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Device therapy

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ABSTRACT 'Device therapy' refers to the use of implantable electronic devices to improve cardiac rhythm and function. Permanent pacemakers, initially developed in the 1960s to prevent bradycardia in patients with sinus node disease and atrioventricular block, represented the first wave of implantable devices that transformed cardiology practice. These devices are now commonplace, and advances in microprocessor and battery cell technology mean that pacemakers are small and highly programmable to patients' individual requirements. Since then, this same technological revolution has led to the development of other implantable devices used in the treatment of patients with life-threatening ventricular tachyarrhythmias and with heart failure. The main focus of this article will be on these new advances in device therapy.

KEYWORDS Device therapy, heart failure

LIST OF ABBREVIATIONS Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), Cardiac resynchronisation therapy (CRT), cardiac resynchronisation therapy defibrillator (CRT-D), coronary artery bypass grafting (CABG), electrophysiological (EP), implantable cardioverter-defibrillators (ICDs), left bundle branch block (LBBB), left ventricular ejection fraction (LVEF), myocardial infarction (MI), National Institute for Clinical Excellence (NICE), New York Heart Association (NYHA), optimal pharmacological therapy (OPT), ventricular fibrillation (VF), ventricular tachycardia (VT)

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IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

Drug therapy for ventricular arrhythmias is limited by pro-arrhythmia – the potential for anti-arrhythmic agents to trigger a potentially hazardous arrhythmia. The only agents known to safely reduce risk of sudden death in patients with coronary heart disease and cardiomyopathies are beta-blockers (CIBIS-II). Amiodarone, used as secondary prevention in patients who have already suffered ventricular fibrillation, does reduce risk but has a formidable side-effect profile. For primary prevention (e.g. in patients after MI) benefit is not established. No new anti-arrhythmic agents have been licensed for general use in Europe in the last two decades.

ICD technology and implantation

Device therapy for malignant ventricular arrhythmias was developed in recognition of the limitation of drug therapies. The implantable defibrillator was initially a large device, implanted in the abdomen, and requiring a cardiac surgeon to attach an epicardial patch electrode to the heart to allow defibrillation. Surgical morbidity was significant, device lifespan short, and arrhythmia diagnostics crude. In the 1990s, rapid advances in technology led to the development of transvenous ICD systems that could be implanted like a permanent pacemaker. The ICD lead is placed in the right ventricle, and has one or two shock coils (see Figure 1). It delivers a shock between the coils and the casing of the device itself. These devices not only provide defibrillation function (see Figure 2), but also can recognise and treat ventricular tachycardia by overdrive pacing (see Figure 3) and have all of the functions of a bradycardia pacemaker. Dual-chamber devices are suitable for patients with AV nodal block, and have an enhanced ability to discriminate between ventricular and supraventricular arrhythmias by sensing both the atrial and ventricular rhythm. Implantation is normally done under conscious sedation. At the time of implant, ventricular fibrillation is induced to

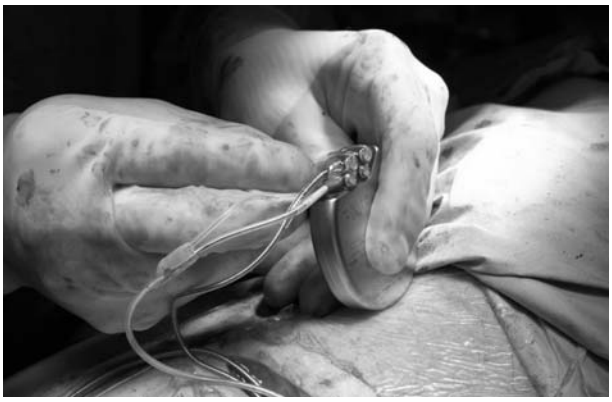

FIGURE 1 Implantable cardioverter-defibrillator and lead.

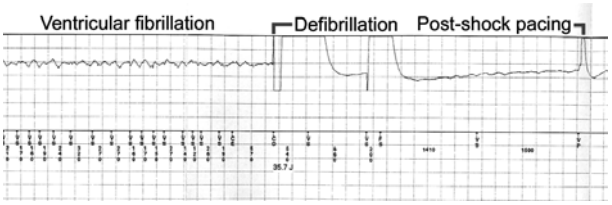

FIGURE 2 Implantable cardioverter-defibrillator device printout showing successful defibrillation.

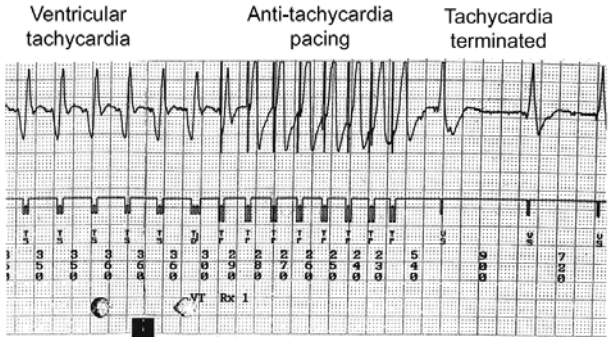

FIGURE 3 Implantable cardioverter-defibrillator device printout showing successful overdrive pacing (anti-tachycardia pacing) for ventricular tachycardia.

TABLE 1 Landmark implantable cardioverter-defibrillator clinical trials.

Trial	Patients	Therapies	*n*	Outcomes
AVID	Resuscitated VF, or VT with one of: LVEF <40%; syncope; haemodynamic compromise.	ICD vs anti arrhythmics (mainly amiodarone)	1,016	39% reduction in mortality at one year and 31% reduction in mortality at three years (p=0·02) in favour of ICD therapy.
MADIT	Post-MI, LVEF ≤35%, non-sustained VT on ambulatory monitor, inducible non-suppressible VT at EP study.	ICD+ OPT vs OPT (incl. amiodarone)	196	51% mortality reduction at mean follow-up 27 months with ICD therapy (p=0·009).
CABG-PATCH	Post-CABG, LVEF ≤35%, abnormal signal-averaged ECG.	ICD + OPT vs OPT	900	No significant difference in mortality when ICD used as primary prevention after CABG.
CIDS	Resuscitated VF or VT, or unmonitored syncope. No restriction in LVEF.	ICD vs amiodarone	659	22% reduction in all-cause mortality (p=0·14) and 33% reduction in arrhythmic mortality (p=0·094); neither statistically significant.
MADIT-2	At least six months post-MI, LVEF ≤30%.	OPT vs ICD+ OPT	1,232	31% mortality reduction over average 20 month follow-up (p=0·016).
DINAMIT	MI within past 6–40 days, LVEF ≤35%, impaired heart rate variability.	OPT vs ICD + OPT	676	No significant mortality reduction with ICD therapy at six months.
SCD-HeFT	NYHA class II or III heart failure with LVEF ≤35%.	OPT vs ICD + OPT	2,521	23% mortality reduction at average 45·5 month follow-up (p=0·007).

determine whether the sensing and defibrillation functions operate correctly for the individual patient. A rescue external shock can be given in the rare event that the device fails to defibrillate, and procedural morbidity and mortality are extremely low. At implantation, the ICD is programmed with several rate 'zones' to allow the device therapies to be tailored to the patient's own arrhythmia rates. Since heart rate is the principal means by which an ICD decides on the rhythm diagnosis, inappropriate shocks are sometimes experienced by ICD patients who develop rapidly conducted supraventricular arrhythmias. Modern ICDs incorporate QRS morphology analysis and atrial rhythm analysis to minimise the risk of this.

ICD evidence base

As devices have become smaller, implant technique more straightforward, and clinical trial data have accumulated, the indications for ICD implantation have widened. A summary of the main ICD trials is given in Table 1. These can be divided into primary and secondary prevention trials. The AVID trial was the first major trial to demonstrate mortality benefit in patients treated with ICDs who had survived VF or haemodynamically significant VT. For primary prevention (i.e. prevention of arrhythmic death in a high-risk population who had not yet had a significant arrhythmic event) the MADIT trial used a complex means of selecting patients at risk of sudden death after MI, which involved invasive electrophysiological testing of patients with impaired left ventricular function who had non-sustained ventricular tachycardia on ambulatory ECG monitoring. Mortality reduction was demonstrated in that trial, but the screening process was unwieldy. Electrophysiogical testing has been subsequently shown to be a poor means of identifying high-risk patients, and the more recent MADIT-2 trial demonstrated that ICD therapy reduces mortality in patients after myocardial infarction who have a LVEF less than 30% without subjecting them to an electrophysiological test. The more recent DINAMIT study has indicated that the timing of ICD implantation after myocardial infarction is important, and that the ICD

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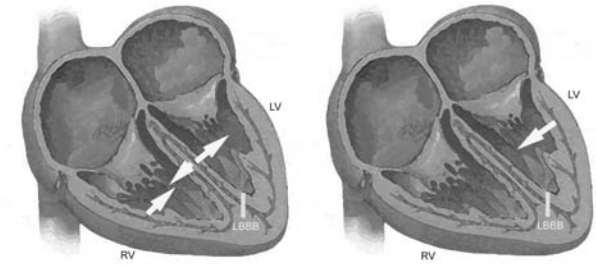

FIGURE 4 Diagram showing the concept of left ventricular dys-synchrony.

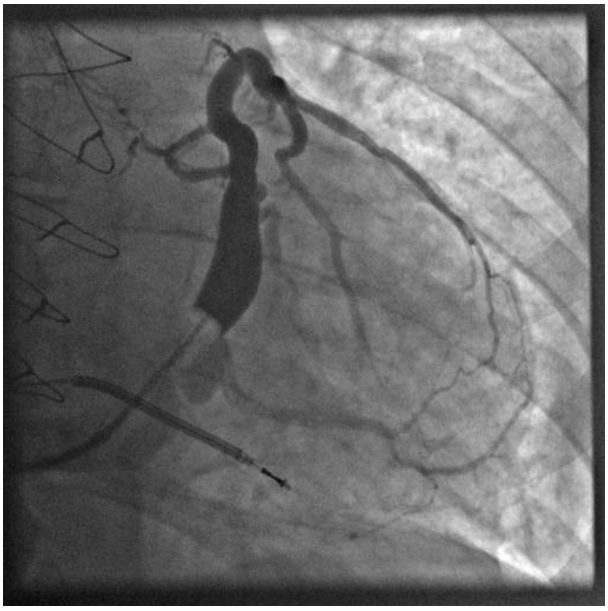

FIGURE 5 Coronary sinus angiogram showing the coronary venous tree.

should be implanted at least one month after the event (CABG-PATCH). Implantable cardioverter-defibrillators are also indicated for patients with inherited cardiac conditions (such as long QT syndrome and hypertrophic cardiomyopathy) in whom high risk markers are identified (e.g. history of syncope or family history of sudden death or arrhythmia), and in selected patients with surgically corrected congenital heart disease.

Most recently, ICDs have been shown to be effective in primary prevention for selected patients with NYHA functional class II and III heart failure due to left ventricular systolic function (SCD-HeFT). This study included patients with ischaemic heart disease and with dilated cardiomyopathies. In many countries, including the UK, the theoretical indications for ICD implantation have outstripped the ability of the healthcare system to deliver this therapy to all of these patients. In the UK, the original NICE guidance was based mainly on the MADIT and AVID trial indications. The updated guidance will not fully adopt the extended primary prevention indications suggested by the MADIT-2 and SCD-HeFT trials. Implantable cardioverter-defibrillator therapy is expensive, although device and implantation costs

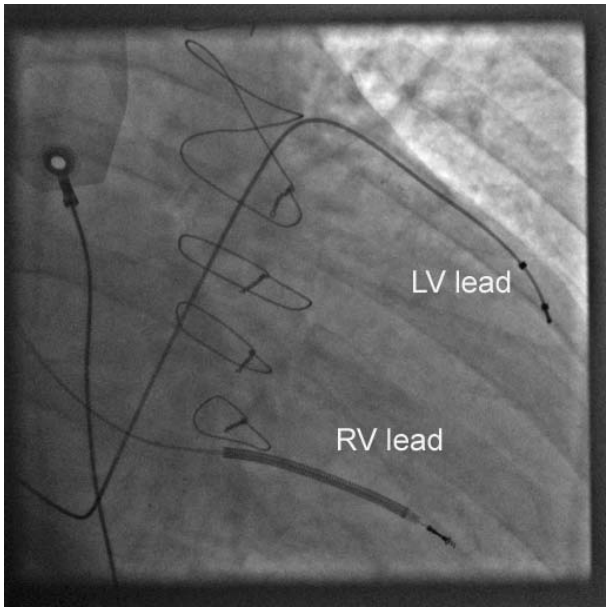

FIGURE 6 Cardiac resynchronisation therapy system.

are falling with time. Cost-effective assessments are critically dependant on ever-changing device costs. As was the case with permanent pacemakers for bradycardia, uptake is slow while infrastructure develops, but it is likely that healthcare systems will eventually adopt ICD therapy as part of the standard care of patients with heart failure or significant left ventricular dysfunction after MI.

Other considerations

Implantable cardioverter-defibrillators should not be implanted in patients with major co-morbidity or end-stage heart failure, and for secondary prevention are not indicated in patients with a clear reversible trigger for their index arrhythmia (e.g. hyperkalaemia, drug overdose). Since ICDs do not prevent ventricular arrhythmia, but rather react to them when they occur, medical therapy needs to be kept optimal in these patients. Most patients with an ICD will have a medical indication for a beta-blocker, and for patients who experience recurrent defibrillator shocks, amiodarone may be required. Psychological problems such as anxiety are relatively common in ICD patients, particularly those who receive frequent shocks from their device. Patients should be warned before ICD implantation that driving restrictions exist – in the UK, for secondary prevention ICDs, driving is not allowed for six months, and for primary prevention for one month. Implantable cardioverter-defibrillator patients are not permitted to drive heavy goods or public service vehicles.

CARDIAC RESYNCHRONISATION THERAPY

CRT – how it works

Approximately 20% of patients with heart failure due to left ventricular systolic dysfunction have LBBB. This conduction

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TABLE 2 Landmark cardiac resynchronisation therapy clinical trials.

Trial	Patients	Therapies	*n*	Outcomes
MIRACLE	NYHA III, IV	CRT + OPT vs OPT alone	453	62% reduction in all-cause hospitalisation (p=0·002); 81% reduction in heart failure hospitalisation (p=0·035). Strong trend for reduction in mortality (OR 0·49 but NS).
COMPANION	NYHA III, IV	CRT + OPT vs CRT-D + OPT vs OPT alone	1,520	CRT: 19 % reduction in all-cause mortality or first hospitalisation (p= 0·015). CRT-D: 36% reduction in all-cause mortality (p= 0·004).
CARE-HF	NYHA III, IV	CRT + OPT vs OPT alone	813	37% reduction in all-cause mortality and hospitalisation. 36% reduction in mortality.

TABLE 3 Indications for cardiac resynchronisation therapy (from CARE-HF study).

- Sinus rhythm.
- Left ventricular ejection fraction ≤35%.
- QRS duration >150 ms or QRS duration ≥120 ms and echo evidence of dys-synchrony.
- NYHA class III or IV heart failure.
- On optimal medical therapy.

abnormality can result in desynchronisation of left ventricular systolic contraction by causing a delay in the contraction of the posterolateral left ventricle relative to the septum. This phenomenon is known as left ventricular dys-synchrony (see Figure 4). Dys-synchrony has a significant negative impact on cardiac haemodynamics and on symptoms. Cardiac resynchronisation therapy partially corrects this abnormality by simultaneous pacing of the septum and left ventricular free wall. The CRT device is similar to a conventional dual-chamber pacemaker, but has an additional ventricular lead which is introduced via a guiding catheter into the coronary venous system via the coronary sinus, which drains into the right atrium. Coronary sinus angiography is used to identify a target vein, ideally on the lateral aspect of the left ventricle (see Figure 5), and the left ventricular lead is introduced over an angioplasty guide wire and wedged into the vein (see Figure 6). Cardiac resynchronisation therapy devices work by sensing sinus node activity via the atrial lead, and simultaneously pacing both ventricles in response to each sensed sinus beat. For this reason, CRT has not yet been extensively evaluated in patients with atrial fibrillation. Typical implant times are 90–120 minutes, and LV lead displacement rates are relatively high at around 5–8 %, necessitating re-operation. Procedure-related complication rates are otherwise low, with mortality rates of 0–2·1% in reported studies and low rates of infection.

Evidence base for CRT

Current CRT practice is the product of an evolution of lead and device technology, evaluated through a stepwise series of progressively larger clinical trials (see Table 2). Current indications for CRT are summarised in Table 3. The MIRACLE study showed that CRT significantly improves exercise time, NYHA functional class, and quality of life, and reduces heart failure related hospitalisations. Of particular interest in that study was a trend toward mortality reduction, suggesting that left ventricular resynchronisation may exert an anti-arrhythmic effect. In recognition of the fact that patients with impaired LV systolic function are at increased risk of death through ventricular arrhythmias, CRT devices have been developed that incorporate a defibrillator function (CRT-D). These devices are substantially more expensive and are physically bulkier than CRT pacemakers, but the implantation technique is the same. The COMPANION study compared OPT (beta-blocker, diuretics, and angiotensin-converting enzyme inhibitors) with CRT + OPT and CRT-D + OPT to examine the incremental contributions of resynchronisation and defibrillation on outcome. A twenty-four percent reduction in mortality was observed with CRT (p=0·059) and a 36% reduction with CRT-D (p=0·003). The observation that CRT alone probably significantly reduces the risk of death was finally confirmed in the CARE-HF study, a large trial which demonstrated a 36% reduction in all-cause mortality. Cardiac resynchronisation therapy is included in the current NICE guidance on heart failure management for patients who broadly meet the criteria set out in Table 3.

Cardiac resynchronisation therapy is generally performed in cardiac centres that provide an electrophysiology service, but can theoretically be performed in any pacemaker implantation centre with access to high quality fluoroscopic screening. After device implantation, pacemaker settings are optimised using echocardiographic guidance. The atrioventricular delay is optimised to maximise the diastolic filling period and to prevent pre-systolic mitral regurgitation which is common in patients with heart failure. The ventriculo-ventricular delay (i.e. the relative timing of septal and left ventricular pacing) can also be optimised. Patients are reviewed every six months and if symptomatic, settings can be re-optimised.

Other considerations

Responses to CRT are often immediate and dramatic, and patients who do respond are usually much improved by the therapy. However, not all patients derive benefit from

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CRT. Perhaps one in four patients will not experience significant symptomatic benefit, and this has led to intensive research into the best means of selecting likely responders. In general, patients with heart failure due to dilated cardiomyopathy do well with CRT, while the experience is more mixed in patients with underlying coronary heart disease. It may not be possible to resynchronise left ventricular contraction in some patients who have extensive LV free wall infarct zones. It is likely that refinements in echocardiographic techniques will afford us the best means of selecting patients for CRT.

Economic substudies place CRT on a par with other modalities of heart failure treatment in terms of cost effectiveness. This is because the initially high procedure cost is largely offset by reduction in the need for hospital admission. The cost per quality-adjusted life year is around €29,000.

KEYPOINTS

- Implantable cardioverter-defibrillators reduce mortality in patients who have survived ventricular fibrillation or haemodynamically significant ventricular tachycardia, and for high-risk patients after recovery from MI.
- Implantable cardioverter-defibrillators should not be implanted in patients with major co-morbidity or end-stage heart failure.
- Cardiac resynchronisation therapy significantly improves symptoms, exercise tolerance, and quality of life in patients with sinus rhythm, moderate to severe heart failure, and left ventricular dys-synchrony.
- Recent trials also show that CRT reduces mortality, and that CRT-D may have an incremental mortality benefit.

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