Overview of devices in advanced heart failure

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Abbreviations

AHA: American Heart Association

ATP: antitachycardia pacing

CRT-D: cardiac resynchronisation therapy defibrillator

CRT-P: cardiac resynchronisation therapy pacemaker

DCM: dilated cardiomyopathy

ESC: European Society of Cardiology

HF: heart failure

HFREF: heart failure with reduced ejection fraction

ICD: implantable cardioverter defibrillator

LBBB: left bundle branch block

LV: left ventricular

LVEF: left ventricular ejection fraction

RCT: randomised controlled trial

RV: right ventricular

Introduction

Despite advances in medical therapy, heart failure (HF) is associated with high mortality. The United Kingdom National Heart Failure Audit reported that during hospital admission for HF the in-patient mortality was 9.5%, with a one-year mortality of 27% in 2013-14 [1]. There is also huge morbidity associated with the condition, representing 5% of emergency admissions and almost 20% of readmissions to hospital. Heart failure prevalence is more common in the elderly, with 10% of people over 75 being affected.

Heart failure due to reduced left ventricular ejection fraction (HFREF) is treated mainly by medication, including ACE inhibitors, beta-receptor blockers and mineralocorticoid receptor antagonists. These treatments have a very good evidence base for improving symptoms and life expectancy. Despite this, many patients remain symptomatic. Advanced HF represents a stage of the disease where patients' symptoms are resistant to therapy and they remain very

limited and at risk of lethal ventricular arrhythmia. In patients who meet the appropriate criteria, device therapy - either an implantable cardioverter defibrillator (ICD), a cardiac resynchronisation therapy pacemaker (CRT-P) or a cardiac resynchronisation therapy defibrillator (CRT-D) - may offer substantial benefit.

In patients with HFREF (particularly with a left ventricular ejection fraction [LVEF] under 35%), there is a risk of lethal arrhythmia (mainly ventricular arrhythmia) despite medical therapy. An ICD can detect these arrhythmias and treat them with antitachycardia pacing (ATP) and, if this is unsuccessful, defibrillation. In patients with HFREF who also have a QRS duration on their electrocardiogram (ECG) of greater than 120 milliseconds, a CRT-P can improve symptoms and prognosis. A CRT-D offers both CRT-P and ICD capability. ICDs and CRT will be discussed separately in this review.

The current use of devices in advanced HF is difficult to calculate exactly. Estimates of CRT implant rates vary hugely from 1:10,000 to 140 per million population in 2011. Calculating the potential number of patients who would benefit from CRT is again fraught with difficulty, with estimates varying between 1:1,000 and 400 per million population. International guidelines are addressing the need to deliver devices in this patient group but both guideline adherence and its implementation must be monitored carefully.

Implantable cardioverter defibrillators (ICDs)

ICDs have been in use for the last thirty years. Initially, they were much larger than they are now and were implanted under general anaesthetic with the generator in the abdomen with epicardial patches; however, over time, the generator has become smaller and can be placed subcutaneously in the pectoral region where pacemakers are implanted, and the leads are placed endocardially in the venous system. The devices can act as pacemakers, and can deliver ATP and shocks via the coils on the lead and the generator.

The decision to implant ICDs should be discussed in detail with patients and their family. As well as being made aware of the risks associated with the actual procedure itself, it is important that patients are aware of any driving restrictions (depending on the licensing authority of the country where they live), the lifetime risks of the device itself, including the need for future generator replacements, lead failure, potential advisories, the potential risk of infection with these procedures, and the small but definite risk of inappropriate therapy. They should be aware that, when a patient is at the “end of life”, the therapies for ventricular arrhythmia may be discontinued to prevent the distress of recurrent shocks. Appropriate written information should be provided to the patient. There are now also many useful websites where this information is available.

Indications for ICDs in patients with heart failure

Secondary prevention

Patients who have haemodynamically unstable ventricular tachycardia or ventricular fibrillation have a class I indication for a defibrillator in both the ESC and AHA guidelines [2,3]. There are three randomised controlled trials (RCTs) where the efficacy of ICDs was examined in secondary prevention. When the results were combined in a meta-analysis, there was a statistically significant reduction in absolute mortality with ICDs [4]. The largest benefit was seen in patients who had a low ejection fraction.

Primary prevention

The two large principal RCTs of patients with HF which suggest a benefit of ICDs in this category are MADIT-II and SCD-HeFT. Both demonstrated a statistically significant relative risk reduction in overall mortality (in the order of 20 to 30%) in patients with an ICD compared to those receiving medical treatment alone [5,6]. The ESC recommend that ICD implantation is a class I indication in patients with an ejection fraction under 35% who are in NYHA Class II-III despite being on optimal medical therapy for three months and who are expected to live for more than 12 months [2]. The AHA guidelines are very similar to this [3].

The risk of sudden death is greater in ischaemic cardiomyopathy (ICM) (10% over 20 months in the MADIT-II cohort) than in dilated cardiomyopathy (DCM), therefore the risk reduction afforded by an ICD is greater in ICM. A meta-analysis of studies examining the efficacy of ICDs in patients with DCM demonstrated a mortality reduction with ICD; however, a recently published RCT demonstrated no benefit in such a group of patients with ICDs [7,8]. One possible explanation for this is that the medical therapy in the recent study was much better than that taken by patients in older studies which significantly decreased the risk of ventricular arrhythmia, mitigating the benefit of the ICD.

Programming strategies

The most common indication for ICD implantation in patients with HF is the primary prevention of sudden death. Previously, the focus of ICD programming has been to have a short detection time for ventricular arrhythmias before therapy (through either ATP or shocks) is delivered. It has become apparent, however, that a large proportion of ventricular tachycardias within these detection zones self-terminate and therefore therapy is unnecessary. Furthermore, short detection times have been associated with a higher rate of inappropriate shocks. Several trials (and meta-analyses) have since suggested that having longer detection times or detection zones at higher rates (greater than 200 beats per minute) reduces both inappropriate and appropriate therapy, improving outcomes without increasing syncope or mortality [9]. As a result, ICDs now being implanted for primary prevention are commonly programmed as a “shock box” with a single therapy zone above 200 beats per minute.

Right ventricular pacing in patients with impaired ventricular function is associated with worsening HF [10]. Therefore, these devices are only programmed to pace when the heart rate is low, for example 40 beats per minute.

Cardiac resynchronisation therapy (CRT)

The use of CRT was first described more than 30 years ago and multiple RCTs have since

demonstrated an improvement in symptoms, exercise capacity, left ventricular function and outcomes (including all-cause mortality) with this therapy. It is primarily aimed at patients with advanced HF (NYHA functional Class III and ambulatory Class IV) who have a left ventricular ejection fraction under 35%, who are in sinus rhythm, and have a QRS duration above 120 ms. The procedure is more complicated than for an ICD because, as well as a right atrial and right ventricular lead, a pacing lead is placed in a branch of the coronary sinus, normally on the posterolateral surface of the heart.

CRT targets patients who have abnormal electrical activation and therefore abnormal mechanical activation which in turn leads to further cardiac inefficiency and performance. The abnormal electrical activation is represented as a prolonged QRS duration on ECG and commonly left bundle branch block (LBBB). The abnormal activation pattern is termed dyssynchrony and can be intraventricular (delayed activation within the left ventricle – normally lateral wall contraction is significantly delayed), interventricular (delayed activation of one ventricle with respect to the other), and atrioventricular where atrial transport to the ventricle is impaired. The atrial synchronised pacing from the right ventricle and left ventricle provided by CRT allows the correction of this cardiac dyssynchrony and improvement of cardiac function.

Evidence for CRT

The patients who benefit most from CRT are those with very wide QRS durations (above 150 ms) and those with LBBB morphology [11,12]. In the ESC guidelines, symptomatic patients with LBBB with a QRS duration greater than 120 ms have a class I indication for CRT, whereas those who have non-LBBB morphology (with a QRS duration greater than 120 ms) have a class II indication [13]. COMPANION and CARE-HF are the two large RCTs which demonstrated a beneficial effect of CRT (both CRT-P and CRT-D) on outcomes (HF hospitalisation or all-cause mortality) in patients with advanced HF [14,15]. The majority of patients were in NYHA Class III.

Further trials have evaluated the effect of CRT in patients with less symptomatic HF (mainly NYHA Class II). There was an improvement in hospitalisation for HF in all studies. In a meta-analysis of these trials there was also a statistically significant reduction in all-cause mortality [16]. The ESC guidelines therefore do not distinguish between patients with advanced or mild HF and state that patients in NYHA Class II, III and ambulatory Class IV patients who fulfil the previously described criteria have an indication for CRT [13]. AHA guidelines strongly mirror the ESC guidelines, except that CRT is also recommended in NYHA Class I patients (who have an LVEF <30%, have ischaemic heart disease, are in sinus rhythm and have LBBB with QRS duration greater than 150 ms) [17].

CRT in patients with atrial fibrillation

Only a few patients with permanent AF have been included in RCTs evaluating CRT; however, in real-world practice AF and HF frequently overlap and, correspondingly, CRT is implanted in a large number of patients. Overall, the literature suggests a worse response with CRT with patients in permanent AF than when in sinus rhythm. A critical barrier for response is that the

underlying conduction from atria to ventricle in AF prevents delivery of CRT and in most studies the amount of CRT delivered is suboptimal. When there is close to 100% CRT delivery in patients with AF (either via medication or AV junction ablation), symptomatic and objective benefits are seen. A systematic review demonstrated that after AV junction ablation there was a significant improvement in mortality and morbidity compared to patients where this was not undertaken [18]. ESC guidelines recommend CRT (with a class II indication) in patients with AF who are in NYHA Class III or ambulatory Class IV and have a QRS duration greater than 120 ms with an LVEF under 35% despite optimal medical therapy, provided close to 100% biventricular pacing is achieved. CRT is also recommended in patients who have AF with uncontrolled heart rates (despite medication), with reduced LVEF who will require AV junction ablation [13].

CRT in patients with bradycardia

There is a clear detrimental effect of a high degree of right ventricular pacing in patients who already have LV dysfunction and HF [10]. In these patients who already have a conventional pacemaker or ICD, there is therefore an option to upgrade these devices to a CRT device where there is a large burden of right ventricular pacing. This practice is already widespread and represents a substantial proportion of CRT implants. Several RCTs have reported improvements in symptoms, cardiac function and HF admissions in patients who have had CRT upgrades [19]. The ESC guidelines have therefore recommended CRT upgrade as a class I indication in patients with a high degree of RV pacing who have an LVEF under 35%, who are in NYHA Class III and ambulatory Class IV [13].

Given the harmful effects of RV pacing in patients with LV dysfunction, there is emerging evidence that, in patients who have an indication for pacing because of a slow heart rate (where there is anticipation of a high burden of RV pacing), CRT should be offered. The largest randomised controlled trial to date in such a cohort of patients reported a reduction in HF admissions with patients assigned to CRT compared with those having conventional RV pacing [20]. ESC guidelines have therefore recommended this as a class II indication for CRT implantation in such patients [13].

Complications

Despite the substantial benefits afforded by CRT, this comes at a price, namely an increased complication rate. There are two main reasons for this. The first is related to patient factors. Given that CRT is implanted in patients with HF, these patients tend to be more unwell and have more comorbidities (e.g., diabetes, renal impairment, increased age and frailty), which increases the risk of complications, especially infection. A large proportion of these patients will also be on anticoagulation and/or antiplatelet medication, which will further increase the risk of haematoma and bleeding. The second reason is related to the procedure itself. CRT is a longer and technically more challenging procedure than conventional ICD and pacemaker implantation, and therefore the complication risk of the procedure is higher. A large meta-analysis of CRT trials looking at 9,000 patients has shown this, with a more than 5% rate of

failure to implant the LV lead, a 3.2% risk of mechanical complication, a 1.4% risk of infection and a 6% risk of lead problems [16]. The complication risk with CRT upgrade or revision procedures is even higher.

Therefore, given the risk of complications, it is important that the procedural risks and benefits are tailored to the individual patient and carefully discussed with the patient and their family before undertaking such a procedure, especially in cases where the outcome is less certain.

CRT non-response

It has been consistently shown in CRT trials that 60-70% of patients respond positively but the other 30-40% of patients are unchanged or get worse. There has been a lot of research into identifying the reasons for “non-response”. There are several causes for this, including those related to patients and those related to the cardiac phenotype and the device itself. In this review, some of these factors have already been discussed: low QRS duration, the presence of non-LBBB QRS morphology and the presence of AF all increase the chance of non-response. Patients with DCM tend to have a better response than patients with ICM: this is probably related to a larger scar burden in ischaemic heart disease, especially if the LV lead is overlying an area of scar. Response is higher in women than in men. Patients with more comorbidities, such as renal impairment and anaemia, tend not to respond as well. LV lead position also probably influences response and the presence of the lead in an apical position is associated with worse outcomes.

CRT-D vs. CRT-P

The decision whether to implant a CRT defibrillator or CRT pacemaker in patients with HF is not completely clear. There is the obvious benefit of CRT-D over CRT-P regarding the treatment of ventricular arrhythmia; however, there is no RCT comparing the two treatments. It is likely that CRT-D would offer a greater reduction in outcome if there was an RCT, but it would require the study to recruit a very large number of patients and may only demonstrate a small benefit. Furthermore, the complication rate and cost with CRT-D is higher than with CRT-P. Factors which may guide CRT-P implantation would be the presence of advanced HF and the presence of major comorbidities. CRT-D, on the other hand, may be of greater benefit in patients with less symptomatic heart failure and a lack of comorbidities. It is important that patients and their carers are given the appropriate information about both therapies so that an informed decision can be made.

Cost, cost-effectiveness and reimbursement

In the United Kingdom in 2011, the average cost for an ICD, a CRT-P and a CRT-D was estimated at £9,692, £3,411, and £12,293, respectively. These amounts, however, do not include additional costs to the provider such as overheads and implantation. In different analyses, all three types of cardiac device have been shown to be cost-effective, with costs per QALYs of less than £30,000 (approximately 35,000 euros at the time of publication).

In order to cover the costs of implanting these devices, the healthcare organisations in the majority of countries in Europe reimburse the costs to hospitals. However, there is substantial variation between countries in how these costs are calculated and implemented, depending on the healthcare financing environment that is present in the country. Reimbursement policy is one cause of the variation in device implantation that exists between countries and between regions within a given country. Despite the clinical benefits and cost-effectiveness of these devices, the increasing financial burden on healthcare of the tariffs involved, though this may become lower in the future, is putting pressure on hospitals to avoid device implantation – an action which might ultimately be detrimental to care for eligible patients.

Conclusion

Device therapy is now well established in pathways for treating patients with heart failure. It is important that all patients who are eligible can have these procedures made available to them. There remains a great deal of inconsistency in device prescription between countries and regions and this needs to be addressed.

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Conflict of interest:

The author has no conflicts of interest to declare.