REVIEW

Device based treatment of heart failure

A Y Patwala, D J Wright

Postgrad Med J 2005;81:286–291. doi: 10.1136/pgmj.2004.026716

As the population ages and survival from ischaemic heart disease improves, the incidence and prevalence of congestive cardiac failure has increased dramatically. Medical treatments including ACE inhibitors, β blockers, and aldosterone antagonists have improved the outlook for most patients. However, despite optimal medical treatment there is a significant group of patients who continue to suffer poor morbidity and mortality. Device based treatment consisting of implantable cardioverter defibrillators (ICD) and cardiac resynchronisation therapy (CRT) devices offer new modes of treatment to patients with symptomatic heart failure despite optimal medical therapy. ICDs have been shown to reduce mortality in patients with severe heart failure while CRT leads to an improvement in functional class, quality of life scores, physiological measures such as peak VO_2 , and reduce hospitalisations. Combination devices, which provide both ICD and CRT functions, have now been seen to provide synergistic benefits in selected patients.

Congestive cardiac failure is a common condition, which has now reached epidemic proportions. In the UK it affects between 1% and 3% of the general population^{1,2} and increases with age to affect 10% of those over 70.² This represents only those patients who are symptomatic, in a recent population based study in England it was shown that the prevalence of left ventricular (LV) systolic dysfunction (defined as an ejection fraction (EF) <40%) in patients aged 45 years and above was 1.8%, and of these 47% had no symptoms.¹ As the population ages and survival from ischaemic heart disease improves the prevalence is likely to increase further. In a simulation model it was shown that between 1985 and 2010 there is likely to be a 70% increase in absolute numbers of heart failure patients.³ In the past decade there have been many important advances in the pharmacological treatment of heart failure, however the condition continues to exact a heavy burden in terms of mortality and morbidity.⁴ Death attributable to heart failure may be sudden (usually arrhythmic) or attributable to progressive heart failure⁵ with gradual deterioration in symptoms. The one year mortality has been shown to increase with worsening symptomatic heart failure. This was 5%–15% for NYHA class II, 20%–50% for class III, and >50% for class IV.^{6–8} The five year mortality after the

diagnosis of heart failure remains about 50%.^{9–11} In the UK heart failure has been reported to consume more than 2.5% of the total healthcare expenditure.² With such continued impact from heart failure we require new modes of treatment in addition to those currently available to improve mortality and morbidity.

MEDICAL TREATMENTS

Pharmacological treatment for heart failure is described in the NICE guidelines¹² and is designed to improve symptoms and reduce mortality. In heart failure there is overexpression of components of the renin-angiotensin-aldosterone and sympathetic nervous systems. This has been shown to suppress myocardial function, cause myocardial hypertrophy and myocyte apoptosis leading to mural thinning and progressive dilatation.¹³ Therefore modulation of these neurohormonal changes has become the cornerstone of treatment. Three main classes of drugs have been shown to improve mortality and symptoms namely drugs affecting the renin-angiotensin system (including angiotensin converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARB)), β adrenoceptor blockers, and aldosterone antagonists.

There have been 34 trials assessing ACE inhibitors in heart failure. A review of all 34 trials showed a significant reduction in total mortality ($p < 0.001$) and combined end point of mortality or hospitalisation ($p < 0.001$).¹⁴ In animal models it has been shown that despite adequate ACE inhibition there is still near normal production of angiotensin II, via ACE independent pathways, within the myocardium.¹⁵ It was therefore postulated that block of the renin-angiotensin system at the angiotensin II type 1 receptor level would be more beneficial than ACE inhibition. In a meta-analysis of 17 trials looking at ARB the results showed that when ARB were compared with placebo there was a non-significant trend towards improved survival ($p = 0.19$) and decreased hospitalisation ($p = 0.33$) with ARB treatment. When ARB were compared with ACE inhibitors there was no difference in survival or hospitalisation and when ARB were added to ACE inhibitors and compared with ACE inhibitors alone there was no difference in mortality but there was a significant reduction in hospitalisation ($p < 0.0001$).¹⁶

Abbreviations: ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronisation therapy; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; MI, myocardial infarction; EPS, electrophysiological study; RV, right ventricular; LV, left ventricular; BiV, biventricular; EF, ejection fraction

See end of article for authors' affiliations

Correspondence to:
Dr A Patwala, The
Cardiothoracic Centre,
Thomas Drive, Liverpool
L14 3PE, UK; a_patwala@
lineone.net

Submitted 12 July 2004
Accepted
19 September 2004

β Adrenoceptor blockers have been shown to significantly improve the functional status ($p = 0.04$),¹⁷ reduce hospitalisation ($p < 0.01$)¹⁷ ($p = 0.036$)¹⁸, reduce all cause mortality ($p = 0.0062$)⁵ ($p < 0.001$)¹⁸ ($p < 0.0001$)¹⁹, and reduce sudden death ($p = 0.0002$)⁵ ($p = 0.0011$)¹⁹.

Two main aldosterone antagonists, namely spironolactone and eplerenone, have been studied in addition to standard treatment, and both produced a significant reduction in mortality ($p < 0.001$)²⁰ ($p = 0.008$)²¹ and morbidity ($p < 0.001$)²⁰ ($p = 0.002$)²¹. Further symptomatic treatment is achieved using diuretics and digoxin.²²

A combination of the above drugs is now widely accepted as being the optimum medical treatment for heart failure however it has been shown that full implementation of evidence based doses is rarely achieved in clinical practice.^{23–25} This is despite the fact that clinical studies have shown that ACE inhibitors at maximum doses are well tolerated by around 80%–90% of patients with chronic heart failure.^{26–27} The ATLAS trial has shown the importance of achieving the maximum tolerated dose. In this large scale trial it was shown that there was a greater benefit to be gained from high dose (32.5–35 mg) compared with low dose (2.5–5 mg) lisinopril in patients with heart failure.²⁸ Unfortunately in a substantial number of patients despite receiving optimal medical treatment they continue to suffer with poorly controlled symptoms and a high risk of death.^{18–29–32} Device based treatment offers new options to prevent both sudden death and death attributable to progressive heart failure using implantable cardioverter defibrillators and cardiac resynchronisation therapy devices respectively.³⁰

IMPLANTABLE CARADIOVERTER DEFIBRILLATORS

The mechanism of sudden death in heart failure patients was assessed in a sub-study of the ATLAS trial. This found that 51% of patients with sudden death had a causative primary arrhythmic event.³³ In view of this high incidence of potentially reversible arrhythmia many trials have evaluated ways of preventing sudden death.

Initially antiarrhythmic drugs were used in post-myocardial infarction (MI) patients with impaired LV function. CAST and CAST II used class I antiarrhythmic agents (encainide, flecainide, or moricizine) compared with placebo. Both trials were terminated prematurely because of increased mortality ($p = 0.0004$)³⁴ ($p = 0.40$)³⁵ in the antiarrhythmic group. In view of these results the focus switched to amiodarone, and to date there have been 13 randomised trials performed.^{36–48} Only three of these have reported a significant reduction in overall mortality.^{36–38} A meta-analysis of all 13 trials showed that there was a 13% reduction in mortality with amiodarone ($p = 0.03$) and a 29% reduction in arrhythmic death ($p = 0.0003$). There was virtually no effect of amiodarone on non-arrhythmic death.⁴⁹

In the mid-1990s attention began to switch towards the use of ICDs. Initially ICDs were compared against antiarrhythmic agents (mainly amiodarone) in patients who had been resuscitated from ventricular arrhythmias. Three large scale multicentre trials have been carried out. AVID found a significant reduction in mortality in the ICD group ($p < 0.02$),⁵⁰ CIDS found a non-significant 19.7% reduction in all cause mortality ($p = 0.142$) and a non-significant 32.8% reduction in the risk of arrhythmic mortality with ICD therapy ($p = 0.094$),⁵¹ and CASH found a non-significant 23% reduction in all cause mortality in the ICD group ($p = 0.081$).⁵² A meta-analysis showed that there was an overall 28% reduction in mortality ($p = 0.0006$) and that this was entirely attributable to a 50% reduction in arrhythmic deaths ($p < 0.0001$). The meta-analysis also showed that

patients with a LVEF $>35\%$ had significantly less benefit from ICD than those with a EF $<35\%$ ($p = 0.011$).⁵³

ICDs were thus established as the treatment of choice in preventing sudden death in patients after resuscitation for ventricular arrhythmias. The next step was to decide whether non-arrest but high risk patients would benefit from ICDs. The high risk group initially identified were patients with LV dysfunction after MI with history of non-sustained ventricular tachycardia (at least three beats) and a positive electrophysiological study (EPS) (defined as inducible non-suppressible ventricular tachyarrhythmias). The two trials looking at this were MADIT I and MUSTT. Both studies randomised patients to treatment with either an ICD or conventional treatment. MADIT I found a 54% reduction in mortality with ICD treatment ($p = 0.009$)⁵⁴ while MUSTT showed a 76% reduction in cardiac arrest or death from arrhythmia in patients treated with an ICD ($p < 0.001$).⁵⁵ The MUSTT trial also showed treatment with serial electrophysiological drug testing without ICD back up, even when a drug was found that effectively suppressed VT induction, had no significant benefit compared with no treatment.⁵⁶

The MADIT II trial researchers reasoned that in patients with a prior MI and advanced LV dysfunction the scarred myocardium would serve as a substrate for ventricular arrhythmia, and therefore EPS testing would not be required for risk stratification.⁵⁷ They therefore took 1232 patients with a history of a previous MI and an EF $<30\%$ and randomised them, without any further testing, to either implantation of a ICD or conventional treatment. In the group with an ICD there was a 31% reduction in mortality compared with optimal conventional treatment ($p = 0.016$). The greatest reduction was seen in those patients with a QRS width >150 ms.⁵⁸ Despite EPS inducibility not being an inclusion criteria 593 patients in the ICD arm underwent EPS testing at the time of ICD implantation. EPS inducibility at baseline did not differentiate between those who were more likely to require ICD therapy for termination of ventricular tachycardia or fibrillation from those who were not.⁵⁹

Most recently the results from SCD-HeFT were reported at the American College of Cardiology's annual scientific session (March 2004). This study took 2521 patients with ischaemic or non-ischaemic NYHA class II and III chronic heart failure and EF $<35\%$, and compared the effects of ICD with amiodarone and with placebo on all cause mortality. There was no significant difference between the placebo and amiodarone group, however the ICD group had a significant 23% reduction in mortality ($p = 0.007$). The improvement in mortality was independent from the aetiology of the heart failure and the benefit was greater in the group with NYHA class II, rather than class III, heart failure.⁶⁰

ICD therapy has therefore become the treatment of choice in primary and secondary prevention of ventricular arrhythmias. Table 1 shows the current NICE guidelines for ICD implantation. However, while it is known that ICDs reduce sudden death, it has now been shown that recurrent ICD discharges are associated with psychological disturbances.⁶¹ Therefore the combination of antiarrhythmic drugs and ICDs are now being investigated. In the only double blinded trial looking at the addition of an antiarrhythmic to patients with a ICD, it was shown that the addition of sotalol led to a 48% reduction in death or first ICD shock ($p < 0.001$).⁶² The evidence for amiodarone is less robust, the CASCADE study was designed to compare amiodarone with EPS guided therapy, however during the course of the trial ICD placement became standard to both groups and in the amiodarone group there were significantly fewer shocks associated with syncope ($p = 0.032$) and a non-significant reduction in total number of shocks ($p = 0.14$)⁶³

Table 1 Current NICE guidelines for ICD implantation

Secondary prevention	Cardiac arrest attributable to either ventricular tachycardia (VT) or ventricular fibrillation (VF) Spontaneous sustained VT causing syncope or significant haemodynamic compromise Sustained VT without syncope/cardiac arrest, and who have an associated reduction in ejection fraction (less than 35%) but are no worse than III of New York Heart Association functional classification of heart failure.
Primary prevention	A history of previous myocardial infarction (MI) and: non-sustained VT on Holter (24 hour ECG) monitoring. Inducible VT on electrophysiological testing. Left ventricular dysfunction with an ejection fraction (EF) less than 35% and no worse than III of the New York Heart Association functional classification of heart failure. A familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, arrhythmogenic right ventricular dysplasia (ARVD), and after repair of tetralogy of Fallot.

CARDIAC RESYNCHRONISATION THERAPY

Conduction system delay (for example, LBBB) occurs as a consequence of the underlying pathophysiological disease in patients with chronic heart failure and results in dyssynchronous ventricular contractions. This triggers adaptive chamber dilatation and neurohormal stimulation⁶⁴ leading to diminished contractile reserve of the heart⁶⁵ and inefficient myocardial contraction.⁶⁶ The mean QRS duration increases as the severity of chronic heart failure increases. The percentage of people with a QRS > 120 ms has been shown to be 9.7% for New York Heart Association (NYHA) class 0–I, 32% for NYHA class II, and 53% for NYHA class III.³¹ In a sub-study of the VEST trial increased QRS width was a independent predictor of mortality ($p < 0.0001$).⁶⁷

Studies were devised to reverse LBBB using temporary pacing wires connected to an external pacemaker box, delivering right ventricular (RV), left ventricular (LV), or biventricular (BiV) pacing. These studies showed RV pacing led to no significant improvement over no pacing.^{68–70} BiV and LV pacing was shown to increase the mean cardiac index ($p < 0.006$),⁶⁸ decrease the pulmonary capillary wedge pressure ($p < 0.01$),^{68–70} decrease mean V wave ($p < 0.004$)⁶⁸ ($p < 0.001$)⁷⁰, increase the systolic blood pressure ($p < 0.03$)⁷⁰ ($p < 0.0001$)⁷¹, and increase the maximum LV pressure derivative ($p < 0.01$)⁶⁹ ($p < 0.0001$)⁷¹. In some of these studies LV pacing had a more beneficial effect than BiV pacing ($p < 0.05$)⁶⁹ ($p < 0.01$)⁷¹. This may have been attributable to the fact that in the BiV pacing group there was synchronous stimulation of both ventricles however this does not recapture the normal activation of the two ventricles and therefore may be suboptimal.⁷²

In view of these acute haemodynamic changes CRT devices were developed with right atrial and ventricular leads as seen in a dual chamber pacemaker and an additional lead that is passed through the coronary sinus to the LV free wall (see fig 1). The pacemaker can then mimic the intrinsic conduction system and ensure that atrial and synchronised ventricular contractions occur to achieve optimal cardiac function and thereby improve symptoms (see fig 2).

Initially small scale observational studies, including PATH-CHF ($n = 41$),⁷³ MUSTIC ($n = 67$)⁷⁴ and the multicentre InSync study ($n = 103$),⁷⁵ were carried out to assess the effects of CRT on symptoms and functional capacity. All the patients were receiving optimal medical treatment but still had persistent symptoms. Treatment with a CRT device led to an improvement in quality of life scores ($p < 0.001$),^{73–75} NYHA class ($p < 0.001$),^{73–75} six minute walk test distance ($p < 0.001$),^{73–75} peak Vo_2 ($p < 0.001$)⁷³ ($p < 0.03$)⁷⁴, and decreased hospitalisations ($p < 0.05$).⁷⁴ In addition CRT was shown to reduce myocardial oxygen consumption,⁷⁶ which is most probably because of decreased LV wall stress through improved coordination of the wall contractions.^{77–78} This is significant as most heart failure treatments directly increasing systolic function do so while also increasing myocardial oxygen consumption. The only other treatment shown to reduce myocardial oxygen consumption but improve systolic function is β block.⁶⁵ Corresponding to these haemodynamic and functional benefits, studies have also shown that CRT leads to a reduction in the LV end diastolic and end systolic volumes and also a improved myocardial performance index.^{75–79–80}

The MIRACLE trial was the first large scale randomised clinical trial looking at CRT in heart failure. A total of 453

Figure 1 (A) PA chest radiograph showing CRT device and leads in a patient with previous mitral and aortic valve replacement. (B) Lateral chest radiograph of the same patient.

patients with moderate to severe heart failure, EF <35%, and QRS durations >130 ms were recruited after successful implantation of a CRT device. The patients were randomised to have the device switched on or off to act as controls. In the active treatment group there was a significant improvement in the six minute walk distance ($p = 0.005$), the functional class ($p < 0.001$), quality of life scores ($p = 0.001$), treadmill exercise time ($p = 0.001$), and EF ($p < 0.001$). The active treatment group also required less hospitalisation or intravenous medication ($p < 0.05$).⁸¹ In a sub-study echocardiograms were performed before and after treatment with a CRT device. In the active treatment group the echocardiograms showed a reduced end diastolic and end systolic volumes ($p < 0.001$), decreased LV mass ($p < 0.01$), reduced mitral regurgitation ($p < 0.001$), improved EF ($p < 0.001$), and improved myocardial performance index ($p < 0.001$).⁸² Therefore the MIRACLE trial showed that CRT improved both symptoms and echocardiographic appearance in patients with moderate to severe heart failure.

It was hypothesised that CRT might improve prognosis in patients with chronic heart failure attributable to the increase in exercise capacity and peak VO_2 . When a meta-analysis of the above trials was carried out it showed that CRT led to a significant 51% reduction in deaths from progressive heart failure (odds ratio (OR) 0.49, 95% confidence intervals (CI) 0.25 to 0.93), a significant 29% reduction in heart failure

hospitalisations (OR 0.71, 95%CI 0.53 to 0.96), and a non-significant 23% reduction in all cause mortality (OR 0.77, 95%CI 0.51 to 1.18). It also showed that CRT had no effect on non-heart failure mortality (OR 1.15, 95%CI 0.65 to 2.02) and was not associated with a reduction in ventricular tachycardia or fibrillation (OR 0.92, 95%CI 0.67 to 1.27).⁸³ Attention thus began to focus on combination devices with both CRT and ICD functions, the latter having been shown to have the greatest impact on mortality in patients fitting selection criteria for the former in MADIT II. Two multicentre randomised trials have evaluated the effect of a combination cardiac resynchronisation and defibrillator device in patients with heart failure, namely the COMPANION trial and the MIRACLE ICD trial.

The COMPANION trial was a three arm study of 1520 patients with NYHA class III/IV heart failure despite optimal treatment. The inclusion criteria were evidence of a conduction system delay on 12 lead ECG (either a PR interval >150 ms or a QRS interval >120 ms), LVEF <35%, end diastolic LV size >60 mm, and hospitalisation for heart failure in the past year. The patients were randomised to drug treatment only, insertion of a CRT device, or insertion of a combination device.⁸⁴ The results showed that the primary end point (all cause mortality and all cause hospitalisation) was reduced by 19% in the CRT only group ($p = 0.014$) and by 20% in the CRT+ICD group ($p = 0.01$). Total mortality was

Figure 2 (A) ECG of a patient before CRT with left bundle branch block (LBBB). (B) After CRT ECG of the same patient showing biventricular pacing.

Current ACC/AHA/NAPSE guidelines for CRT (2002)

- Patients with symptomatic heart failure (New York Heart Association class III or IV) despite optimal medical treatment.
- Prolonged QRS width (greater than 130 ms) on 12 lead ECG.
- Left ventricular end diastolic diameter greater than 55 mm.
- Ejection fraction less than 35%.

reduced by a non-significant 24% in patients receiving CRT alone ($p = 0.059$) and by a significant 36% in the CRT+ICD group ($p = 0.003$).⁸⁵

The MIRACLE ICD trial had 369 patients with NYHA III/IV heart failure on optimal treatment, with an EF <35% and a QRS interval >130 ms. All the patients had a combination device placed, in the control group ($n = 182$) the CRT portion of the device was switched off, in the active treatment group ($n = 187$) the CRT portion was switched on. All of the patients had the ICD facility switched on. At six months after device implantation, the active treatment group showed improved quality of life scores ($p = 0.02$), improved functional class ($p = 0.007$), improved peak oxygen consumption ($p = 0.04$), and improved exercise function on a treadmill ($p < 0.001$). No pro-arrhythmic tendencies were seen in the active treatment group. In this group there was also no impairment of arrhythmia termination capabilities by the ICD portion. Unfortunately, the MIRACLE ICD trial was not powered or designed to evaluate an effect on mortality.⁸⁶

These two trials therefore showed that combination devices could be used safely to provide a significant improvement in both symptoms and mortality. The current ACC/AHA/NAPSE guidelines for CRT insertion are shown in the box, NICE are currently in the process of establishing guidelines for CRT and these should be available in the near future.

However, the trials have also shown some potential problems. Implantation time is long, median duration in MIRACLE was 2.7 hours.⁸¹ Placement of a lead in the coronary sinus has proved to be difficult in some patients, with failure rates of between 8% to 12%.^{81, 86} and lead dislodgement in up to a further 12%.⁸⁶ As operator experience improves and more advanced leads are introduced the failure rate should decrease. However, in a small group the anatomy of the coronary sinus will preclude satisfactory placement of a transvenous lead and an epicardially placed lead must be considered.

The other potential problem identified from the trials above is that around 15%–35% of patients who have a CRT device implanted are non-responders when classic indications are used.⁸⁷ The probable reason for this is that a wide QRS width may not be the most accurate method of evaluating cardiac dyssynchrony. In a recent study it was shown that the presence of intra-LV asynchrony on tissue Doppler echocardiography was an independent predictor of worsening heart failure requiring periodic hospitalisation ($p < 0.001$) and that 56% of patients with a EF <45% but with a normal QRS width (<120 ms), who would under the current criteria not be suitable for CRT, had evidence of major intra-LV asynchrony,⁸⁸ and therefore were potentially suitable for CRT. When echocardiographic parameters were used to assign patients to CRT treatment it was shown that the response rate increased to 85%.⁸⁹

The treatment options available for heart failure patients, has undergone a substantial increase over the past two decades.

CRT and ICD devices have been shown individually and in combination to improve mortality and morbidity in patients with severe heart failure already receiving optimal medical treatment. They should thus be considered in patients with resistant symptoms and at high risk of sudden death.

Authors' affiliations

A Y Patwala, D J Wright, The Cardiothoracic Centre, Liverpool, UK

Funding: none.

Conflicts of interest: none declared.

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