The large benefit observed in clinical trials of CRT despite the inclusion of many patients who had mild symptoms suggest that if the entry criteria for CRT trials had been extended to a broader population, the trials would still have shown benefit. Stricter application of the entry criteria to patients in the clinical practice population than to the patients in the trial may not be appropriate.

In conclusion, this is a technically excellent analysis of the wrong data and consequently a misleading interpretation that does a grave disservice to patients. The Ontario data should not form the basis of planning for the provision of CRT for heart failure by those entrusted to deliver life-saving and cost-effective therapy. Better quality data will be available soon.

Conflict of interest: J.G.F.C. was the principle investigator of the CARE-HF study sponsored by Medtronic. K.G. and N.K. were employed by the EuroHeart Failure Survey for analysis of ECGs. O.K. is studying the prevalence of dyssynchrony in a large community-based study.

References


