# Cardiac resynchronisation therapy for chronic heart failure

Richard M Cubbon, Klaus K A Witte

Division of Cardiovascular and Diabetes Research, University of Leeds, Leeds LS2 9JT

Correspondence to: K K A Witte
klauswitte@hotmail.com

Cite this as: *BMJ* 2009;338:b1265
doi:10.1136/bmj.b1265

Chronic heart failure is common, affecting about 900 000 people in the United Kingdom and with a prevalence of about 6-10% in people aged over 65 years[1]; despite modern drug treatment, it carries a high morbidity and a 10% annual mortality. About a third of patients with chronic heart failure have a left ventricular ejection fraction ≤35%,[2] up to 40% of whom are at risk of worse outcomes and more severe heart failure identified by conduction delay (QRS duration on a surface electrocardiogram of >120 ms).[3]

A recent addition to therapeutic algorithms for chronic heart failure is cardiac resynchronisation therapy (also known as biventricular pacing). Cardiac resynchronisation therapy is a well proved treatment for patients with heart failure who have left ventricular systolic dysfunction and conduction delay, and it can reduce symptoms and admission to hospital and improve quality of life and prognosis. Clear mortality benefits have moved it from a treatment for intractable symptoms to one that, alongside β blockers, angiotensin converting enzyme inhibitors, and aldosterone antagonists, is now a routine therapy for patients with current or previous severe chronic heart failure.

Identifying suitable patients is straightforward; there is no upper age limit of benefit; the implant technique is of low risk; and the treatment is highly cost effective. This article reviews the evidence and indications for cardiac resynchronisation therapy, discusses the clinical features that should alert general physicians and general practitioners to patients who may benefit from this therapy, and considers future directions for such therapy for heart failure ("device therapy") in the UK.

## What is cardiac resynchronisation therapy?

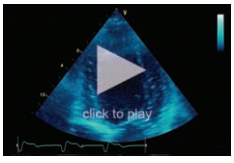
Cardiac resynchronisation therapy is a form of cardiac pacing that aims to improve the coordination of the atria and both ventricles. Pacing leads are placed into the right atrial appendage, at the right ventricular apex, which is also the anterior wall of the left ventricle, and, via a lateral tributary of the coronary sinus, into the left ventricular posterolateral wall (fig 1). Venous access is through the subclavian vein as for normal pacing, and the procedure is usually done under local anaesthetic through an infraclavicular incision. The target vein on the lateral wall is identified by retrograde balloon venography of the coronary sinus (fig 2; see videoclip 1 on bmj.com). The leads are connected to a subcutaneous generator, which can then be programmed to deliver simultaneous left ventricular and right ventricular pacing. To over-ride intrinsic conduction, the atrioventricular delay is set shorter than the intrinsic PR interval. In selected patients cardiac resynchronisation therapy can be combined with additional protection from sudden cardiac death by implantation of an automatic implantable cardioverter defibrillator.[4]

## How does cardiac resynchronisation therapy work?

Conduction system disease is common in patients with chronic heart failure and can be identified by a broad QRS complex on a surface electrocardiogram (fig 3). This is commonly accompanied by dyssynchronous, inefficient cardiac contraction, increased mitral regurgitation, and regional ischaemia, all of which contribute to further adverse remodelling and a downward spiral of cardiac function (see videoclip 2 on bmj.com). By pacing both sides of the left ventricle, thereby improving the coordination of left (and right) ventricular contraction, cardiac resynchronisation therapy can

### TIPS FOR NON-SPECIALISTS

- High risk features in chronic heart failure include more severe (or worsening) symptoms; recent decompensation; left bundle branch block; renal impairment; hypotension (systolic pressure <90 mm Hg)
- Need for increasing amounts of diuretic is a sign of impending or current instability
- Early referral to a heart failure clinic can prevent admission
- Older patients benefit from intensive heart failure therapy as much as younger patients
- Patients intolerant of optimal drug treatment such as β blockers and angiotensin converting enzyme inhibitors will often tolerate higher doses of these after biventricular pacing with additional prognostic and symptomatic benefit




Three videoclips showing how cardiac resynchronisation works are on bmj.com

**SOURCES AND SELECTION CRITERIA**

We searched Medline and the Cochrane database for evidence from systematic reviews and clinical trials. We also used our personal experience of clinical trials, cardiac imaging, and device implantation and searched for relevant reports from the Healthcare Commission.

improve cardiac output, reduce mitral regurgitation during rest and exercise,[5] and improve regional perfusion defects (see videoclip 3 on bmj.com).

## What is the evidence for cardiac resynchronisation therapy?

Early double blind randomised controlled clinical trials of cardiac resynchronisation therapy (achieved by implanting a full system but randomly allocating patients to having the left ventricular lead switched off) found that during biventricular pacing there were improvements in cardiac function, left ventricular dimensions, mitral regurgitation,[5-7] and exercise capacity.[8 9] The largest study (CARE-HF), published in 2005, randomised 813 patients either to optimal drug treatment or to optimal drug treatment plus cardiac resynchronisation therapy. Over the 29 month follow-up period, 30% of those receiving only the drug treatment died, compared with 20% of those also receiving biventricular pacemakers (absolute risk reduction of 10 percentage points). Biventricular pacing was associated with lower mortality resulting from both heart failure and sudden death. Every nine devices implanted (for cardiac resynchronisation) prevented one death and three admissions to hospital over the follow-up period (fig 4).[4 10 11] Morbidity related to the implanted device was uncommon (about 10%), and there was only one death related to the device (this was caused by deteriorating heart failure owing to lead displacement). An economic analysis using a model populated by data from the CARE-HF study showed that cardiac resynchronisation therapy is cost effective, with an estimated cost per quality of life year gained of about £7000 (€7500; $10 000).[12]

## Who is suitable for cardiac resynchronisation therapy?

Before the publication of the CARE-HF study, cardiologists tried to select patients most likely to have a symptomatic response. Since the publication of data showing mortality benefits, selection has become much easier.

**The New York Heart Association's classification of symptoms in chronic heart failure**

| Class | Symptoms |
|---|---|
| I | No limitation: ordinary physical exercise does not cause undue fatigue, dyspnoea, or palpitations |
| II | Slight limitation of physical activity: comfortable at rest, but ordinary exercise results in fatigue, palpitations, or dyspnoea |
| III | Marked limitation of physical activity: comfortable at rest, but less than ordinary activity results in symptoms |
| IV | Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest, with increased discomfort with any physical activity |

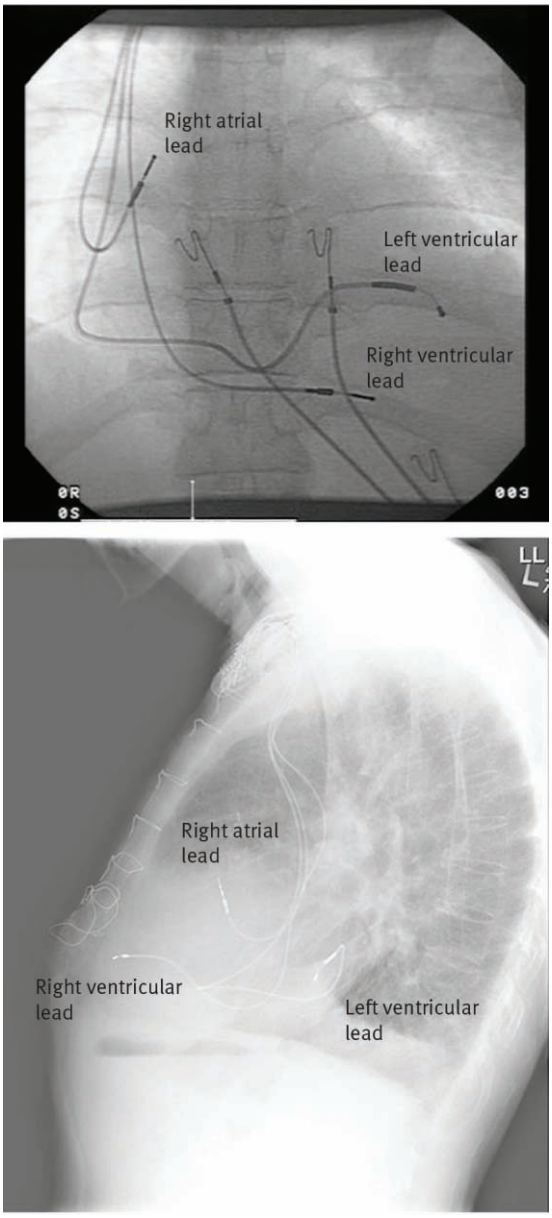



**Fig 1** | **Top: Anteroposterior chest fluoroscopy image showing right ventricular, right atrial, and left ventricular leads (the left ventricular lead is advanced through the coronary sinus and placed in a lateral vein). Bottom: Lateral chest radiograph showing right ventricular, right atrial, and left ventricular leads in position**

American and European guidelines recommend cardiac resynchronisation therapy for patients with New York Heart Association (NYHA) classes III and IV heart failure (table), an ejection fraction ≤35%, and a QRS duration of ≥120 ms.[13] Guidelines published by the National Institute for Health and Clinical Excellence (NICE; www.nice.org.uk/TA120), differ slightly and include patients with "recent or persistent" moderate or severe (classes III and IV) heart failure despite optimal drug treatment, and a QRS duration of >150 ms. In the UK, patients with a shorter QRS duration (120-149 ms) should have confirmation of mechanical dyssynchrony by echocardiography. Current UK guidelines also

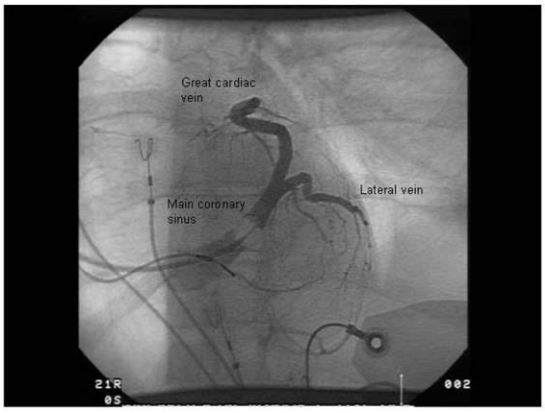



**Fig 2** | Contrast venogram of coronary sinus showing lateral vein suitable for left ventricular lead placement

require the presence of sinus rhythm, but patients with atrial fibrillation probably fare no worse than those in sinus rhythm provided that intrinsic conduction can be suppressed pharmacologically or by atrioventricular node ablation.[14] Although randomised controlled trials have focused on patients with left bundle branch block, guidelines do not distinguish between patients with right and left bundle branch block, and patients with right bundle branch block and important symptoms may be considered for biventricular pacing.

Age is unrelated to improvements in mortality and morbidity from heart failure treatments, including cardiac resynchronisation therapy (but not implantable cardioverter defibrillators),[15] so advanced age alone should not affect a decision on whether to refer for possible cardiac resynchronisation therapy.

Electrocardiography, a simple non-invasive test that can be performed and interpreted by non-specialists and repeated easily, means that non-specialists can screen their patients with chronic heart failure for the potential to benefit from cardiac resynchronisation therapy.

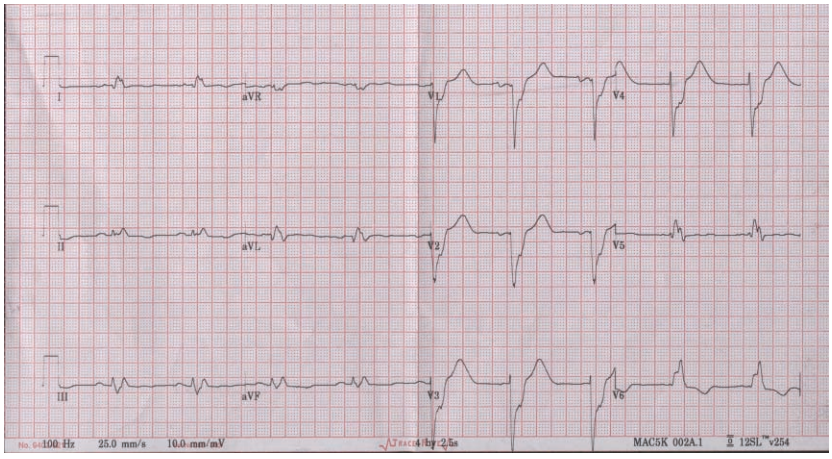



**Fig 3** | Electrocardiogram showing the characteristic R-R pattern in $V_5$ and $V_6$ of left bundle branch block and a QRS duration of 200 ms in a patient with heart failure

## Do all patients with conduction delay benefit from cardiac resynchronisation therapy?

Between 60% and 70% of patients with chronic heart failure who have left bundle branch block show an improvement in symptoms after biventricular pacing. The degree of improvement in any individual is unpredictable, although an improvement by one class of the NYHA classification of heart failure is common.

The consequence of a perceived "failure to respond" of 30-40% before the publication of the CARE-HF study was the development of many echocardiographic measures of mechanical dyssynchrony, which in observational studies seemed to identify patients with a greater likelihood of an improvement in symptoms and cardiac function. None of these measures has proved useful when applied in a larger multicentre trial,[16] probably because the presence of dyssynchrony at baseline identifies patients with a better overall prognosis,[17] because dyssynchrony is not

### PATIENT'S STORY

In 2002, aged 27, I began to experience shortness of breath and fatigue. I was repeatedly reassured (that I was "out of shape") but I knew something was wrong. I tried to overcome the fatigue by going to the gym more frequently. I was putting on weight rapidly and I felt lazy. I became increasingly depressed. Eventually, I was admitted to hospital, and heart failure was diagnosed.

My care was transferred to the heart failure unit in Toronto, where I was told that I might need a heart transplant. This had a terrible impact on me. I became withdrawn and increasingly frustrated and angry. I lost motivation in my executive career path and I quit my job.

In 2004, I was told I was suitable for a new type of pacemaker (a biventricular pacemaker defibrillator). The implant procedure took place under local anaesthetic. I could feel the doctor's movements and hear him talk. The procedure left a scar about two inches long below my collar bone and a bulge the size of a small cigarette lighter under my skin. Three leads had been placed in my heart, and the device was programmed to improve the heart's function and also give a shock in the event of fast, life threatening irregular heart rhythms.

The improvement was immediate. Within 24 hours, I was able to get up and walk around. For the first time in years, I could sleep without four pillows to keep me upright. It was as though a light switch had been thrown. I actually felt alive again. I enrolled in a cardiac rehabilitation programme and soon I was walking three miles a day and cycling. I finally felt well enough to resume my life and I went back to my job.

During 2007 I received inappropriate shocks from the defibrillator. The cause was a failing pacemaker lead, and this was replaced. However, the fear of further shocks became disabling, and I requested that the defibrillator portion was turned off. I am told my heart function has returned almost to normal.

I'm back at work, doing a fulfilling job I enjoy, and the overall trajectory of my life finally feels right again.

Matt Nelson, Canada

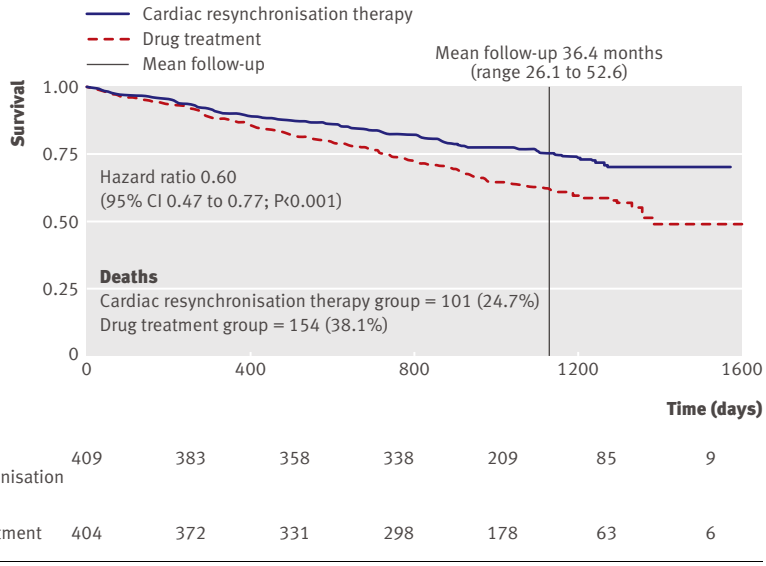



**Fig 4** | Kaplan-Meier curves from the CARE-HF study showing reductions in mortality with cardiac resynchronisation therapy compared with optimal drug treatment. Adapted from Cleland et al[10]

fixed,[18] and because dyssynchrony measures have poor inter-observer reproducibility and cannot be assessed in all subjects.[16] The best predictor of symptomatic response remains a surface electrocardiogram showing a QRS duration of ≥120 ms.

Now that we know that biventricular pacing brings mortality benefits, cardiac resynchronisation therapy also now focuses on mortality and morbidity outcomes (and is no longer just a treatment primarily for symptoms). This shift in indication implies that in any individual it is impossible to say whether they have had no response at all to biventricular pacing, as this might manifest merely as a stabilisation or slowing of the condition (fig 5). Even "non-responders" deteriorate when the device is temporarily switched off, implying an underlying progression of the disease. Hence a failure to improve after cardiac resynchronisation therapy in an individual is not equivalent to a failure to respond.

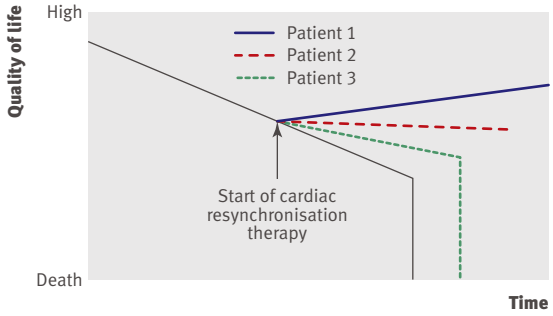



**Fig 5** | Representation of quality of life in patients with heart failure, showing potential outcomes after cardiac resynchronisation therapy. Patient 1 is a traditional responder, with an improvement in quality of life and prognosis; patients 2 and 3 are patients with no symptomatic improvement, traditionally labelled "failure to respond," but both have prognostic benefits, and symptomatic deterioration is slowed

Whether patients with a short QRS duration (<120 ms) experience a mortality benefit from biventricular pacing remains unknown.

### What are the complications of cardiac resynchronisation therapy?

Major morbidity and death as a consequence of biventricular pacing are rare. Failure to implant the left ventricular lead is <5% in large series, and lead displacement after successful implantation is about 1%. The course of the left phrenic nerve over the posterolateral wall of the heart occasionally leads to uncomfortable diaphragmatic stimulation. If this is identified during implantation the lead can be repositioned; if it occurs after implantation, the discomfort can often be limited by reprogramming. The serious though uncommon (around 1%) major complication of the procedure—infection and the attendant risks of extraction—is closely related to procedure time and hence to the experience of the cardiologist doing the procedure. Patients with a biventricular pacemaker should not drive for one week after the implantation (one month if combined with an implantable cardioverter defibrillator).

### Should every patient also receive an implantable cardioverter defibrillator?

The use of implantable cardioverter defibrillators in patients with ischaemic heart disease and severe heart failure without a previous arrhythmic event (primary prevention) remains controversial. Subgroup analysis of large trials suggests mortality benefits from these devices only in patients with mild chronic heart failure (NYHA class I or II). The current NICE guidelines recommend that patients with symptoms "no worse than class III," left ventricular dysfunction (left ventricular ejection fraction <30%), and conduction delay with a QRS duration of >120 ms should receive a cardioverter defibrillator (www.nice.org.uk/Guidance/TA95). The NICE guidelines for cardiac resynchronisation therapy and for implantable cardioverter defibrillators overlap therefore only in patients with class III heart failure. Despite this, many cardiologists think that a single procedure is prudent in patients with class II symptoms as many will deteriorate over the lifetime of the device. Such patients often therefore

#### QUESTIONS FOR FURTHER RESEARCH

- Does cardiac resynchronisation therapy improve prognosis in patients with mild chronic heart failure and is the New York Heart Association's classification of heart failure sufficient to identify those who should and should not be offered such therapy?
- Does cardiac resynchronisation therapy improve outcomes in patients with QRS of short duration?
- Should all patients with a standard pacemaker and requiring a high percentage of pacing receive an upgrade at the time they get their pacemaker generator replaced?

## SUMMARY POINTS

Consider cardiac resynchronisation therapy for any patient with chronic heart failure if they have, or have recently had, moderate or severe symptoms of heart failure; if their left ventricular ejection fraction is ≤35%; and if their QRS duration is ≥150 ms or 120-149 ms with dyssynchrony measured on echocardiography

Cardiac resynchronisation therapy can improve symptoms and prognosis

Advanced age does not reduce the effectiveness of the therapy

All healthcare professionals involved in the management of heart failure need to be aware of the potential benefits of cardiac resynchronisation therapy and who to refer

Evaluation of the QRS duration and heart rhythm on the electrocardiogram should be part of the standard management of any patient with heart failure and repeated at least yearly

receive a device capable of both defibrillation and biventricular pacing. In contrast, the decision to implant a cardioverter defibrillator in a patient with class III symptoms must be considered carefully. Although such devices reduce sudden death in these patients, there is an increased frequency of deaths from heart failure, such that overall mortality is unchanged. In addition, implantable cardioverter defibrillators are associated with a higher complication rate than cardiac resynchronisation therapy alone, including inappropriate discharges (with an associated increased mortality[19]) and a higher chance of lead failure. Therefore, frank discussions are needed with patients with NYHA class III symptoms, those aged over 75 years,[20] and those with very poor ventricular function (<10%)[21] about how and where they might like to die.

The findings of three primary prevention trials and a subsequent meta-analysis of use of implantable cardioverter defibrillators in patients with non-ischaemic cardiomyopathy were neutral,[22] and although there was a trend towards improved outcomes in the device arm of non-ischaemic subgroups of larger trials,[4 23] no consensus yet exists on whether these patients should receive implantable cardioverter defibrillators. In patients tolerating high dose β blockade, particularly young patients in whom lead complications and inappropriate discharges are more frequent, biventricular pacing alone might be sufficient.

### ADDITIONAL EDUCATIONAL RESOURCES

**For patients**

- Arrhythmia Alliance (www.heartrhythmcharity.org.uk/)—UK charity with patient orientated information on arrhythmias and their treatment
- Leeds Institute of Genetics, Health and Therapeutics (www.leeds.ac.uk/light/research/cdr/Clinical%20Research%20Section.html)—Information about the Leeds heart failure clinic and research currently under way
- St Jude Medical (www.sjm.com/procedures/procedure.aspx?name=Cardiac+Resynchronization+Therapy+(CRT))—Information about cardiac resynchronisation therapy
- Boston Scientific (www.bostonscientific-international.com/procedure/ProcedureLanding.bsci/,,/navRelId/1000.1002/method/Procedure/id/10084822/seo.serve)—Cardiac pacemaker company with patient information about pacemakers and the implantation procedure

**For healthcare professionals**

- *Cardiac resynchronisation therapy for the treatment of heart failure* (www.nice.org.uk/Guidance/TA120)—Guidelines from the National Institute for Health and Clinical Excellence
- Medtronic (www.medtronic.com/physician/hf/)—Website by a manufacturer of devices with images and explanations
- Cardiac Network Device Survey Group (www.devicesurvey.com/)—Website providing yearly updated survey of UK implant rates for pacemakers, implantable cardioverter defibrillators, and cardiac resynchronisation therapy

### What about patients with existing pacemakers?

Left ventricular dysfunction and heart failure are common in patients with standard right ventricular pacemakers.[24] Right ventricular pacing induces dyssynchrony that is the same as that seen with intrinsic left bundle branch block[25] and can induce new or worsen existing left ventricular dysfunction. The risk of hospital admission for heart failure is directly related to the percentage of paced beats required.[26] No randomised controlled trial of upgrading right ventricular pacemakers to biventricular pacemakers has been performed, but the frequency and magnitude of increases in left ventricular ejection fraction and improvements in symptoms are the same in patients with previous right ventricular pacemakers as in those with intrinsic left bundle branch block.[25]

### Are the indications for cardiac resynchronisation therapy expanding?

The UK indications for cardiac resynchronisation therapy are likely to broaden in the future to include patients with a QRS duration of ≥120 ms whether or not there is echocardiographic dyssynchrony.[27] Patients with less severe heart failure symptoms (NYHA classes I and II) have improvements in left ventricular function and exercise capacity of a similar magnitude to those in patients with NYHA classes III and IV symptoms,[28] and the relative risk reduction from cardiac resynchronisation therapy in the CARE-HF study was larger in patients with less severe heart failure.[29] Further, severity and nature of symptoms at baseline do not seem to be a good marker of prognostic benefit.[30 31] The MADIT-CRT study examining "early" cardiac resynchronisation therapy in patients with mild or no symptoms of heart failure and who are also having a cardioverter defibrillator implanted has completed recruitment and will report in 2009. Symptoms may soon be less frequently used to identify patients suitable for biventricular pacing. Randomised studies with hard end points are needed in patients with a QRS duration of <120 ms.

### Who should refer patients for possible cardiac resynchronisation therapy and when?

All individuals involved in the care of patients with chronic heart failure must be aware of the indications, potential benefits, and cost effectiveness[12] of device therapy. A systematic approach to the long term follow-up of patients with chronic heart failure both in the community and by general physicians is required to identify patients needing treatment in a timely fashion. Mortality after hospital admission with heart failure is particularly high. Patients with a recent or persistent episode of moderate or severe heart failure should have 12 lead electrocardiography at follow-up and those with a QRS duration of ≥120 ms (three or more small squares on a standard recording at 25 mm/s) should be referred for consideration of cardiac resynchronisation therapy. Patients with chronic heart failure who are not initially considered suitable for biventricular pacing should be reassessed with electrocardiography after each exacerbation, or yearly if stable, as conduction delay develops as chronic heart failure progresses.[3]

**Contributors:** Both authors wrote the article; KKAW is the guarantor.
**Competing interests:** KKAW has received research funding and speaker's honorariums from Medtronic and Boston Scientific, which manufacture cardiac resynchronisation devices.
**Provenance and peer review:** Commissioned; externally peer reviewed
Patient consent obtained.

1 Cowie MR, Mosterd A, Wood DA. The epidemiology of heart failure. *Eur Heart J* 1997;18:208-25.
2 Khan NK, Goode KM, Cleland JG, Rigby AS, Freemantle N, Eastaugh J, et al. Prevalence of ECG abnormalities in an international survey of patients with suspected or confirmed heart failure at death or discharge. *Eur J Heart Fail* 2007;9:491-501.
3 Clark AL, Goode K, Cleland JG. The prevalence and incidence of left bundle branch block in ambulant patients with chronic heart failure. *Eur J Heart Fail* 2008;10:696-702.
4 Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, de Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-50.
5 Witte KK, Sasson Z, Persaud JA, Jolliffe R, Wald RW, Parker JD. Biventricular pacing: impact on exercise-induced increases in mitral insufficiency in patients with chronic heart failure. *Can J Cardiol* 2008;24:379-84.
6 Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-53.
7 Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE-ICD Trial. *JAMA* 2003;289:2685-94.
8 Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;344:873-80.
9 Freemantle N, Tharmanathan P, Calvert MJ, Abraham WT, Ghosh J, Cleland JG. Cardiac resynchronisation for patients with heart failure due to left ventricular systolic dysfunction—a systematic review and meta-analysis. *Eur J Heart Fail* 2006;8:433-40.
10 Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539-49.
11 Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J* 2006;27:1928-32.
12 Yao G, Freemantle N, Calvert MJ, Bryan S, Daubert JC, Cleland JG. The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. *Eur Heart J* 2007;28:42-51.
13 Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology, Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008;29:2388-442.
14 Upadhyay GA, Choudhry NK, Auricchio A, Ruskin J, Singh JP. Cardiac resynchronization in patients with atrial fibrillation: a meta-analysis of prospective cohort studies. *J Am Coll Cardiol* 2008;52:1239-46.
15 Foley PW, Chalil S, Khadjooi K, Smith RE, Frenneaux MP, Leyva F. Long-term effects of cardiac resynchronization therapy in octogenarians: a comparative study with a younger population. *Europace* 2008;10:1302-7.
16 Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation* 2008;117:2608-16.
17 Cleland J, Freemantle N, Ghio S, Fruhwald F, Shankar A, Marijanowski M, et al. Predicting the long-term effects of cardiac resynchronization therapy on mortality from baseline variables and the early response. A report from the CARE-HF (Cardiac Resynchronization in Heart Failure) Trial. *J Am Coll Cardiol* 2008;52:438-45.
18 Chattopadhyay S, Alamgir MF, Nikitin NP, Fraser AG, Clark AL, Cleland JG. The effect of pharmacological stress on intraventricular dyssynchrony in left ventricular systolic dysfunction. *Eur J Heart Fail* 2008;10:412-20.
19 Daubert JP, Zareba W, Cannom DS, McNitt S, Rosero SZ, Wang P, et al. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency, mechanisms, predictors, and survival impact. *J Am Coll Cardiol* 2008;51:1357-65.
20 Healey JS, Hallstrom AP, Kuck KH, Nair G, Schron EP, Roberts RS, et al. Role of the implantable defibrillator among elderly patients with a history of life-threatening ventricular arrhythmias. *Eur Heart J* 2007;28:1746-9.
21 Yap YG, Duong T, Bland JM, Malik M, Torp-Pedersen C, Køber L, et al. Optimising the dichotomy limit for left ventricular ejection fraction in selecting patients for defibrillator therapy after myocardial infarction. *Heart* 2007;93:832-6.
22 Desai AS, Fang JC, Maisel WH, Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. *JAMA* 2004;292:2874-9.
23 Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225-37.
24 Thackray SD, Witte KK, Nikitin NP, Clark AL, Kaye GC, Cleland JG. The prevalence of heart failure and asymptomatic left ventricular systolic dysfunction in a typical regional pacemaker population. *Eur Heart J* 2003;24:1143-52.
25 Witte KK, Pipes RR, Nanthakumar K, Parker JD. Biventricular pacemaker upgrade in previously paced heart failure patients—improvements in ventricular dyssynchrony. *J Cardiol Fail* 2006;12:199-204.
26 Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation* 2003;107:2932-7.
27 Beshai JF, Grimm RA, Nagueh SF, Baker JH 2nd, Beau SL, Greenberg SM, et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med* 2007;357:2461-71.
28 Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C, et al. 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;52:1834-43.
29 Uretsky BF, Thygesen K, Daubert JC, Erdmann E, Freemantle N, Gras D, et al. Predictors of mortality from pump failure and sudden cardiac death in patients with systolic heart failure and left ventricular dyssynchrony: results of the CARE-HF trial. *J Cardiol Fail* 2008;14:670-5.
30 Witte KK, Clark AL. Dyspnoea versus fatigue: Additional prognostic information from symptoms in chronic heart failure? *Eur J Heart Fail* 2008;10:1224-8.
31 Cleland JG, Freemantle N, Daubert JC, Toff WD, Leisch F, Tavazzi L. Long-term effect of cardiac resynchronisation in patients reporting mild symptoms of heart failure: a report from the CARE-HF study. *Heart* 2008;94:278-83.