NATIONAL INSTITUTE FOR HEALTH
AND CLINICAL EXCELLENCE

Multiple Technology Appraisal

Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120)

Submission for: **Heart Rhythm UK**

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Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
AF	atrial fibrillation
ARVC	arrhythmogenic right ventricular cardiomyopathy
AVJ	atrio-ventricular junction (node)
BHF	British Heart Foundation
CASQ2	cardiac calsequestrin gene 2
cMR	cardiac magnetic resonance imaging
CPVT	catecholaminergic polymorphic ventricular tachycardia
CRT	cardiac resynchronisation therapy
CRT-D	implantable cardioverter defibrillator delivering cardiac resynchronisation therapy
CRT-P	pacemaker delivering cardiac resynchronisation therapy
DCM	dilated cardiomyopathy
ECG	electrocardiogram
EF	ejection fraction
ESC	European Society of Cardiology
HCM	hypertrophic cardiomyopathy
HF	heart failure
HRS	Heart Rhythm Society
ICD	implantable cardioverter defibrillator
IHD	ischaemic heart disease
LBBB	left bundle branch block
LQTS	long QT syndrome
LV	left ventricle
LVEF	left ventricular ejection fraction
LVNC	non-compaction of the left ventricle
MI	myocardial infarction
MuGA	multi-gated acquisition (scan)
NICM	non-ischaemic cardiomyopathy
NYHA	New York Heart Association (functional class)
ms	millisecond
OPT	optimal pharmacological (medical) therapy
QT	ECG interval between first deflection of the QRS complex and end of the T wave
QTc	QT interval corrected for heart rate
RBBB	right bundle branch block
RYR2	cardiac ryanodine receptor gene 2
SCD	sudden cardiac death
SICD	subcutaneous implantable cardioverter defibrillator
SPECT	single photon emission computed tomography (scan)
TdP	torsades de pointes
TGA	transposition of the great arteries
ToF	tetralogy of Fallot
VF	ventricular fibrillation
VT	ventricular tachycardia

Clinical trial acronyms and principal publications

Acronym	Trial name	Abbreviated reference
AMIOVERT	Amiodarone Versus Implantable Cardioverter-Defibrillator	*J Am Coll Cardiol* 2003; **41**:1707–12
AVID	Antiarrhythmics Versus Implantable Defibrillators	*N Engl J Med* 1997;**337**:1576-83
CABG-Patch	Coronary Artery Bypass Graft Patch	*N Engl J Med* 1997;**337**:1569-75
CARE-HF	Cardiac Resynchronization Heart Failure	*N Engl J Med* 2005;**352**:1539-49.
CASH	Cardiac Arrest Study Hamburg	*Circulation* 2000;**102**:748-754
CAT	Cardiomyopathy Trial	*Circulation* 2002, **105**:1453-1458
CIDS	Canadian Implantable Defibrillator Study	*Circulation* 2000;**101**:1660-1664
COMPANION	Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure	*N Engl J Med* 2004;**350**:2140-50
CONTAK-CD	Boston Scientific device name	*J Am Coll Cardiol* 2003;**42**:1454–9
DEFINITE	Defibrillators in Non-Ischaemic cardiomyopathy Treatment Evaluation	*Circulation* 2006;**113**;776-782
DINAMIT	Defibrillator in Acute Myocardial Infarction Trial	*N Engl J Med* 2004;**351**:2481-8
HOBIPACE	Homburg Biventricular Pacing Evaluation	*J Am Coll Cardiol* 2006;**47**:1927–37
MADIT	Multicenter Automatic Defibrillator Implantation Trial	*N Engl J Med* 1996;**335**:1933-40
MADIT II	Multicenter Automatic Defibrillator Implantation Trial II	*N Engl J Med* 2002;**346**:877-83
MADIT-CRT	Multicenter Automatic Defibrillator Implantation Trial Cardiac Resynchronization Trial	*N Engl J Med* 2009;**361**:1329-38
MIRACLE ICD	Multicenter InSync ICD Randomized Clinical Evaluation	*JAMA* 2003;**289**:2685-2694
MOST	Mode Selection Trial	*Circulation* 2003;**107**:2932–7
MUSTIC	Multicenter InSync Randomized Clinical Evaluation	*N Engl J Med* 2002;**346**:1845-53
MUSTT	Multicenter UnSustained Tachycardia Trial	*J Am Coll Cardiol* 2001;**38**:344 –51
PROSPECT	Predictors of Response to CRT	*Circulation* 2008;**117**:2608-2616
RAFT	Resynchronization–Defibrillation for Ambulatory Heart Failure Trial	*N Engl J Med* 2010;*363*:2385-95
RethinQ	Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS trial	*N Engl J Med* 2007;**357**:2461-71
REVERSE	REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction	*J Am Coll Cardiol* 2008;**52**:1834–43
SCD-HeFT	Sudden Cardiac Death Heart Failure Trial	*N Engl J Med* 2005;**352**:225-37

1) Executive summary

This appraisal concerns implanted devices which deliver electrical therapy to the heart to treat life-threatening heart rhythm disorders (implantable cardioverter defibrillators, ICDs) and/or dyssynchrony of cardiac contraction (cardiac resynchronisation therapy, CRT). A single device can deliver either or both of these therapies. The therapies have different indications, but the indications are often present in the same individuals so it is appropriate to consider the technologies together in a single appraisal process. This mirrors clinical decision making where a choice is first made between continuing medical therapy and device implantation and then between treatment modalities. Since the publication of NICE guidance covering ICDs in 2006 and CRT in 2007, further trial data, meta-analyses and international guidance have been published making it appropriate to revise and combine this guidance. All patients should receive optimal pharmacological therapy – any device should be considered as an addition to this. Contraindications to device therapy should also be assessed. Patients should have their condition and treatment options clearly explained in order to make a fully informed decision.

1.1) Implantable cardioverter defibrillators (ICDs)

ICDs monitor and treat ventricular arrhythmias automatically within seconds. They are used in patients who have survived a cardiac arrest because of the high risk of recurrence (secondary prevention), and in patients at high risk of sudden cardiac death but who may have no history of ventricular arrhythmia (primary prevention). The majority of ICD patients have structural heart disease due to myocardial infarction or cardiomyopathy, a much smaller number have primary inherited electrical abnormalities. The pivotal clinical trials of ICD therapy in secondary prevention were conducted in the 1990s with more recent clinical trials in primary prevention. Increasing data from rarer conditions have subsequently become available.

Key points:

- ICD therapy is superior to medical therapy for patients surviving a cardiac arrest or spontaneous sustained ventricular arrhythmia with haemodynamic compromise – it is considered unethical to perform further clinical trials in this population.
- Syncope has been shown to be prognostically equivalent to spontaneous recovery from a cardiac arrest or spontaneous ventricular arrhythmia with haemodynamic compromise in high-risk individuals.
- The cause of cardiomyopathy – ischaemic or non-ischaemic – does not significantly influence the effectiveness of ICD therapy and these should be regarded as equivalent indications.
- Left ventricular function is a significant predictor of risk. Other stratifiers including non-sustained ventricular tachycardia, ventricular tachycardia induced by programmed electrical stimulation and QRS duration have limited sensitivity or specificity to predict those who will and will not benefit from ICD implantation.
- Measurement of left ventricular ejection fraction is imprecise. Currently available measurement techniques require estimation of left ventricular volumes and have inherent uncertainty. Although clinical trials used a variety of LVEF levels as inclusion criteria, the patients randomised in the major clinical trials had relatively uniform LVEF estimates. For these reasons, we advocate the adoption of a single threshold of severe left ventricular systolic impairment equivalent to an LVEF of ≤35%.

- There are rare conditions associated with sudden cardiac death for which there is no prospect of a randomised controlled trial of ICD therapy. In these situations the best available data and clinical judgement should be used to inform treatment decisions.

1.2) Cardiac resynchronisation therapy (CRT)

The implantation of a CRT device, which stimulates contraction of the left and right ventricles, can significantly improve electrical synchronisation, reducing heart failure symptoms and all-cause mortality. Recent trials have shown benefit in patients with mild heart failure symptoms.

Key points:

- Patients with severe left ventricular impairment (LVEF ≤35%), evidence of dyssynchrony on ECG (QRS ≥120ms) and heart failure symptoms despite optimal pharmacological therapy benefit from CRT with improved symptoms, reduced hospitalisation and reduced all-cause mortality.
- Other measures of mechanical dyssynchrony have not shown sufficient sensitivity and specificity to be clinically useful in the identification of patients who will benefit from CRT.
- The full benefit of CRT is achieved in those receiving a high proportion of biventricular pacing – for patients in atrial fibrillation this may require pharmacological or ablation therapy to induce atrioventricular block.

1.3) Treatment delivery

To achieve the clinical and cost-effectiveness outcomes demonstrated in clinical trials requires a high quality, efficient assessment, implantation and follow-up service. The patients who benefit from ICD and/or CRT treatment often have complex medical conditions with multiple co-morbidities and are implanted with complex devices which require highly specialised programming. Much device follow-up can now be achieved through remote internet-based data transfer, reducing the burden of travel on patients and their carers. Heart Rhythm UK recommends that device implantation and follow-up should be performed by high-volume operators in appropriately resourced high-volume centres.

Access to ICD and CRT therapy is low and uneven across the UK compared to other developed countries. This is caused by differences in ascertainment, differences in assessment and the complexity of current UK and international guidance. The exclusion of non-ischaemic cardiomyopathy from previous NICE guidance has contributed to differences in practice across the UK. It is important to develop guidance which is clear, memorable and efficient to deliver. Clinical trial protocols are developed to test specific hypotheses. The direct adoption of their inclusion and exclusion criteria into guidance would lead to complex and potentially contradictory treatment indications. We recommend a pragmatic approach, taking the best available evidence as a whole to produce clear, workable guidance to improve access to evidence-based treatments equitably across the UK.

1.4) Guidance Recommendations

Based on the currently available data, we recommend that patients on optimal pharmacological therapy, in the absence of a fully reversible cause (including an arrhythmia which can be prevented by ablation therapy), with expectation of life expectancy of ≥1 year and with a quality of life acceptable to the patient:

Patients with LVEF ≤35% (regardless of aetiology) should routinely be considered for a device based on their symptoms (NYHA functional class) and QRS duration:

	NYHA I	NYHA II	NYHA III	ambulant NYHA IV
QRS <120ms	ICD	ICD	ICD	OPT
120-149 no LBBB	ICD	ICD	CRT-D	CRT-D
120-149 + LBBB	CRT-D	CRT-D	CRT-D	CRT-D
≥150ms	CRT-D	CRT-D	CRT-D	CRT-D

CRT-P (pacemaker) implantation should be offered in place of CRT-D (defibrillator) when ICD therapy is contraindicated or declined by the patient.

1) **Patients with LVEF >35%** (without NYHA IV symptoms):
   - with spontaneous sustained ventricular arrhythmias
     or
   - with inherited conditions with high risk features for sudden cardiac death according to the best available evidence

     should routinely be considered for: ICD

2) ICD implantation should not be performed within 4 weeks of a myocardial infarction or revascularisation unless the patient has a secondary prevention indication.

2) Background information

2.1) Arrhythmias

The heart is a muscular pump controlled by specialised electrical tissues. Normal heart function requires optimal electrical coordination of contraction. Any abnormal cardiac rhythm, or arrhythmia, which disturbs normal physiological sinus rhythm, reduces cardiac efficiency. Arrhythmias arising in the ventricles, ventricular tachycardia (VT) and ventricular fibrillation (VF), can result in insufficient blood being pumped by the heart to sustain life. This is the mechanism of over 80% of sudden cardiac deaths, killing 90,000 people in the UK each year. The most common risk factor for sudden cardiac death is ischaemic heart disease but other causes of reduced cardiac function such as cardiomyopathy also increase this risk. There are also many rare inherited conditions which increase the risk of ventricular arrhythmias and sudden death, particularly in younger people.

The most effective way to prevent cardiac arrhythmias is to the treat the underlying heart condition with medications and other interventions. Prevention is an essential part of every patient's management, but the only effective treatment once a life-threatening ventricular arrhythmia has occurred is electrical defibrillation. This can be performed with an external defibrillator but unfortunately, because of the short time before irreversible brain damage occurs, only 5% of people survive a cardiac arrest outside a hospital. The alternative is implantation of an automatic device, an implantable cardioverter defibrillator (ICD).

2.2) Implantable cardioverter defibrillators (ICDs)

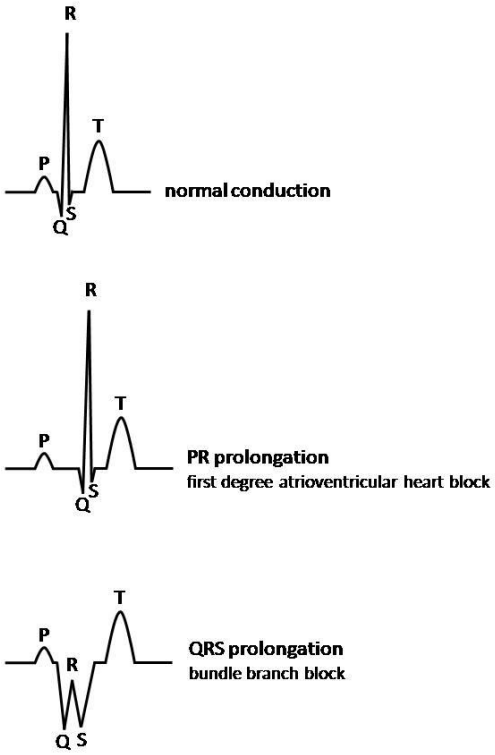
An ICD is an electronic device implanted in a patient at increased risk of life-threatening arrhythmias. It monitors cardiac rhythm continuously and automatically delivers therapy in the form of rapid low-voltage pacing and/or high voltage defibrillation shocks within a few seconds of a dangerous ventricular arrhythmia being detected. Most devices implanted in the UK comprise one or more leads placed transvenously in the heart and connected to a device implanted beneath the skin of the chest. These devices are all capable of pacing functions to treat slow heart rhythms (bradycardia). This technology is recommended in NICE technology appraisal 95 which states that ICD implantation is indicated for primary (no previous cardiac arrest or ventricular arrhythmia with haemodynamic compromise) and secondary (resuscitated cardiac arrest or ventricular arrhythmia with haemodynamic compromise) prevention. A recently developed subcutaneous ICD (SICD) is able to detect arrhythmias and deliver defibrillation using a lead which is placed under the skin of the chest but does not enter the heart. SICDs represent an alternative method of delivering ICD therapy. This assessment examines indications for therapy rather than methods of delivering therapy. The SICD is being considered by the Interventional Procedures Advisory Committee (IPAC - http://guidance.nice.org.uk/IP/1012).

2.3) Heart failure

Heart failure is a complex syndrome of signs and symptoms which results from the heart's inability to supply the circulatory requirements of the body. Heart failure is common, affecting around 900,000 people in the UK with almost as many again having asymptomatic left ventricular dysfunction. The incidence and prevalence of heart failure increase steeply with age, so our ageing population, improvements in the survival of people with ischaemic heart disease and more effective medical and interventional treatments, mean that the number of people affected will

continue to increase. Heart failure has a worse prognosis than many cancers, with up to 40% of patients dying within a year of diagnosis, and a greater effect on quality of life than many other chronic diseases such as chronic lung disease and arthritis. Most heart failure is caused by structural heart disease resulting from ischaemic or non-ischaemic cardiomyopathy. Heart failure also occurs in patients with preserved ejection fraction. These patients have not been shown to benefit from device therapy and are not included in the remit of this document. The medical management of heart failure in adults in primary and secondary care is described in the NICE National Clinical Guideline Centre (2010) Chronic heart failure: the management of chronic heart failure in adults in primary and secondary care. London: National Clinical Guideline Centre (http://guidance.nice.org.uk/CG108/Guidance/pdf/English).

People with normal cardiac function have considerable cardiovascular reserve and can tolerate significant physiological and pathological cardiovascular stresses. People with reduced cardiac function have greatly reduced reserve. Anything which reduces cardiac efficiency further can have a dramatic effect on their symptoms and quality of life. Approximately 30% of patients with heart failure due to left ventricular systolic dysfunction have sub-optimal coordination of heart contraction. This is described as atrio-ventricular and/or intra-ventricular dyssynchrony which is seen on the 12-lead ECG as a prolonged PR interval and/or increased QRS complex duration:



2.4) Left ventricular ejection fraction

The left ventricular ejection fraction (LVEF) represents the proportion of blood expelled by the left ventricle during systolic contraction. It was originally developed as an estimate of cardiac function and was derived from contrast ventriculography. It is now most commonly estimated from echocardiography although nuclear scans (multi-gated acquisition, MuGA, and SPECT) and cardiac magnetic resonance imaging (cMR) are alternatives. Each of these modalities has its limitations and sources of error. Because of these differences, a patient undergoing LVEF estimation by different modalities will have different estimates. Equally, it must be recognised that LVEF is not

fixed but varies with loading conditions, biochemical and neuro-hormonal status. Nevertheless, multiple invasive and non-invasive risk stratifiers have been developed and used in clinical trials but none has surpassed LVEF as a predictor of sudden cardiac death.

Clinical trials have adopted a variety of LVEF inclusion criteria: MUSTT used LVEF ≤40% although the median ejection fraction of randomised patients was 30% with a range of 20 to 35%. Most other trials adopted ≤35% although MADIT II used ≤30% resulting in a mean or 25 ± 5% in the ICD treated group. As current North American device guidance states, "the determination of LVEF lacks a "gold standard" and ... there may be variation among the commonly used clinical techniques. All clinical methods of LVEF determination lack precision, and the accuracy of techniques varies amongst laboratories and institutions". Heart Rhythm UK recommends the adoption of "severely impaired" as the most clinically appropriate criterion for increased risk of sudden cardiac death and likely benefit from CRT. This is internationally defined by echocardiography as an LVEF of ≤35% (Lang *et al. J Am Soc Echocardiogr* 2005;**18**:1440–1463) and is consistent with the majority of published cardiac rhythm management device trial data.

2.5) New York Heart Association functional class

The current classification of heart failure symptoms was first proposed by the New York Association of Cardiac Clinics and published by White and Myers in 1921 (*JAMA* 1921;**77**:1414-1415). It evolved with increasing cardiovascular knowledge into the New York Heart Association functional classification. The currently accepted definitions were published by the Criteria Committee of the New York Heart Association in Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Edition Boston, Mass: Little, Brown & Co; 1994:253-256.

Functional Capacity Objective Assessment	
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnoea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Despite the day-to-day variability in patients' symptoms and the subjective nature of some of the assessments, NYHA functional class has proven to be robust in its clinical utility and prognostic accuracy. It remains the best assessment of functional capacity available in heart failure patients.

2.6) Cardiac resynchronisation therapy (CRT)

Conventional bradycardia pacemakers comprise leads connecting the right atrium and/or ventricle to a computerised device implanted beneath the skin of the chest. They monitor heart rhythm continuously and deliver electrical stimulation to induce myocardial contraction when the heart falls below a pre-specified rate or ventricular contraction does not follow atrial contraction after a

pre-specified interval. In this way, they can prevent bradycardia and restore synchronisation between atrial and ventricular contraction.

In heart failure patients with abnormal electrical conduction, synchronisation can be improved by the implantation of a device which can sense and stimulate the right atrium and/or ventricle as in a conventional pacemaker but with the addition of a lead directly pacing the left ventricle. This is usually placed in a branch of the coronary sinus, the vein draining blood from the muscle of the left ventricle into the right atrium. This CRT functionality can be added to a pacemaker (CRT-P) or an ICD (CRT-D) and can improve cardiac function and reduce heart failure symptoms.

2.7) Optimal pharmacological therapy (OPT)

There is excellent evidence for the efficacy of medical treatments in reducing mortality and improving quality of life for patients with cardiovascular disease:

- Chronic heart failure (CG108)
- Hypertension (CG127)
- Hypertension in pregnancy (CG107)
- Atrial fibrillation (CG36)
- Stable angina (CG126)
- Chest pain of recent onset (CG95)
- Unstable angina and NSTEMI (CG94)
- MI: secondary prevention (CG48)
- Lipid modification (CG67)
- Familial hypercholesterolaemia (CG71)
- Stroke (CG68)

Optimal pharmacological therapy (OPT) is the corner stone of the treatment of these conditions and should be received by all patients.

2.8) Cardiac rhythm management device therapy

When assessing whether a patient would benefit from the implantation of an ICD or CRT device, clinicians assess the risk of a life-threatening ventricular arrhythmia and also the likelihood of symptomatic and prognostic benefit from CRT. This is a complex process as these indications overlap very considerably, either or both functions can be combined in a single device and patient wishes regarding the practical aspects of the procedure and long-term effects are paramount.

For people with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite optimal pharmacological treatment, the treatment decision is between cardiac resynchronisation therapy (CRT) with OPT against OPT alone. CRT may be delivered as a CRT-P (pacemaker) or CRT-D (defibrillator) depending on whether or not the patient has an additional requirement for ICD therapy.

For people at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite optimal pharmacological treatment, the treatment decision is between a defibrillator with OPT against OPT alone. Defibrillator therapy may be delivered as ICD or CRT-D depending on whether or not the patient has a requirement for CRT.

We recommend that the clearest way to define the populations and their comparators is in a 2x2 matrix:

	People at increased risk of sudden cardiac death as a result of ventricular arrhythmias despite optimal pharmacological treatment (OPT)	People without an increased risk of sudden cardiac death
People with heart failure as a result of left ventricular systolic dysfunction and cardiac dyssynchrony despite optimal pharmacological treatment (OPT)	Intervention: **CRT-D + OPT** [Comparator: **OPT alone]**	Intervention: **CRT-P + OPT** [Comparator: **OPT alone]**
People without heart failure	Intervention: **ICD + OPT** [Comparator: **OPT alone]**	Intervention: **OPT alone**

2.9) Cardiac conditions associated with heart failure and/or arrhythmias

The conditions in which cardiac rhythm management device implantation may be appropriate can be divided into those associated with structural abnormalities and those where the heart appears structurally and functionally normal.

Structural heart disease

2.9.1) Ischaemic heart disease

Ischaemic heart disease (IHD) is the commonest cause of cardiovascular morbidity and mortality in the UK. Coronary artery atheroma results in acute and chronic shortage of blood to the myocytes which constitute the muscle of the heart. This ischaemia can result in loss of myocytes, reduced muscular contractility and heart failure. Ischaemia and myocardial scar also increase the electrical instability of the myocardium and can trigger arrhythmias.

2.9.2) Non-ischaemic cardiomyopathy

A small proportion of patients with reduced myocardial function have a primary abnormality of myocytes, a cardiomyopathy. Non-ischaemic cardiomyopathy (NICM) encompasses a

heterogeneous group of conditions unified only by the absence of myocardial ischaemia as its aetiology. NICM has many causes including haemodynamic stress, infection, immunologically medicated inflammation and the direct effects of toxins. Genetic factors are increasingly recognised to underlie the predisposition to the development of the cardiomyopathy phenotype but our knowledge of the genes involved and their specific actions remains at an early stage.

2.9.3) Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the commonest inherited structural heart disease affecting approximately 1 in 500 people. It is usually inherited as an autosomal dominant trait with variable clinical penetrance and expression, as a mutation in genes encoding cardiac sarcomeric proteins. HCM is characterised by hypertrophy, thickening of the myocardium of the left ventricle, typically affecting the interventricular septum, in the absence of pressure overload, infiltration or storage disease. Myocyte and myofibril disarray with myocardial fibrosis are thought to form the substrate for ventricular arrhythmias. The diagnosis is usually made on echocardiography, although cardiac magnetic resonance imaging with late gadolinium enhancement is increasingly being used because of its sensitivity and specificity. The clinical course in HCM is highly variable between individuals. Most patients have a normal life expectancy with few symptoms but all patients should be followed up and assessed for their risk of sudden cardiac death as HCM is the commonest cause of cardiac arrest in people under the age of 40-years.

2.9.4) Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic heart muscle disorder characterised by fibro-fatty replacement of the ventricular myocardium. Diagnosis is often difficult, especially in the early stages of the disease (Marcus *et al. European Heart J* 2010;**31**:806-814). Inheritance is autosomal dominant although recessive forms are recognised. To date, seven genes have been characterised with genetic mutations in the desmosomes responsible for cell-to-cell binding. It is associated with an increased risk of sudden cardiac death due to ventricular arrhythmias.

2.9.5) Left ventricular non-compaction

Non-compaction of the left ventricular myocardium (LVNC) is a rare inherited cardiomyopathy characterised by prominent trabeculation of the left ventricle without impairment of systolic function due to arrest in the compaction process during the first trimester of inter-uterine life. It is a genetically inherited condition with autosomal dominant or X-linked transmission. It is associated with heart failure, arrhythmias, sudden cardiac death and systemic embolic events. Sudden cardiac death is the most common cause of mortality and is attributed to complex ventricular arrhythmias.

2.9.6) Congenital Heart Disease

Congenital heart disease represents a broad range of inherited structural cardiac abnormalities which together represent the commonest form of birth defect, affecting 1 in 125 babies. There have been remarkable advances in the diagnosis and treatment of these conditions over the past 50 years and most children now live into adulthood with excellent quality of life. However, sudden cardiac deaths due to brady- and/or tachy-arrhythmias account for 15-26% of deaths after the initial surgical post-operative period and patients should be assessed for these risks.

No structural heart disease

2.9.7) Brugada syndrome

Since its first description in 1992 as a pattern of abnormal repolarisation on the ECG, usually in leads V1-V3, without structural heart disease, Brugada syndrome has been associated with sudden cardiac death, typically at rest or during sleep. More than 100 mutations in seven different genes have now been found to be associated with Brugada syndrome which is usually inherited in an autosomal dominant pattern and affescts approximately 5 per 10,000 of the population.

2.9.8) Long-QT syndromes

The inherited long QT syndromes are characterised by prolonged QT intervals on the ECG, syncope and sudden cardiac death due to ventricular arrhythmias – characteristically the polymorphic ventricular tachycardia, torsades de pointes. Many mutations in cardiac ion channels and membrane proteins have been reported in LQTS which is now classified into at least ten subtypes.

2.9.9) Short-QT syndrome

Short QT syndrome is a very rare abnormality of cardiac ion channels. It is inherited in an autosomal dominant fashion and is associated with sudden cardiac death. The ECG is characterized by a short QT interval (usually <320 ms) and tall, peaked, narrow-based T waves. Gain-of-function mutations have been found in 3 genes encoding potassium channels.

2.9.10) Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare inherited arrhythmia syndrome, characterised by polymorphic ventricular tachycardia induced by adrenergic stress. CPVT is associated mutations the cardiac ryanodine receptor gene (RYR2) or mutations in the cardiac calsequestrin gene CASQ2. Patients with CPVT often present with syncope induced by exercise or emotion although its first presentation can also be with sudden cardiac death.

2.9.11) Cardiac arrest without an identifiable aetiology

Despite the advances in our understanding of cardiac arrhythmias in recent decades, there remain patients with clinically significant ventricular arrhythmias which cannot be classified into any known disease entity. In the absence of a structural or biochemical target for preventative therapy, the only form of treatment available to prevent sudden cardiac death is the implantation of an ICD.

3) Healthcare professional perspective

There are many healthcare professionals involved in the identification, treatment and follow-up of patients with indications for ICD and CRT therapy. Primary and secondary care physicians identify and treat patients with heart failure and increased risk of sudden cardiac death. Identification of these patients is essential to the delivery of evidence-based care and lack of awareness and complex selection criteria contribute to inequity of access. Cardiologists specialising in electrophysiology, device therapy or heart failure are those primarily responsible for determining whether device therapy is indicated, implanting the devices and providing specialist clinical follow-up. Heart failure nurses play a major part in the follow-up of heart failure patients, particularly in the community. Device programming and follow-up is largely provided by highly specialised physiologists in the UK. Long-term coordination of these healthcare professionals throughout the patient journey is essential for optimal care.

3.1) What is the place of the technology in current practice?

Cardiology practice has developed very rapidly in the past 20 years. In the field of heart rhythm management, drug therapy remains important in the treatment of underlying heart disease, but multiple trials have shown that so-called anti-arrhythmic drugs may alleviate symptoms but do not improve prognosis. The only effective treatment for life-threatening arrhythmias is the implantation of an ICD. These devices have become safer to implant, more reliable, more sophisticated in avoiding unnecessary therapy and now have significantly improved battery life. Indications for their implantation have evolved from purely secondary prevention after a resuscitated cardiac arrest, to include primary prevention in those at high risk of sudden cardiac death. Simple assessment based on LVEF and underlying cardiac disease can predict those who benefit from ICD implantation. CRT has revolutionised the treatment of severe heart failure in those with dyssynchrony. Again, simple assessment based on LVEF and the duration of the QRS complex on the standard 12-lead ECG can predict those who are likely to benefit.

In the UK, implantation rates are increasing, but remain well-below rates in Western Europe or North America. Analysis of the National Devices Database (www.devicesurvey.com) and other audits show that access to device therapy is not uniform across the UK and suggest that failure to identify patients suitable for device therapy is responsible for this disparity. A simplification of indications and investigations in line with trial evidence and international guidelines would reduce this inequity of access.

3.2) The advantages and disadvantages of the technology

In selected patients, ICD implantation reduces the risk of death while CRT implantation reduces the burden of heart failure symptoms and mortality. The disadvantages of the technology are the discomfort and risk of the implantation procedure, its complications, the burden of regular device follow-up and social effects including restriction of driving. These have been assessed in the clinical trial dataset and the benefits of device therapy remain significant and sustained. Adverse events can be minimised by appropriate patient selection, highly competent implantation and follow-up services using remote technologies. The identification of an increased risk of sudden cardiac death, ICD implantation and subsequent therapy can adversely affect quality of life and psychological well-being. All centres implanting and following-up ICD and CRT patients should provide psychological assessment and support whenever necessary. Current UK practice has become significantly more efficient since the publication of the pivotal clinical trials – patients wait

less long for treatment and have shorter admissions to hospital for device implantation. Devices have also become more reliable with longer battery life, improving cost-effectiveness.

3.3) Additional sources of evidence

By the nature of clinical trial publications, they refer to selected populations and previous generations of devices. It is important to include contemporaneous UK data. We are fortunate to have analyses from UK national data collection. The Pacemaker and ICD database has collected data from all implanting centres and increasingly detailed annual reports have been published (www.devicesurvey.com). This has revealed incremental increases in implantation rates but these remain far below those in other developed countries. We have also found great differences in rates between adjacent areas of the UK emphasising the importance of referral from non-specialists and the role of clear national guidance.

Because the lifetime cost of ICD therapy is highly sensitive to device longevity, we would suggest that the characteristics of currently implanted devices should be used in cost effectiveness modelling, rather than historical data from devices with previous generations of battery technology.

Further data relating to device therapy in the UK may become available during the appraisal process.

3.4) Implementation issues

To achieve equity of access to ICD and CRT therapy will require changes in practice and an increase in device implantation, particularly in low implanting areas. Any increase in ICD and/or CRT implantation and follow-up will clearly have cost and logistical implications. The NHS has proved highly capable of increasing capacity in response to demand for device therapy and delivering this within shortened waiting-time targets. Implantation and follow-up resources have not limited access to treatment and this is not anticipated in the future. For clinical governance and efficiency reasons, Heart Rhythm UK recommends ICD and CRT device implantation by high-volume operators working in high-volume centres. As was seen with previous NICE guidance, increases in implantation rates will occur progressively rather than suddenly. This will minimise the impact on commissioning and service delivery.

4) Implantable cardioverter defibrillator therapy

Since the introduction into routine clinical practice of the ICD in the 1980s and CRT in the 1990s, these technologies have been tested in multiple clinical trials and used clinically in millions of patients. The technologies, and the evidence to support their use, continue to improve. Here we present a summary of the available evidence.

ICD therapy is the delivery of rapid ventricular pacing or a defibrillation shock to treat potentially lethal ventricular arrhythmias. The implantation of a device after a patient has survived a malignant ventricular arrhythmia is classified as secondary prevention. This is often after a resuscitated cardiac arrest or recorded sustained ventricular arrhythmia but this recording may be absent if the arrhythmia terminated spontaneously. Primary prevention in this context requires the implantation of an ICD into people at high risk of sudden cardiac death but who are not known to have suffered a malignant ventricular arrhythmia.

4.1) Secondary prevention

Cardiac arrest outside a hospital environment carries a high mortality - only 1 in 20 patients survive to leave hospital in the UK. The commonest cause is acute myocardial infarction and the availability of immediate external defibrillation is one of the major benefits of early medical intervention. Cardiac arrest which occurs without a clear reversible cause, such as acute myocardial infarction or extreme biochemical derangement, has a high risk of recurrence resulting in sudden death. These patients have been shown to benefit from the implantation of an ICD for secondary prevention.

4.1.1) Current national international guidance

4.1.1.1) UK

Current NICE guidance (Technology Appraisal 95: Implantable cardioverter defibrillators for arrhythmias, January 2006 www.nice.org.uk/TA095) states:

1.1 ICDs are recommended for patients in the following categories.

1.11 'Secondary prevention', that is, for patients who present, in the absence of a treatable cause, with one of the following:

- having survived a cardiac arrest due to either ventricular tachycardia (VT) or ventricular fibrillation (VF)
- spontaneous sustained VT causing syncope or significant haemodynamic compromise
- sustained VT without syncope or cardiac arrest, and who have an associated reduction in ejection fraction (LVEF of less than 35%) (no worse than class III of the New York Heart Association functional classification of heart failure).

A Heart Rhythm UK position statement on clinical indications for ICD implantation in adults with familial sudden cardiac death syndromes was published in 2010 (Garratt *et al. Europace*

2010;**12**:1156-1175). This details the available evidence in these rare syndromes and is used in this section of the document.

4.1.1.2) North America

Current American College of Cardiology, American Heart Association and Heart Rhythm Society guidance (ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines *J Am Coll Cardiol* 2008;**51**;e1-e62 http://content.onlinejacc.org/cgi/content/full/51/21/e1).

Class I (procedure should be performed) and **IIa** (it is reasonable to perform the procedure):

CLASS I

1. **ICD therapy is indicated in patients who are survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes. *(Level of Evidence: A)*** (16,319–324)
2. **ICD therapy is indicated in patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable. *(Level of Evidence: B)*** (16,319–324)
3. **ICD therapy is indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study. *(Level of Evidence: B)*** (16,322)

CLASS IIa

1. **ICD implantation is reasonable for patients with unexplained syncope, significant LV dysfunction, and nonischemic DCM. *(Level of Evidence: C)***

5. **ICD implantation is reasonable to reduce SCD in patients with long-QT syndrome who are experiencing syncope and/or VT while receiving beta blockers. *(Level of Evidence: B)*** (349–354)

7. **ICD implantation is reasonable for patients with Brugada syndrome who have had syncope. *(Level of Evidence: C)***

9. **ICD implantation is reasonable for patients with catecholaminergic polymorphic VT who have syncope and/or documented sustained VT while receiving beta blockers. *(Level of Evidence: C)***

4.1.1.3) European Society of Cardiology

ESC guidance on acute and chronic heart failure (McMurray *et al. European Heart Journal* 2012;**33**:1787–1847) states:

Recommendations for the use of implanted cardioverter defibrillators in patients with heart failure

Recommendations	Class[a]	Level[b]	Ref[c]
Secondary prevention An ICD is recommended in a patient with a ventricular arrhythmia causing haemodynamic instability, who is expected to survive for >1 year with good functional status, to reduce the risk of sudden death.	I	A	144–147

4.1.2) Resuscitated cardiac arrest

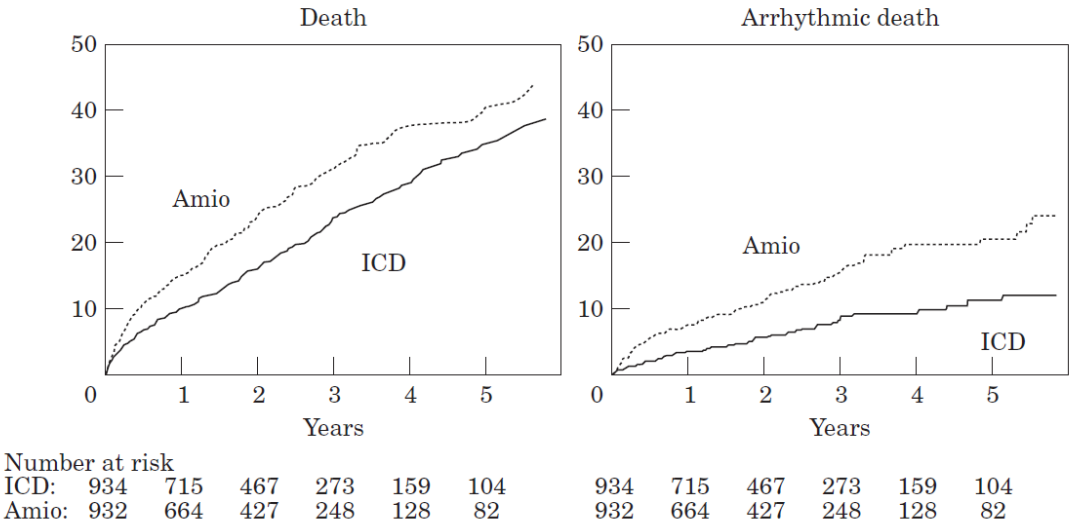
Before ICDs were part of routine clinical practice, patients surviving malignant ventricular arrhythmias were treated with a variety of rhythm modifying drugs including amiodarone, sotalol and class I agents (e.g. flecainide, encainide, propafenone). However, the only intervention to demonstrate improved patient survival is the implantation of an ICD.

No new secondary prevention trial data have been produced since the publication of NICE TA 95 in 2006, nor is any further evidence likely to be published in the future as it is considered unethical not to offer ICD therapy to cardiac arrest survivors.

4.1.2.1) Ischaemic heart disease

Four randomised controlled trials have assessed the efficacy of ICD implantation in the secondary prevention of sudden cardiac death from cardiac arrest and these have been subjected to meta-analysis. (Wever *et al. Circulation* 1995;**91**:2195-2203, AVID: *N Engl J Med* 1997;**337**:1576-1583, CASH: Kuck *et al. Circulation* 2000;**102**:748-754, CIDS: Connolly SJ *et al. Circulation* 2000;**101**:1297-1302, Meta-analysis: Connolly SJ *et al. Eur Heart J* 2000;**21**:2071-2078).

Despite their different protocols and inclusion criteria, patients enrolled in these trials had remarkably homogenous characteristics and the results of the trials comparing ICD therapy with drug treatment were remarkably consistent: A meta-analysis (Connolly *et al. Eur Heart J* 2000;**21**:2071-2078) demonstrates a relative risk reduction in all-cause mortality of 28% (a 3.5% annual absolute risk reduction) favouring ICD implantation which resulted almost entirely from a 50% reduction in arrhythmic death:



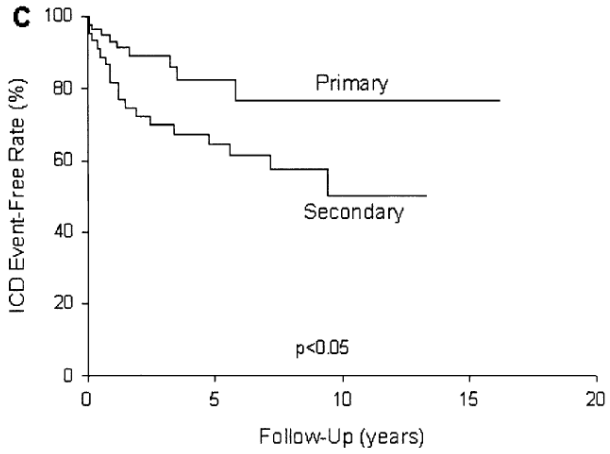
The majority of patients included in these trials had a history of prior myocardial infarction, but those with other heart disease showed similar benefit from ICD implantation.

4.1.2.2) Non-ischaemic cardiomyopathy

Although patients with non-ischaemic cardiomyopathy (sometimes referred to as dilated cardiomyopathy, DCM) represented only 14% of patients in the secondary prevention trials (15% in AVID, 11% in CASH and 10% in CIDS), the point estimates of benefit are essentially the same as those for patients with ischaemic cardiomyopathy: The hazard ratio for ICD therapy in patients with non-ischaemic cardiomyopathy was 0.77 compared with 0.78 for patients with ischaemic cardiomyopathy. These patients should therefore be regarded as at similar risk of recurrent life-threatening arrhythmia and receive ICD therapy according to the same selection criteria (Connolly *et al. Eur Heart J* 2000;**21**:2071-2078).

4.1.2.3) Hypertrophic cardiomyopathy

There are no randomised controlled trials of ICD therapy for secondary prevention in HCM. In a consecutive series of 132 patients with HCM receiving ICD implantation, the rate of death or appropriate ICD therapy following resuscitated cardiac arrest was 39% rate over 5-years' follow-up (Begley *et al.* PACE 2003;**26**:1887-1896).



Other observational data show a survival free from death or appropriate ICD discharge of 59% at 5 years (Maron *et al. N Engl J Med* 2000;**342**:365-373, Elliott *et al. J Am Coll Cardiol* 2006;**27**:1933-1941):

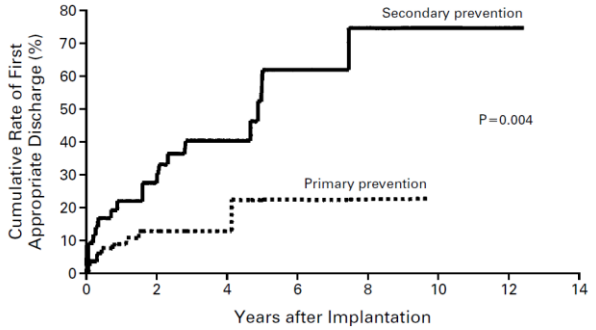


Figure 4. Estimated Cumulative Rates of First Appropriate Discharges, Calculated Separately for the 85 Patients with Defibrillators for Primary Prevention and the 43 Patients with Defibrillators for Secondary Prevention.

This is consistent with multi-centre registry data which report annual rates of appropriate ICD therapy of approximately 11% per year following resuscitation from VT or VF (Maron *et al. N Engl J*

Med 2000;**342**:365-373, Begley *et al. Pacing Clin Electrophysiol* 2003;**26**:1887-1896, Maron *et al. JAMA* 2007;**298**:405-412).

Patients with hypertrophic cardiomyopathy presenting with ventricular fibrillation, cardiac arrest or sustained ventricular tachycardia without reversible cause should undergo ICD implantation.

4.1.2.4) Arrhythmogenic right ventricular cardiomyopathy (ARVC)

There are no randomised controlled trials of ICD therapy for secondary prevention in ARVC but observational studies show a consistent benefit of ICD therapy with high proportions of patients receiving appropriate ICD therapy during follow-up.

In a multicentre study of 132 patients with ARVC (Corrado *et al. Circulation*. 2003;**108**:3084-3091) 9 of the 13 (69%) patients implanted with an ICD following cardiac arrest had life-saving ICD therapy at a rate of 21% per year. This is consistent with other reported series:

ARVC patients with ICD for secondary prevention receiving appropriate therapy	mean follow-up (months)	publication
7 of 9 (78%)	32	Tavernier *et al. Heart* 2001;**85**:53-56
9 of 13 (69%)	39	Corrado *et al. Circulation*. 2003;**108**:3084-3091
39 of 56 (70%)	80	Wichter *et al. Circulation*. 2004;**109**:1503-1508
11 of 16 (69%)	8.2	Pezawas *et al. Int J Cardiol* 2006;**107**:360-368

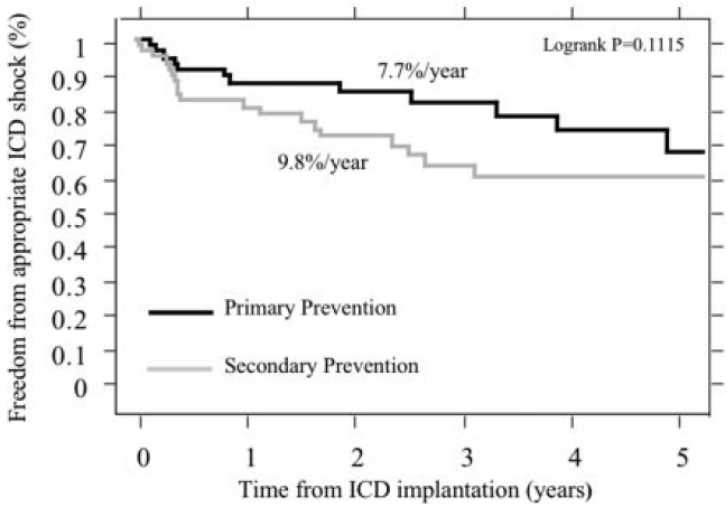
ARVC patients presenting with ventricular fibrillation, cardiac arrest or haemodynamically significant ventricular tachycardia should b eoffered ICD implantation.

4.1.2.5) Left ventricular non-compaction

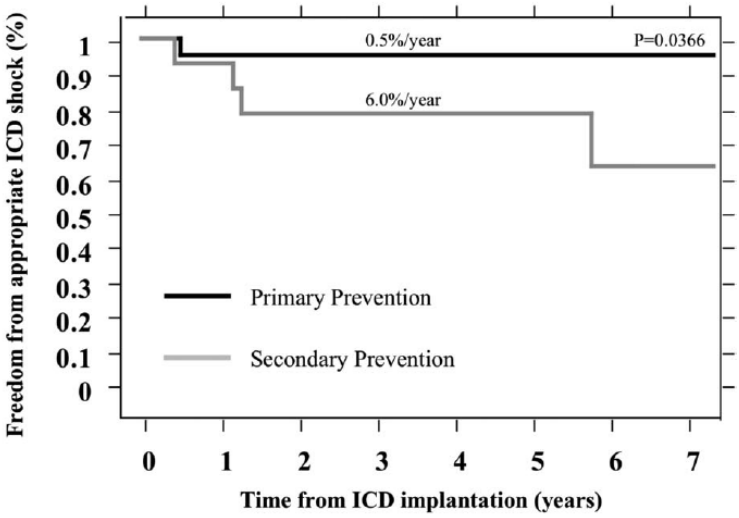
There are no prospective trials of ICD implantation for secondary prevention in patients with LVNC. In a series of 12 patients with LVNC undergoing ICD implantation (*Kobza et al. Pacing Clin Electrophysiol* 2008;**31**:461-467), 8 had prior cardiac arrest. Of those, 4 (50%) received appropriate ICD therapy over a mean follow-up of 36 months (17% per year). This supports a strategy of ICD implantation following a resuscitated cardiac arrest in this condition (Yasukawa *et al. Pediatr Cardiol* 2001;**22**:512-514, Celiker *et al. Pacing Clin Electrophysiol* 2004;**27**:104-108).

4.1.2.6) Congenital heart disease

A multicentre series of 53 patients with tetralogy of Fallot implanted with an ICD after sustained ventricular tachyarrhythmia (37 patients, 69.8%) or resuscitated sudden death (16 patients, 30.2%) showed an annual rate of appropriate shocks of 9.8% (Khairy *et al. Circulation* 2008;**117**:363-370).



A multicentre series of 14 patients with transposition of the great arteries (TGA) treated with a Mustard or a Senning procedure with an intra-atrial baffle implanted with ICDs following a resuscitated cardiac arrest (10 patients, 71.4%) or sustained VT (4 patients, 28.6%), showed a 6.6% annual rate of appropriate ICD shocks (Khairy *et al. Circulation Electrophysiol* 2008;**1**:250-257).



ICD implantation is appropriate following resuscitated cardiac arrest or sustained VT in patients with high-risk congenital heart disease.

4.1.2.7) Brugada syndrome

There is no randomised controlled trial of ICD therapy for secondary prevention in Brugada syndrome. Five international registries of patients with Brugada syndrome have been analysed for risk factors for sudden cardiac death (Brugada & Brugada *J Am Coll Cardiol* 1992;**20**:1391-1396, Brugada, Brugada & Brugada *Circulation* 1998;**97**:457-460, Brugada *et al. Circulation* 2002;**105**:73-78, Brugada *et al. Circulation* 2003;**108**:3092-3096, Brugada *et al. J Cardiovasc Electrophysiol* 2003;**14**:455-457, Priori *et al. Circulation* 2000;**102**:2509-2515, Priori *et al. Circulation* 2002;**105**:1342-1347, Eckardt *et al. Eur Heart J* 2002;**23**:1394, Eckardt *et al. Circulation* 2005;**111**:257-263, Probst *et al. Circulation* 2010;**121**:635-643, Takagi *et al. J Cardiovasc Electrophysiol* 2007;**18**:1244-1251, Sacher *et al. Circulation* 2006;**114**:2317-2324, Sarkozy *et al. Eur Heart J* 2007;**28**:334-344).

Observational series estimate the annual risk of death or appropriate ICD discharge at between 7.7% and 13.8% and ICD implantation is therefore recommended (Brugada *et al. Circulation* 2002;**105**:73-78, Sacher *et al. Circulation* 2006;**114**:2317-2324, Takagi *et al. J Cardiovasc Electrophysiol* 2007;**18**:1244-1251, Sarkozy *et al. Eur Heart J* 2007;**28**:334-344, Probst *et al. Circulation* 2010;**121**:635-643):

Table 1 Cardiac event rates per annum from different study populations for different clinical presentations of Brugada syndrome calculated from available data

	Brugada *et al.*[41]	Sacher *et al.*[50]	Takagi *et al.*[49]	Sarkozy *et al.*[51]	Probst *et al.*[48]
Total patient numbers	334	220	188	47	1029
Prior cardiac arrest	13.8%	10.7%	9.8%	Not studied	7.7%
Previous syncope	8.8%	3.15%	1.9%	2.9%	1.9%
Asymptomatic	(72% FH) 3.74%	(54% FH) 1.7%	(10% FH) 0%	(57% FH) 4.8%	(37% FH) 0.5%
Asymptomatic spontaneous type 1 ECG	6.4%	2.54%	0%	Unavailable	0.81%
Asymptomatic drug-induced type 1 ECG	0%	0.73%	0%	Unavailable	0.35%

Event rates are rates per annum of sudden cardiac death, ventricular fibrillation, or (in patients with ICDs) appropriate shocks per annum.

Brugada syndrome patients presenting with VF or cardiac arrest without reversible precipitant should be offered ICD implantation.

4.1.2.8) Long QT syndromes

There are no prospective trials of the risk of recurrent cardiac arrest in long QT syndrome (LQTS) patients. In a report of historical control patients (Zareba *et al. J Cardiovasc Electrophysiol* 2003;**14**:337-341), 27 out of 89 patients (30.3%) died or suffered recurrent cardiac arrest over 9 years' follow-up – a risk of 3.4% per year. LQTS patients presenting with ventricular fibrillation or cardiac arrest without reversible precipitant should be offered ICD implantation in addition to oral beta-blocker therapy.

4.1.2.9) Short QT syndrome

There are no randomised controlled trial data in this very rare condition. Because of the high risk of arrhythmias and sudden cardiac death, ICD implantation is recommended for secondary prevention in patients with short QT syndrome (Priori *et al. Circ Res* 2005;**96**:800-807, Veltmann *et al. Herz* 2009;**34**:518–527, Cross *et al. J Interv Card Electrophysiol* 2011;**31**:25–31). Care must be taken in device programming to prevent inappropriate therapy due to T-wave over-sensing in this condition (Schimpf *et al. J Cardiovasc Electrophysiol* 2003;**14**:1273-1277).

4.1.2.10) Catecholaminergic polymorphic ventricular tachycardia (CPVT)

Patients with CPVT presenting with aborted cardiac arrest have been shown to be at increased risk of life-threatening arrhythmias with a mortality of 1.2% per year despite beta-blockade (Hayashi *et al. Circulation* 2009;**119**:2426-2434). ICD implantation is recommended in addition to beta blockade for CPVT patients presenting with VF or cardiac arrest without reversible cause.

4.1.2.11) Ventricular arrhythmias of unknown aetiology

A small number of patients resuscitated from cardiac arrest are found to have no structural abnormality, reversible cause or known ion-channel abnormality. ICD implantation is appropriate for secondary prevention in these patients.

4.1.3) Syncope

Syncope, a sudden loss of consciousness due to global cerebral hypoperfusion, is most commonly due to an uncomplicated faint, which is benign. A careful history, examination and focused

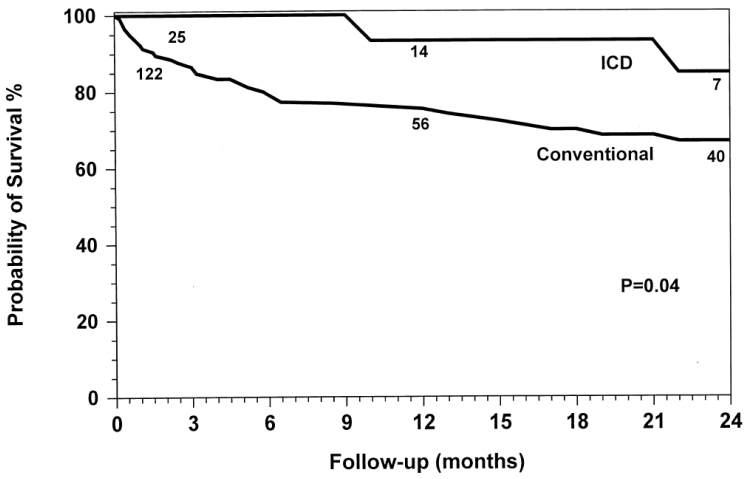
investigations are required to make this diagnosis (NICE CG109, Transient loss of consciousness in adults and young people, August 2010). However, when syncope is associated with cardiac dysfunction or arrhythmia, it is associated with a high mortality. In high-risk cardiac conditions, syncope carries a similar prognosis to resuscitated cardiac arrest, the most likely mechanism being spontaneous termination of the life-threatening arrhythmia.

4.1.3.1) Ischaemic heart disease

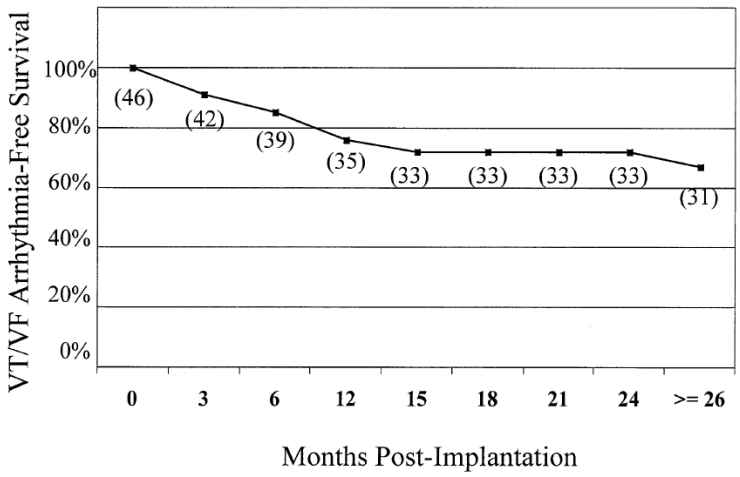
CIDS (Connolly SJ *et al. Circulation* 2000;**101**:1297-1302) included 92 patients (14%) presenting with syncope in the absence of documented ventricular arrhythmia. All had subsequent documentation of either spontaneous VT ≥ 10 seconds or inducible sustained monomorphic VT. The all-cause mortality of patients included because of syncope was higher (13.4%) than those with documented arrhythmias (8.7%, p=0.034). The AVID registry (Anderson *et al. Circulation* 1999;**99**:1692-1699) included 158 patients presenting with unexplained syncope. These patients had a 15.9% 2-year mortality, similar to those with demonstrated arrhythmias. ICD implantation is recommended in patients with ischaemic heart disease and LVEF ≤35% presenting with syncope.

4.1.3.2) Non-ischaemic cardiomyopathy

In a series of 147 patients with heart failure due to non-ischaemic cardiomyopathy with LVEF ≤35% and a history of syncope but no prior history of sustained ventricular tachycardia (Fonarow *et al. Am J Cardiol* 2000;**85**:981-985), 25 patients were managed with an ICD and 122 patients managed with conventional medical therapy. During a mean follow-up of 22 months, there were 31 deaths, 18 sudden, in patients treated with conventional therapy, whereas there were 2 deaths, none sudden, in patients treated with an ICD. An appropriate shock occurred in 40% of the ICD patients. Actuarial survival at 2 years was 84.9% with ICD therapy and 66.9% with conventional therapy (p = 0.04).



70% of these patients received appropriate ICD therapy for sustained ventricular arrhythmias with a mean follow-up of 17 months:

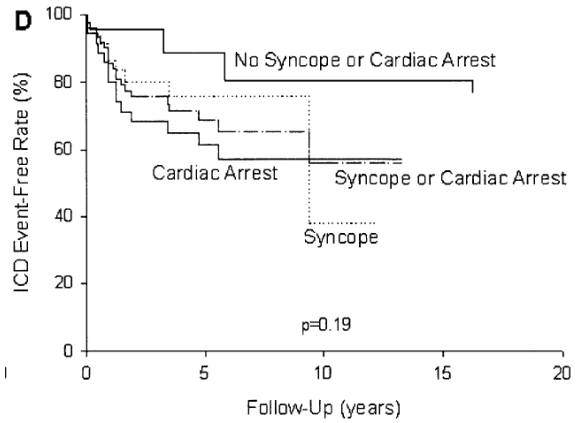


SCD-HeFT (Bardy *et al. N Engl J Med* 2005;**352**:225-37) randomised only 162 patients (6%) with a history of syncope but analysis (Olshansky *et al. J Am Coll Cardiol* 2008;**51**:1277–82) has shown that pre-randomisation syncope was associated with an increased risk of appropriate ICD therapy 38% versus 19% (HR 1.75, 95% CI 1.10 to 2.80, p=0.019).

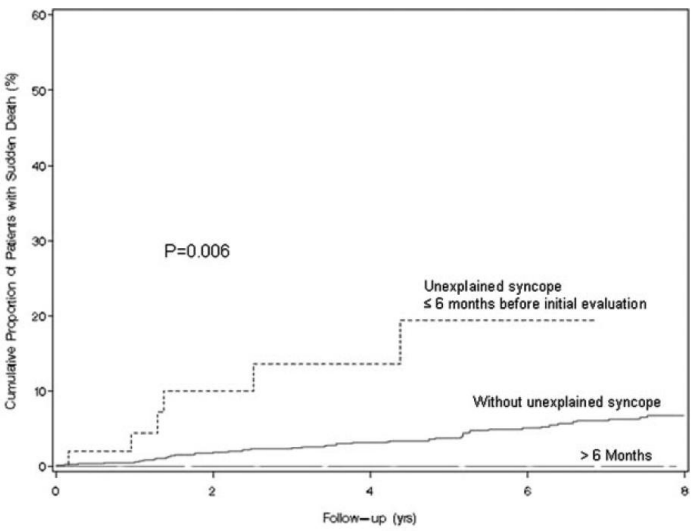
Thus, in patients with non-ischemic cardiomyopathy, LVEF ≤35% and syncope, therapy with an ICD is associated with a reduction in sudden death and an improvement in overall survival (Fonaro GC *et al. Am J Cardiol* 2000;**85**:981-985, Russo *et al. Am J Cardiol* 2001;**88**:1444-1446) similar to that seen in patients surviving a cardiac arrest.

4.1.3.3) Hypertrophic cardiomyopathy

In a consecutive series of 132 HCM patients receiving ICD implantation, 24% of those with unexplained syncope had appropriate ICD therapy during 5-years' follow-up (Begley *et al.* PACE 2003;**26**:1887-1896). This is similar to the risk in those resuscitated from cardiac arrest.



A large study of 1511 patients with HCM showed a 20% risk of sudden death within 5 years of unexplained syncope (Spirito *et al. Circulation* 2009;**119**:1703-1710):

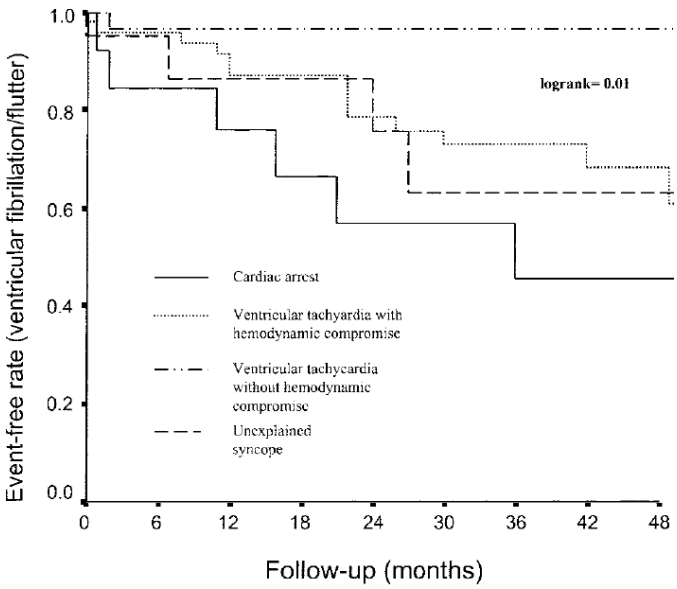


This is consistent with another report showing that patients receiving ICDs with unexplained syncope as their sole risk marker had a 5% annual rate of appropriate interventions compared with an annual rate of 3.5% in the overall study group with primary prevention ICDs (Maron *et al. JAMA* 2007;**298**:405-412). Multivariate analysis of a single centre series of 917 patients (Elliott *et al. Eur Heart J* 2006;**27**:1933-1941) confirmed that syncope was a significant predictor of sudden death with a hazard ratio of 2.27 (1.2-4.2, p=0.01).

These data strongly support the use of ICD therapy following cardiac syncope in patients with hypertrophic cardiomyopathy.

4.1.3.4) Arrhythmogenic right ventricular cardiomyopathy (ARVC)

Observational studies support the use of ICD implantation in high risk patients identified by unexplained syncope. In the Corrado *et al.* series (*Circulation.* 2003;**108**:3084-3091), the clinical presentation was unexplained syncope in 21 patients (16%). Over a mean follow-up of 39 months, 8 of these patients (38%) received appropriate ICD therapy for ventricular arrhythmia:



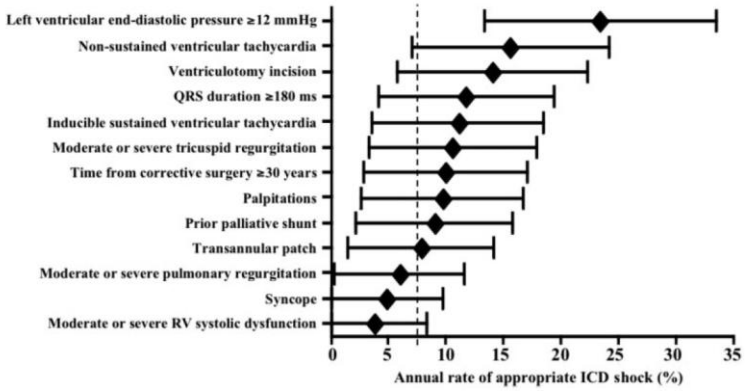
ARVC patients presenting with syncope, when VT and VF have not been excluded as the cause, should be offered ICD implantation.

4.1.3.5) Left ventricular non-compaction

In a series of 12 patients with LVNC (Kobaza *et al. PACE* 2008;31:461-467), only one underwent ICD implantation because of syncope. He received 2 appropriate ICD therapies over a 39-month follow-up period. There is too little information on which to formulate evidence-based recommendations for ICD implantation in this situation. Expert opinion recommends ICD implantation in patients with LVNC presenting with syncope, symptomatic ventricular arrhythmias or with severely impaired LV systolic function (LVEF ≤35%) (Oechslin E, Jenni R. *European Heart Journal* 2011;**32**:1446-1456).

4.1.3.6) Congenital heart disease

In a multicentre series (Khairy *et al. Circulation* 2008;**117**:363-370), 30 patients with tetralogy of Fallot underwent ICD implantation because of syncope. Their annual rate of appropriate ICD therapy was 5%.



In a similar multicentre series (Khairy *et al. Circulation Electrophysiol* 2008;**1**:250-257), 8 patients with transposition of the great arteries underwent ICD implantation because of syncope. Their rate of appropriate ICD therapy was not reported separately from the primary prevention group, but overall this was only 0.5%.

On the available evidence, ICD implantation appears to be indicated following syncope in patients with Tetralogy of Fallot. There are insufficient data to make a recommendation in patients with transposition of the great arteries.

4.1.3.7) Brugada syndrome

Published series show that in patients with Brugada syndrome the risk of sudden cardiac death or appropriate ICD therapy following previous syncope is between 1.9% and 8.8% per year (Garratt *et al. Europace* 2010;**12**:1156-1175).

Table 1 Cardiac event rates per annum from different study populations for different clinical presentations of Brugada syndrome calculated from available data

	Brugada et al.[41]	Sacher et al.[50]	Takagi et al.[49]	Sarkozy et al.[51]	Probst et al.[48]
Total patient numbers	334	220	188	47	1029
Prior cardiac arrest	13.8%	10.7%	9.8%	Not studied	7.7%
Previous syncope	8.8%	3.15%	1.9%	2.9%	1.9%
Asymptomatic	(72% FH) 3.74%	(54% FH) 1.7%	(10% FH) 0%	(57% FH) 4.8%	(37% FH) 0.5%
Asymptomatic spontaneous type 1 ECG	6.4%	2.54%	0%	Unavailable	0.81%
Asymptomatic drug-induced type 1 ECG	0%	0.73%	0%	Unavailable	0.35%

Event rates are rates per annum of sudden cardiac death, ventricular fibrillation, or (in patients with ICDs) appropriate shocks per annum.

ICD implantation is recommended for Brugada syndrome patients with syncope when VT/VF has not been excluded as the cause of syncope.

4.1.3.8) Long QT syndromes

Patients with LQTS presenting with syncope should receive evidence-based beta blocker treatment. A published series (Zareba *et al. J Cardiovasc Electrophysiol* 2003;**14**:337-341) showed that 11 of 72 patients (2.2% per year) with recurrent syncope died or had a cardiac arrest during 7 years' follow-up. Although there are differences between the LQTS sub-types, there is insufficient evidence to base recommendations on these.

LQTS patients experiencing continuing syncope despite beta-blockade (or left cervical sympathetic denervation) when VT/VF has not been excluded as the cause of syncope should be offered ICD implantation.

4.1.3.9) Short QT syndromes

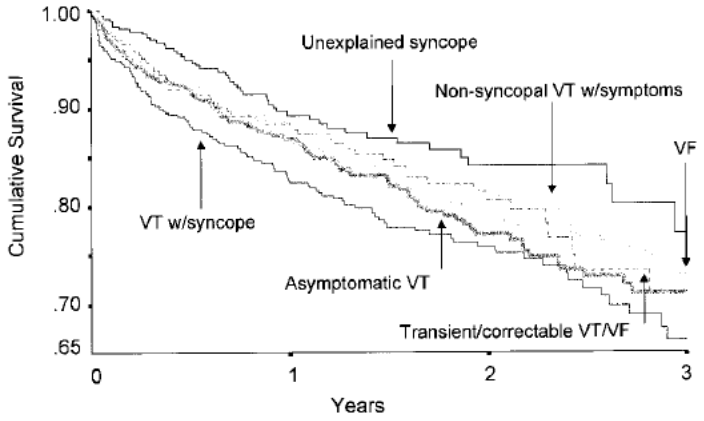
There are no randomised controlled trial data in this syndrome. A high incidence of sudden cardiac death has been reported in affected families and unstable ventricular arrhythmias are often inducible on electrophysiology study. Published expert opinion is to offer ICDs to these patients for primary prevention (Cross B *et al. J Interv Card Electrophysiol* 2011;**31**:25-31)

4.1.3.10) Catecholaminergic polymorphic ventricular tachycardia

There are no trials of continuing medical therapy with beta blockade in CPVT patients presenting with recurrent syncope. ICD implantation is recommended because of the high risk of sudden cardiac death in this small patient group (Hayashi *et al. Circulation* 2009;**119**:2426-2434).

4.1.3.11) Ventricular tachycardia without haemodynamic compromise

Not all ventricular arrhythmias cause circulatory collapse and result in syncope or sudden cardiac death. The index event in 34% (345) of patients in the AVID registry and 25% (165) in CIDS was asymptomatic ventricular tachycardia. Survival was lower in patients in the AVID registry (Anderson *et al. Circulation*. 1999;**99**:1692-1699) with asymptomatic VT than with VF as their presenting arrhythmia:



arrhythmia	number of patients	2-year mortality
VF	1399	20.3%
VT with syncope	598	24.3%
Non-syncopal VT with symptoms	1065	18.7%
Asymptomatic VT	497	22.6%
Transient/correctable VT/VF	270	19.4%
Unexplained syncope	390	15.9%

ICD implantation is recommended for patients with severe left ventricular impairment (LVEF ≤35%) and documented sustained ventricular arrhythmia regardless of its acute haemodynamic effects.

4.2) Primary prevention

In medicine, the risk of an event occurring for a second time is generally significantly higher than for any identifiable at-risk group in which this event has not yet occurred. Thus, the number needed to treat is generally lower for secondary than primary prevention. ICD therapy represents a unique situation where we are able to identify groups of patients on simple clinical criteria who have not suffered a cardiac arrest but are at higher absolute risk than those who have, and gain more from ICD therapy with a lower number needed to treat to save a life.

4.2.1) Current national and international guidance

4.2.1.1) UK

Current NICE guidance (Technology Appraisal 95 Implantable cardioverter defibrillators for arrhythmias, January 2006) states:

1.1.2 'primary prevention', that is for patients who have:

- A history of previous (more than four weeks) myocardial infarction (MI) and:

either

  - Left ventricular dysfunction with an LVEF of less than 35% (no worse than class III of the New York Heart Association functional classification of heart failure), and
  - Non-sustained VT on Holter (24 hour electrocardiogram [ECG]) monitoring, and
  - Inducible VT on electrophysiological (EP) testing

  or

  - Left ventricular dysfunction with an LVEF of less than 35% (no worse than class III of the New York Heart Association functional classification of heart failure),

  and

  - QRS duration of equal to or more than 120ms

- A familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, or arrhythmogenic right ventricular dysplasia(ARVD), or have undergone surgical repair of congenital heart disease

A Heart Rhythm UK position statement on clinical indications for ICD implantation in adults with familial sudden cardiac death syndromes was published in 2010 (Garratt *et al. Europace* 2010;**12**:1156-1175). This details the available evidence in these rare syndromes and is used in this section of the document.

4.2.1.2) North America

Current American College of Cardiology, American Heart Association and Heart Rhythm Society guidance (Epstein *et al.* Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American ACC/AHA/HRS 2008. *J Am Coll Cardiol* 2008;**51**:e1-e62 http://content.onlinejacc.org/cgi/content/full/51/21/e1):

Class I (procedure should be performed) and **IIa** (it is reasonable to perform the procedure):

CLASS I

4. **ICD therapy is indicated in patients with LVEF less than or equal to 35% due to prior MI who are at least 40 days post-MI and are in NYHA functional Class II or III.** ***(Level of Evidence: A)*** (16,333)
5. **ICD therapy is indicated in patients with nonischemic DCM who have an LVEF less than or equal to 35% and who are in NYHA functional Class II or III.** ***(Level of Evidence: B)*** (16,333,369,379)
6. **ICD therapy is indicated in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF less than or equal to 30%, and are in NYHA functional Class I.** ***(Level of Evidence: A)*** (16,332)
7. **ICD therapy is indicated in patients with nonsustained VT due to prior MI, LVEF less than or equal to 40%, and inducible VF or sustained VT at electrophysiological study.** ***(Level of Evidence: B)*** (16,327,329)

CLASS IIa

2. **ICD implantation is reasonable for patients with sustained VT and normal or near-normal ventricular function.** ***(Level of Evidence: C)***
3. **ICD implantation is reasonable for patients with HCM who have 1 or more major† risk factors for SCD.** ***(Level of Evidence: C)***
4. **ICD implantation is reasonable for the prevention of SCD in patients with ARVD/C who have 1 or more risk factors for SCD.** ***(Level of Evidence: C)***

6. **ICD implantation is reasonable for non hospitalized patients awaiting transplantation.** ***(Level of Evidence: C)***

8. **ICD implantation is reasonable for patients with Brugada syndrome who have documented VT that has not resulted in cardiac arrest.** ***(Level of Evidence: C)***
10. **ICD implantation is reasonable for patients with cardiac sarcoidosis, giant cell myocarditis, or Chagas disease.** ***(Level of Evidence: C)***

4.2.1.3) European Society of Cardiology

Current ESC guidance (Guidance on the diagnosis and treatment of acute and chronic heart failure 2012, McMurray *et al. European Heart Journal* 2012;**33**:1787-1847) states:

Primary prevention An ICD is recommended in a patient with symptomatic HF (NYHA class II–III) and an EF ≤35% despite ≥3 months of treatment with optimal pharmacological therapy, who is expected to survive for >1 year with good functional status, to reduce the risk of sudden death			
(i) Ischaemic aetiology and >40 days after acute myocardial infarction	I	A	148, 149
(ii) Non-ischaemic aetiology	I	B	149

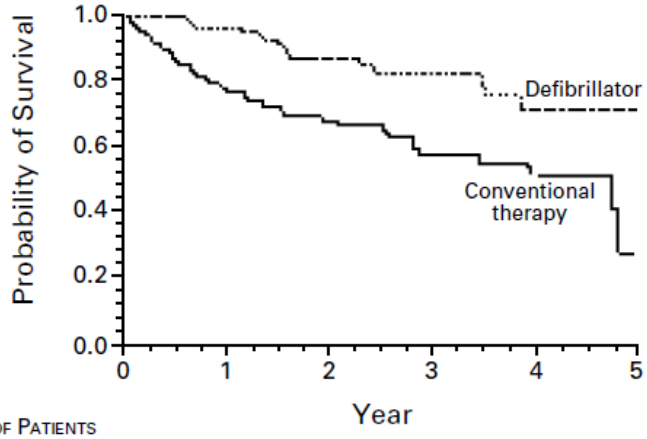
4.2.2) Published evidence

4.2.2.1) Ischaemic heart disease

The Multicenter Automatic Defibrillator Implantation Trial (MADIT, Moss *et al. N Engl J Med* 1996;**335**:1933-40) randomised 95 patients to ICD implantation and 101 to medical therapy while in the Multicenter UnSustained Tachycardia Trial (MUSTT, Buxton *et al. N Engl J Med* 2000; **342**:1937-1945, Wyse *et al. J Am Coll Cardiol* 2001;**38**:344 –51) 351 patients were randomised to electrophysiology guided strategy and 161 patients received ICD implantation while 190 received medical therapy. All patients had a history of prior myocardial infarction, spontaneous non-sustained ventricular tachycardia and left ventricular impairment. The selection criteria for LVEF were slightly different in the two trials (≤35% in MADIT and ≤40% in MUSTT) but the randomised patients had very similar LVEFs:

	MADIT		MUSTT	
	ICD	**Conventional therapy**	**EP guided strategy**	**No antiarrhythmic therapy**
LVEF	0.25±0.07	0.27±0.07	30 (20-35)	29 (22-35)

MADIT demonstrated at 22.8% absolute reduction in all-cause mortality (39/101, 38.6% compared to 15/95, 15.8%) and a 54% relative reduction in all-cause mortality with ICD therapy:



No. of Patients						
Defibrillator	95	80	53	31	17	3
Conventional therapy	101	67	48	29	17	0

Figure 2. Kaplan–Meier Analysis of the Probability of Survival, According to Assigned Treatment.

The difference in survival between the two treatment groups was significant (P = 0.009).

MUSTT demonstrated a 29.4% absolute reduction in all-cause mortality and a 60% relative reduction in all-cause mortality with ICD therapy:

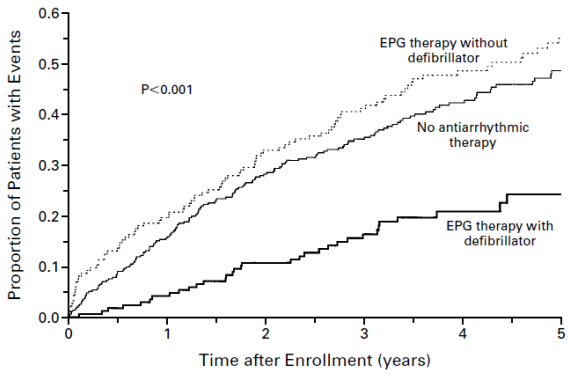
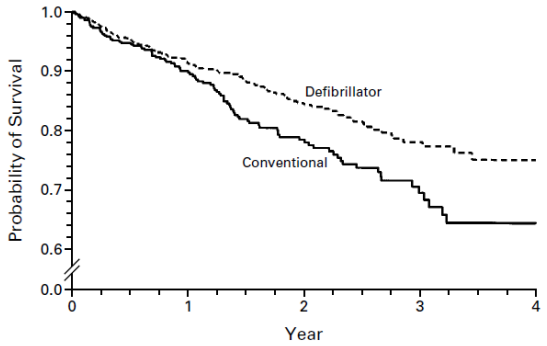


Figure 4. Kaplan–Meier Estimates of the Rates of Overall Mortality According to Whether the Patients Received Treatment with a Defibrillator.

The P value refers to two comparisons: between the patients in the group assigned to electrophysiologically guided (EPG) therapy who received treatment with a defibrillator and those who did not receive such treatment, and between the patients assigned to electrophysiologically guided therapy who received treatment with a defibrillator and those assigned to no antiarrhythmic therapy.

MADIT II (Moss *et al. N Engl J Med* 2002;**346**:877-883) enrolled 1232 patients with ischaemic cardiomyopathy and LVEF ≤30% without any further risk stratification. In fact, the patients' LVEF were very similar to those in MADIT and MUSTT with a mean of 23±5%:

MADIT II demonstrated a 5.6% absolute reduction in all-cause mortality and a 31% relative reduction in all-cause mortality with ICD therapy:



No. at Risk					
Defibrillator	742	503 (0.91)	274 (0.84)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

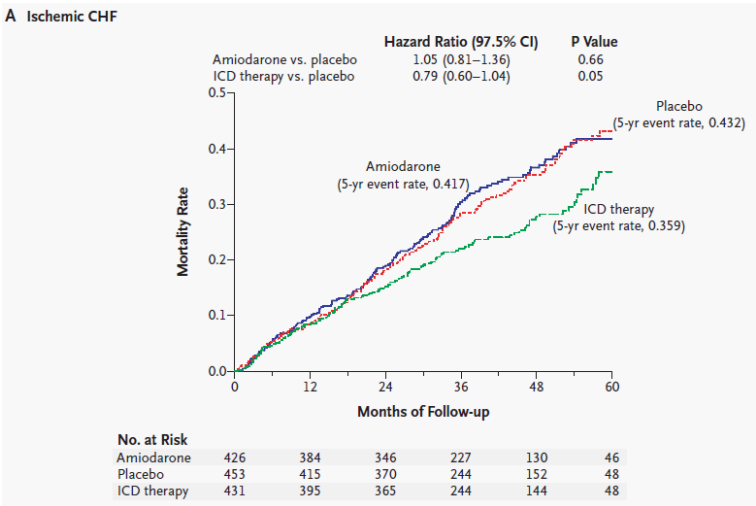
Figure 2. Kaplan–Meier Estimates of the Probability of Survival in the Group Assigned to Receive an Implantable Defibrillator and the Group Assigned to Receive Conventional Medical Therapy.
The difference in survival between the two groups was significant (nominal P=0.007, by the log-rank test).

Mortality in the ICD treated groups is strikingly similar in the two MADIT trials at approximately 25% at 4 years. The mortality in the non-ICD, conventional treatment groups, was however much lower in MADIT 2 resulting in a lower relative risk reduction. This is likely to be due to the improved optimal medical management in the later trial:

non-ICD patients	MADIT (1996)	MADIT 2 (2002)
β-blocker use	15%	70%
ACE-inhibitor use	55%	72%

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT, Bardy *et al. N Engl J Med* 2005;**352**:225-37) randomised 1311 patients with ischaemic heart disease, LVEF ≤35% and NYHA II/III heart failure symptoms to ICD or amiodarone therapy over a median follow-up of 45.5 months.

The median LVEF was 25% (20-30%). There was a 7.3% absolute and a 21% relative risk reduction in all-cause mortality in the ICD group with ischaemic aetiology:



The selection criteria in MADIT and MUSTT required inducibility of ventricular arrhythmia by programmed electrical stimulation whereas MADIT 2 and SCD-HeFT did not. The all-cause mortality after 4-years' follow-up in patients receiving ICD implantation was similar in all 4 trials suggesting that inducibility does not select a higher risk group or a group with more to gain from ICD therapy:

	EPS selection criterion	4-year all-cause mortality	
		ICD group	conventional group
MADIT (1996)	**yes**	**25%**	**44%**
MUSTT (2001)	**yes**	**22%**	**41%**
MADIT 2 (2004)	**no**	**25%**	**36%**
SCD-HeFT (2005)	**no**	**26%**	**36%**

Sub-set analysis of the MADIT-II data was used in previous NICE guidance to restrict ICD therapy to those with QRS duration >120ms and LVEF ≤30%. However, analysis of the trial data has shown that there were no significant differences in the effect of ICD therapy on survival when patients were stratified by age, sex, ejection fraction, NYHA class, or the QRS duration. This sub-set stratification is therefore not statistically valid and has never been tested in a clinical trial.

Two trials did not demonstrate benefit from ICD implantation. The coronary artery bypass graft-patch trial (CABG-Patch, Bigger *et al. N Engl J Med* 1997;**337**:1569-75) randomised 900 patients with LVEF ≤35% and abnormal signal-averaged ECG (duration of the filtered QRS complex, ≥114 ms; root-mean-square voltage in the terminal 40ms of the QRS complex, <20µV; or duration of the terminal filtered QRS complex at <40µV, >38 ms) to epicardial ICD implantation at the time of planned coronary artery bypass grafting. Over a mean of 36 months' follow-up, there was no difference in overall mortality between the randomised groups with a hazard ratio for death from any cause was 1.07 (0.81-1.42; p=0.64).

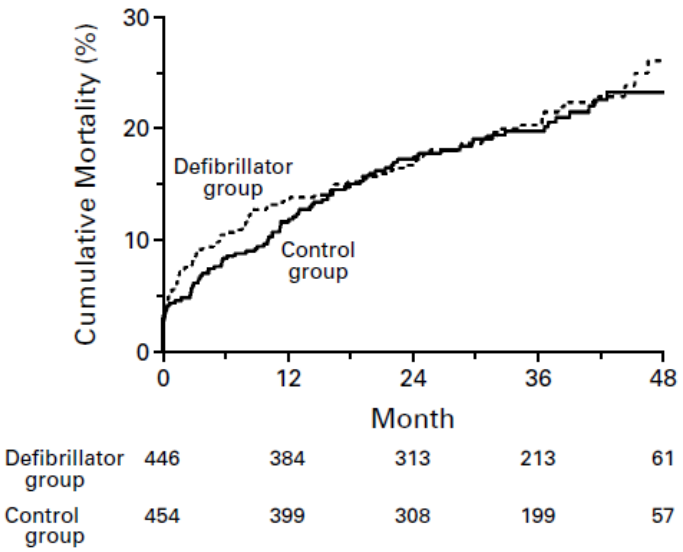


Figure 1. Kaplan–Meier Analysis of the Probability of Death According to Study Group.

The defibrillator in acute myocardial infarction trial (DINAMIT, Hohnloser *et al. N Engl J Med* 2004;**351**:2481-2488), the only study of ICD implantation early after myocardial infarction, randomised 674 patients with LVEF ≤35% and impaired cardiovascular autonomic function 6 to 40 days after myocardial infarction to endocardial ICD implantation or conventional medical therapy.

Over a mean follow-up of 30 months, there was no reduction in all-cause mortality (7.5%/y ICD, 6.9%/y control, hazard ratio 1.08 (0.76-1.55; p=0.66):

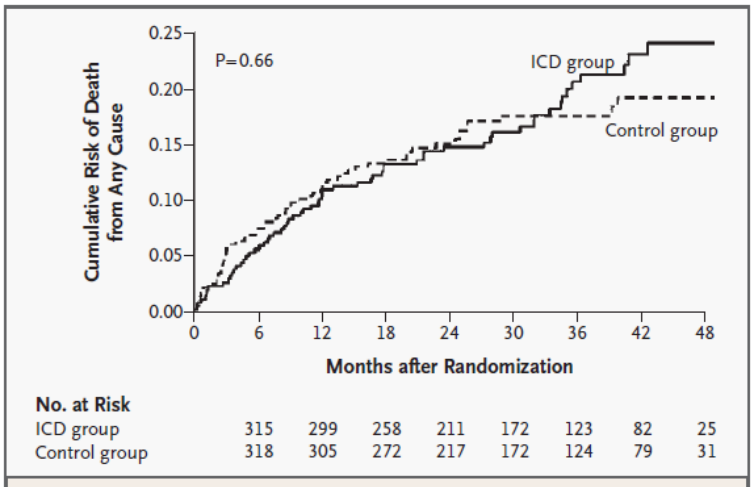


Figure 1. Kaplan–Meier Estimates of the Cumulative Risk of Death from Any Cause, According to Study Group.
ICD denotes implantable cardioverter–defibrillator.

There was, however, a significant reduction in arrhythmic death in the ICD group (1.5%/y ICD, 3.5%/y control, hazard ratio 0.42; p=0.009), but this was cancelled out by a significant increase in non-arrhythmic death (6.1%/y ICD, 3.5%/y control, hazard ration 1.75; p=0.02).

The most likely explanation of this finding is that, early after myocardial infarction, patients defibrillated from ventricular fibrillation are at increased risk of non-arrhythmic death and that in this group of patients the ICD is changing the mode of death rather than overall-mortality. The hypothesis that the proximity of recent myocardial infarction identifies a group of patients who benefit less from ICD implantation is supported by an analysis of the MADIT II trial (Wilber *et al. Circulation.* 2004;**109**:1082-1084) in which there was a smaller all-cause mortality benefit in patients receiving ICD implantation in the lowest quartile (18 months) after myocardial infarction compared to later time points.

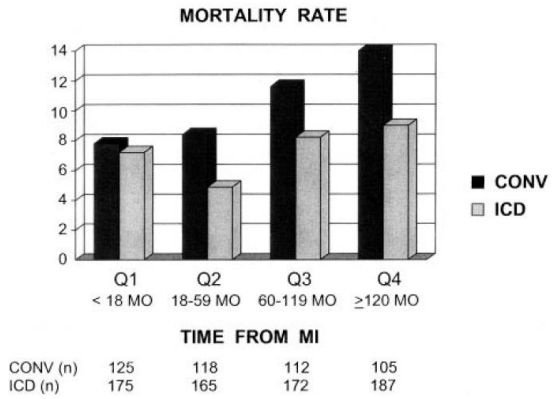


TABLE 1. Effect of the ICD by Elapsed Time From MI

MI Time, mo	HR	95% CI	*P*
<18	0.98	0.52–1.84	0.95
18–59	0.52	0.26–1.05	0.07
60–119	0.50	0.28–0.91	0.02
≥120	0.62	0.36–1.08	0.09

HR indicates hazard ratio for ICD vs conventional therapy.

This and other studies demonstrate that patients at increased arrhythmic risk after myocardial infarction remain at increased risk over long-term follow-up. The absence of arrhythmia many years after the infarction does not imply a low risk.

4.2.2.2) Non-ischaemic cardiomyopathy

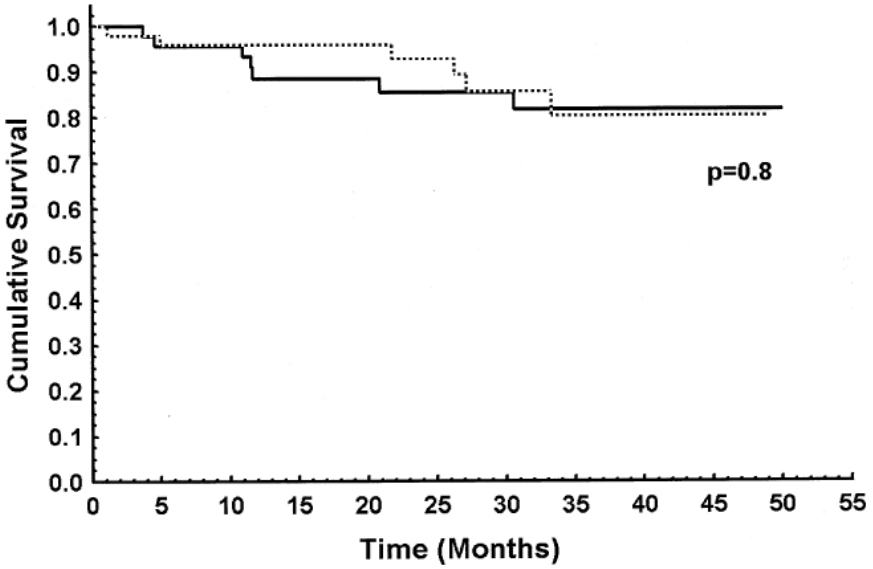
There have been multiple randomised prospective trials investigating the role of ICD implantation in the primary prevention if sudden cardiac death in patients with non-ischaemic cardiomyopathy.

4.2.2.2.1) CAT

The cardiomyopathy trial (CAT, Bänsch *et al. Circulation*. 2002;**105**:1453-1458) randomised 104 patients within 9 months of a diagnosis of non-ischaemic cardiomyopathy with LVEF ≤30% to ICD or medical care. All-cause mortality was much lower than expected at 26% in the ICD group and 31% in the medical group resulting in a lack of power to demonstrate a statistical difference.

4.2.2.2.2) AMIOVERT

The amiodarone versus implantable defibrillator in patients with non-ischaemic cardiomyopathy and asymptomatic non-sustained ventricular tachycardia (AMIOVERT, Strickberger *et al. J Am Coll Cardiol* 2003;**41**:1707–12) trial randomised 103 patients with chronic dilated cardiomyopathy, non-sustained VT (3 beats to 30s at >100bpm) and LVEF ≤35% to ICD or amiodarone. All-cause mortality did not differ significantly between the groups (11.8% ICD, 13.5% amiodarone; p=0.8):



4.2.2.2.3) DEFINITE

The defibrillators in non-ischaemic cardiomyopathy treatment evaluation (DEFINITE, Kadish *et al. N Engl J Med* 2004;**350**:2151-8) trial randomised 458 patients with non-ischaemic cardiomyopathy, NYHA I to III heart failure symptoms (99, 21.6%, patients were NYHA I), LVEF ≤35%, >10 ventricular premature beats per hour or non-sustained ventricular tachycardia to ICD or continued medical therapy. There were numerically fewer deaths in the ICD group at 1 and two year follow up but this did not reach statistical significance. Sudden death was reduced with an absolute reduction of 4.8% over a mean follow-up of 29 months (hazard ratio 0.21; p=0.006):

	ICD + OPT	OPT	
1y all-cause mortality	2.6%	6.2%	ns
2y all-cause mortality	7.9%	14.1%	ns
sudden cardiac death	1.3%	6.1%	HR 0.20, p=0.006

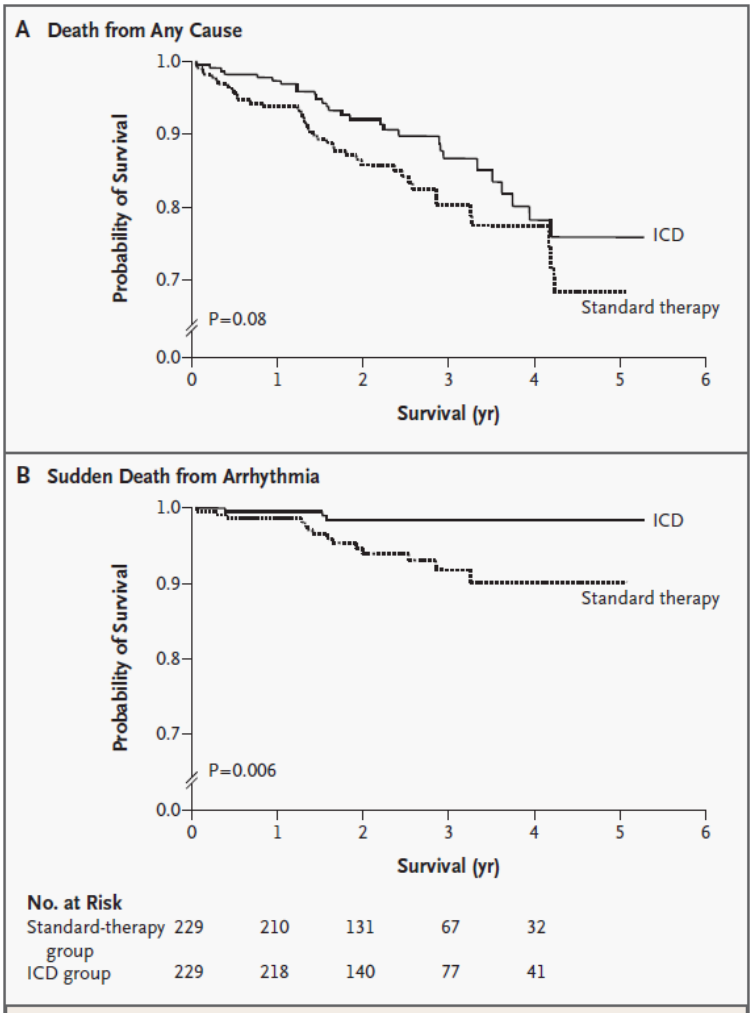
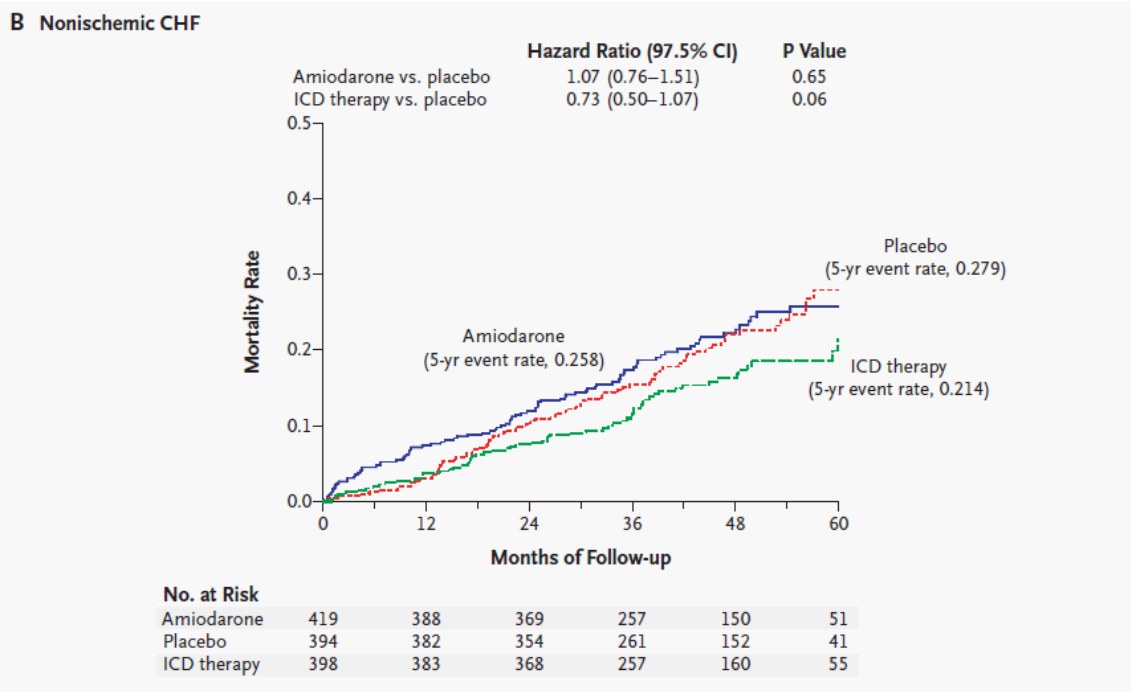


Figure 1. Kaplan–Meier Estimates of Death from Any Cause (Panel A) and Sudden Death from Arrhythmia (Panel B) among Patients Who Received Standard Therapy and Those Who Received an Implantable Cardioverter–Defibrillator (ICD).

In the ICD group, as compared with the standard-therapy group, the hazard ratio for death from any cause was 0.65 (95 percent confidence interval, 0.40 to 1.06) and the hazard ratio for sudden death from arrhythmia was 0.20 (95 percent confidence interval, 0.06 to 0.71).

4.2.2.2.4) SCD-HeFT

The sudden cardiac death heart failure trial (SCD-HeFT, Bardy *et al. N Engl J Med* 2005;**352**:225-37) randomised 1210 patients with non-ischaemic cardiomyopathy (and 1311 with ischaemic cardiomyopathy as described above), NYHA II or III and LVEF ≤35% to ICD, amiodarone or placebo. Over a median follow-up of 45.5 months, there was a 6.5% absolute and a 27% relative risk reduction in all-cause mortality in the ICD group with non-ischaemic aetiology (p=0.06):



	ischaemic	non-ischaemic
5y all-cause mortality – placebo	43.2%	27.9%
5y all-cause mortality - ICD	35.9%	21.4%
absolute mortality reduction with ICD	7.3%	6.5%
relative risk reduction	21%	27%
p value	0.05	0.06

The relative risk reduction was actually greater in the non-ischaemic (27%) than the ischaemic (21%) group. The lower event rate in the non-ischaemic group resulted in similar absolute risk reductions in both groups.

4.2.2.3) Hypertrophic cardiomyopathy (HCM)

There have been no randomised controlled trials of ICD implantation for primary prevention in HCM, but there are multiple non-randomised, observational and registry publications. The risk factors identified represent surrogate markers for the arrhythmia risk inherent in the underlying myocardial disease.

Prior cardiac arrest and syncope have been discussed above. Other major risk factors identified from observational studies include sustained or non-sustained ventricular tachycardia (HR >2.5), family history of sudden cardiac death (HR 1.27), left ventricular septal thickness of ≥30mm (HR 4.0) and abnormal blood pressure response on exercise (HR 2.4 to 9.6). Other risk factors include atrial fibrillation, myocardial ischaemia, left ventricular out-flow tract obstruction, high-risk mutations and intensive physical exertion (Garratt *et al. Eur Heart J* 2010;**12**:1156-1175).

Based on the best evidence currently available, ICD implantation is recommended in patients with one or more of these risk factors for sudden cardiac death.

4.2.2.4) Arrhythmogenic right ventricular cardiomyopathy (ARVC)

Observational data and registries have identified the risk factors of inducible VT, non-sustained VT, male gender, severe dilation or extensive right ventricular involvement, left ventricular involvement, age less than 5-years at presentation, prior cardiac arrest, unexplained syncope and

high-risk genotypes. Hodgkinson *et al.* (*J Am Coll Cardiol* 2005:**45**:400-8) described a genetically homogeneous ARVC population considered at high risk. There were no deaths in the ICD treated group, compared with a five year mortality of 28% in matched high risk males without ICDs and 9% in matched high risk females. The majority of patients reported in these series have received ICD implantation following a clinical arrhythmia. There is less information on the risk of appropriate ICD therapy in patients with other presentations. There are insufficient data to make recommendations on the implantation of an ICD in asymptomatic patients with mild structural disease and these decisions must be individualised and based on the best available data.

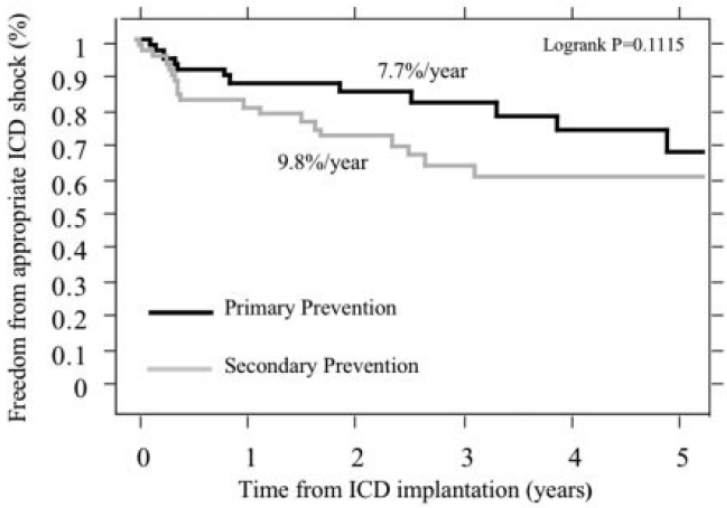
ICD therapy is indicated as primary prevention in ARVC patients with high risk features.

4.2.2.5) Left ventricular non-compaction

LVNC is usually diagnosed following a symptomatic arrhythmia of because of heart failure. There are no published data on the efficacy of ICD therapy in truly asymptomatic individuals. Expert opinion recommends that in addition to optimal pharmacological therapy, ICD implantation for primary prevention is appropriate in patients with LVNC presenting severely impaired LV systolic function (LVEF ≤35%) (Oechslin E, Jenni R. *European Heart Journal* 2011;**32**:1446–1456, Chin *et al. Circulation* 1990;**82**:507-513, Celiker *et al. Pacing Clin Electrophysiol* 2004;**27**:104-108).

4.2.2.6) Congenital heart disease

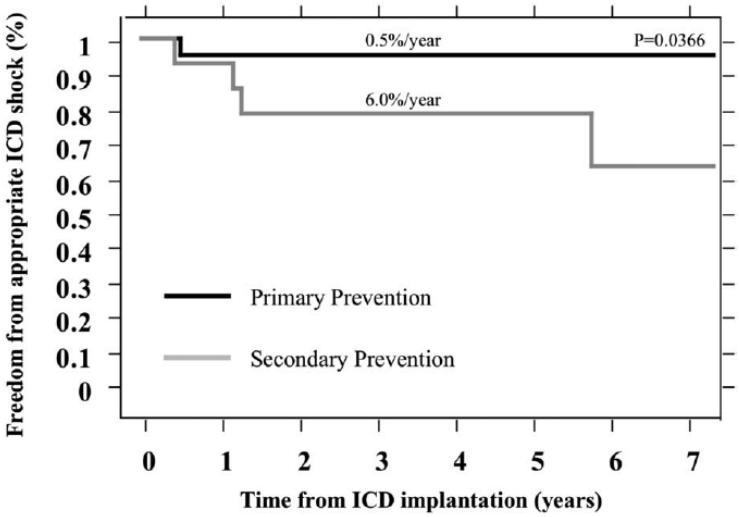
A multicentre series of 68 patients with tetralogy of Fallot were implanted with an ICD for primary prevention because of presyncope (13 patients, 19.1%), syncope (30 patients, 44.1%), palpitations (33, 48.5%), QRS duration >180 ms (19 patients, 27.9%), non-sustained ventricular tachycardia (25 patients, 36.8%), left ventricular ejection fraction ≤35% (2, 2.9%) or inducible sustained ventricular tachycardia (28, 41.2%). These patients showed an annual rate of appropriate shocks of 7.7% (Khairy *et al. Circulation* 2008;**117**:363-370).



Multivariate analysis showed that factors associated with appropriate shocks were higher LV end diastolic pressure (HR 1.3 per mmHg), and non-sustained ventricular tachycardia (HR 3.7). The authors devised a risk score, based on clinical characteristics, allowing patients to be categorised as low, intermediate or high risk for appropriate shocks. The high risk group had an annualised rate of appropriate shocks of 17.5%, the intermediate group 3.8% and the low risk group did not receive appropriate shocks.

A multicentre series of 23 patients with transposition of the great arteries (TGA) (Khairy *et al. Circulation Electrophysiol* 2008;**1**:250-257) treated with a Mustard or a Senning procedure

including an intra-atrial baffle underwent ICD implantation for primary prevention indications (presyncope in 3 patients (13.0%), syncope in 8 patients (34.8%), palpitations in 12 patients (52.2%), non-sustained ventricular tachycardia in 11 patients (47.8%), systemic right ventricular ejection fraction ≤35% in 8 patients (34.8%), QRS duration ≥180ms in 7 patients (30.4%), and inducible sustained ventricular tachycardia in 7 patients (30.4%)). These patients showed a 0.5% annual rate of appropriate ICD shocks.

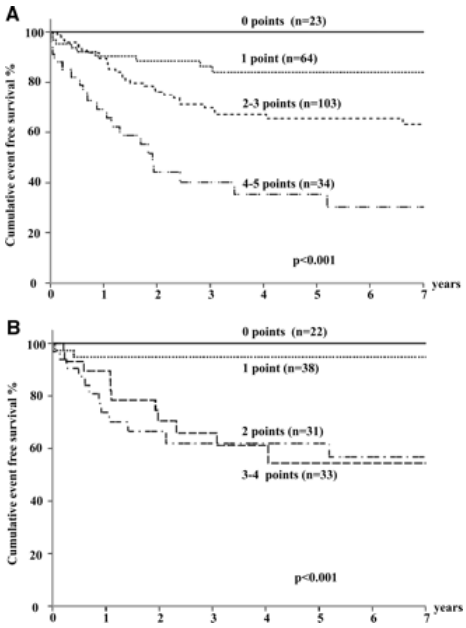


On the available evidence, ICD implantation appears to be indicated for primary prevention indications in patients with Tetralogy of Fallot. There are insufficient data to make a recommendation in patients with transposition of the great arteries.

4.2.2.7) Long QT syndromes

Asymptomatic patients with LQTS represent a lower risk group than those with a history of syncope or cardiac arrest, with a risk of death of <1% per year (Priori *et al. N Engl J Med* 2003;**348**:1866-1874). All should receive optimal pharmacological therapy including beta-blockade. Of the commonest genotypes, LQT1 is associated with the lowest risk of 0.3% per year while LQT2 and LQT3 have similar risks of 0.6% per year. Patients with corrected QT intervals over 500ms represent a high-risk sub-group with a hazard ratio of 3.34 for QT intervals 500-549ms and 6.35 for those with QTc ≥500ms (Schwartz *et al. Heart Rhythm* 2009;**6**:113-120, Sauer *et al. J Am Coll Cardiol* 2007;**49**:329-337).

Schwartz *et al.* (*Circulation* 2010;**122**:1272-82) described an international registry of 233 patients with LQTS and ICD implantation. Only 9 were asymptomatic; two of these received appropriate ICD therapy during follow up. A risk score, based on symptoms, length of QT and age was developed, and distinguished those in the whole group who received appropriate therapy from those who did not, and can be used to guide selection for ICD implantation.



A study from the same registry examined the risk to an individual with LQTS when a sibling with LQTS has died. Sibling death was not significantly associated with cardiac arrest (Kaufman *et al. Heart Rhythm* 2008;**5**:831-836).

ICD implantation is appropriate in asymptomatic LQTS patients with high-risk features based on the best available data.

4.2.2.8) Short QT syndromes

There are no randomised controlled trial data in this very rare syndrome. A high incidence of sudden cardiac death has been reported in affected families and unstable ventricular arrhythmias are often inducible on electrophysiology study. Published expert opinion is to offer ICD implantation to these patients for primary prevention (Cross B *et al. J Interv Card Electrophysiol* 2011;**31**:25–31).

4.2.2.9) Brugada syndrome

Brugada syndrome patients without symptoms or a spontaneous type 1 ECG abnormality represent a low-risk sub-group where ICD implantation has not been shown to improve survival.

The available data are consistent that asymptomatic patients with Brugada syndrome and a spontaneous type 1 ECG abnormality are at increased risk of sudden death, but series vary in the magnitude of that risk from <1% to 6.4% per year (Garratt *et al. Europace* 2010;**12**:1156-1175). Both a conservative strategy and ICD implantation guided by electrophysiology study are supported by published series although the value of electrophysiology study in this context remains to be fully established.

4.2.2.10) Catecholaminergic polymorphic ventricular tachycardia (CPVT)

CPVT patients not receiving beta-blockers are at high risk of fatal or near fatal arrhythmias with an incidence of 3.1% per year. All patients with the CPVT gene mutations should be treated with beta-blockers regardless of symptoms. Data on further risk stratification is scarce because of the rarity of the condition and electrophysiology testing does not appear to have sufficient sensitivity or specificity to be clinically useful in this condition (Zipes *et al. J Am Coll Cardiol* 2006;**48**:e247-

346, Priori *et al. Eur Heart J* 2001;**22**:1374-1450, Marks *et al. J Cell Physiol* 2002;**190**:1-6). A decision on ICD implantation must be individualised and made on the best available data.

4.2.2.11) Patients awaiting cardiac transplantation

By definition, patients awaiting cardiac transplantation for heart failure have severe cardiac disease and a high short-term mortality. This is demonstrated by a high rate of sudden cardiac death in patients on the transplant waiting list. Whilst, if transplantation were not to take place, many patients would not survive 12 months, with transplantation 10-year survival exceeds 50%. It is therefore reasonable to implant an ICD in patients with a high likelihood of surviving to transplantation in the absence of a ventricular arrhythmia.

4.2.2.12) Children, adolescents and adults with congenital heart disease

It must be recognised that the dataset for ICD therapy is almost entirely derived from studies in adults. In addition, there are factors unique to the young people that increase both the risks and benefits of ICD therapy (Chatrath *et al. Mayo Clin Proc* 2002;**77**:226-231). Nevertheless, data from non-randomised studies support the use of ICD implantation in young people resuscitated from cardiac arrest following the exclusion of a reversible or curable cause with the same indications as adults.

There are few data specifically related to primary prevention in children and adolescents. Some have been derived from the international long QT registry, and were discussed above. There are some data available in adolescents and adults following surgery for congenital heart disease. This was also discussed above.

5) Cardiac resynchronisation therapy

Cardiac resynchronisation therapy (CRT) is a technology which increases the efficiency of left ventricular contraction by direct electrical stimulation of the left ventricle. Its original indication was to improve symptoms of heart failure but more recent data also show evidence of improved survival, the prevention of heart failure symptoms and reduced admission to hospital with decompensation.

Heart failure due to left ventricular systolic dysfunction is often accompanied by reduced electrical synchronisation. The most common abnormalities being delayed conduction through the atrioventricular node – PR prolongation, first degree heart block – and slowed ventricular depolarisation – QRS prolongation, bundle-branch block. This results in delayed contraction of parts of the left ventricle which can reduce ejection fraction, increase metabolic demands and cause functional mitral regurgitation with dilation of the heart. These electrical abnormalities are seen in approximately 1/3 of patients with advanced heart failure and are associated with heart failure progression, sudden cardiac death and all-cause mortality.

5.1) Current national and international guidance

5.1.1) UK

Current NICE guidance (NICE technology appraisal guidance 120: Cardiac resynchronisation therapy for the treatment of heart failure TA120, May 2007, www.nice.org.uk/TA120) states:

1.1 Cardiac resynchronisation therapy with a pacing device (CRT-P) is is recommended as a treatment option for people with heart failure who fulfil all the following criteria.

- They are currently experiencing or have recently experienced New York Heart Association (NYHA) class III-IV symptoms.
- They are in sinus rhythm:
  - **either** with a QRS duration of 150ms or longer estimated by standard electrocardiogram (ECG)
  - **or** with a QRS duration of 120-149ms estimated by ECG **and** mechanical dyssynchrony that is confirmed by echocardiography.
- They have a left ventricular ejection fraction of 35% or less.
- They are receiving optimal pharmacological therapy.

1.2 Cardiac resynchronisation therapy with a defibrillator device (CRT-D) may be considered for people who fulfil the criteria for implantation of a CRT-P device in section 1.1 and who also separately fulfil the criteria for the use of an ICD device as recommended in NICE technology appraisal guidance 95.

5.1.2) North America

Current American College of Cardiology, American Heart Association and Heart Rhythm Society guidance (ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm

Abnormalities: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines *J. Am. Coll. Cardiol.* 2008;**51**;e1-e62 http://content.onlinejacc.org/cgi/content/full/51/21/e1)

Class I (procedure should be performed) and **IIa** (it is reasonable to perform the procedure):

CLASS I

1. For patients who have LVEF less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and sinus rhythm, CRT with or without an ICD is indicated for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms with optimal recommended medical therapy. *(Level of Evidence: A)* (222,224,225,231)

CLASS IIa

1. For patients who have LVEF less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and AF, CRT with or without an ICD is reasonable for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms on optimal recommended medical therapy. *(Level of Evidence: B)* (220,231)
2. For patients with LVEF less than or equal to 35% with NYHA functional Class III or ambulatory Class IV symptoms who are receiving optimal recommended medical therapy and who have frequent dependence on ventricular pacing, CRT is reasonable. *(Level of Evidence: C)* (231)

CLASS IIb

1. For patients with LVEF less than or equal to 35% with NYHA functional Class I or II symptoms who are receiving optimal recommended medical therapy and who are undergoing implantation of a permanent pacemaker and/or ICD with anticipated frequent ventricular pacing, CRT may be considered. *(Level of Evidence: C)* (231)

5.1.3) European Society of Cardiology

Current ESC guidance (Focused Update of ESC Guidelines on device therapy in heart failure 2010. Dickstein *et al. European Heart Journal* 2010;**31**:2677–2687) states:

Recommendation in patients with heart failure in New York Heart Association function class III/IV

Recommendation	Patient population	Class[a]	Level[b]	Ref.[c]
CRT-P/CRT-D is recommended to reduce morbidity and mortality[d]	NYHA function class III/IV LVEF ≤35%, QRS ≥120 ms, SR Optimal medical therapy Class IV patients should be ambulatory[e]	I	A	5–19

Heart Rhythm UK

Recommendation in patients with heart failure in New York Heart Association function class II

Recommendation	Patient population	Class[a]	Level[b]	Ref.[c]
CRT preferentially by CRT-D is recommended to reduce morbidity or to prevent disease progression[d]	NYHA function class II LVEF ≤35%, QRS ≥150 ms, SR Optimal medical therapy	I	A	9, 20–22

Recommendations in patients with heart failure and permanent atrial fibrillation

Recommendations	Patient population	Class[a]	Level[b]	Ref.[c]
CRT-P/CRT-D[d] should be considered to reduce morbidity	NYHA function class III/IV LVEF ≤35%, QRS ≥130 ms Pacemaker dependency induced by AV nodal ablation	IIa	B	27–40
CRT-P/CRT-D[d] should be considered to reduce morbidity	NYHA function class III/IV LVEF ≤35%, QRS ≥130 ms Slow ventricular rate and frequent pacing[e]	IIa	C	—

Recommendations in patients with heart failure and a concomitant class I pacemaker indication

Recommendations	Patient population	Class[a]	Level[b]	Ref.[c]
CRT-P/CRT-D[d] is recommended to reduce morbidity	NYHA function class III/IV LVEF ≤35%, QRS ≥120 ms	I	B	41–48
CRT-P/CRT-D[d] should be considered to reduce morbidity	NYHA function class III/IV LVEF ≤35%, QRS <120 ms	IIa	C	—
CRT-P/CRT-D[d] may be considered to reduce morbidity	NYHA function class II LVEF ≤35%, QRS <120 ms	IIb	C	—

Current ESC guidance on acute and chronic heart failure states (McMurray *et al. Eur Heart J* 2012;**33**:1787-1847):

Recommendations for the use of CRT where the evidence is strong—patients in sinus rhythm with NYHA functional class III and ambulatory class IV heart failure and a persistently reduced ejection fraction, despite optimal pharmacological therapy

Recommendations	Class[a]	Level[b]	Ref[c]
LBBB QRS morphology CRT-P/CRT-D is recommended in patients in sinus rhythm with a QRS duration of ≥120 ms, LBBB QRS morphology, and an EF ≤35%, who are expected to survive with good functional status for >1 year, to reduce the risk of HF hospitalization and the risk of premature death.	I	A	156, 157
Non-LBBB QRS morphology CRT-P/CRT-D should be considered in patients in sinus rhythm with a QRS duration of ≥150 ms, irrespective of QRS morphology, and an EF ≤35%, who are expected to survive with good functional status for >1 year, to reduce the risk of HF hospitalization and the risk of premature death.	IIa	A	156, 157

Recommendations for the use of CRT where the evidence is strong—patients in sinus rhythm with NYHA functional class II heart failure and a persistently reduced ejection fraction, despite optimal pharmacological therapy

Recommendations	Class[a]	Level[b]	Ref[c]
LBBB QRS morphology CRT, preferably CRT-D is recommended in patients in sinus rhythm with a QRS duration of ≥130 ms, LBBB QRS morphology, and an EF ≤30%, who are expected to survive for >1 year with good functional status, to reduce the risk of HF hospitalization and the risk of premature death.	I	A	154, 155
Non-LBBB QRS morphology CRT, preferably CRT-D should be considered in patients in sinus rhythm with a QRS duration of ≥150 ms, irrespective of QRS morphology, and an EF ≤30%, who are expected to survive for >1 year with good functional status, to reduce the risk of HF hospitalization and the risk of premature death.	IIa	A	154, 155

Recommendations for the use of CRT where the evidence is uncertain—patients with symptomatic HF (NYHA functional class II–IV) and a persistently reduced EF despite optimal pharmacological therapy and in AF or with a conventional pacing indication

Recommendations	Class[a]	Level[b]	Ref[c]
Patients in permanent AF			
CRT-P/CRT-D may be considered in patients in NYHA functional class III or ambulatory class IV with a QRS duration ≥120 ms and an EF ≤35%, who are expected to survive with good functional status for >1 year, to reduce the risk of HF worsening if:			
• The patient requires pacing because of an intrinsically slow ventricular rate	IIb	C	–
• The patient is pacemaker dependent as a result of AV nodal ablation	IIb	C	–
• The patient's ventricular rate is ≤60 b.p.m. at rest and ≤90 b.p.m. on exercise.	IIb	C	–
Patients with an indication for conventional pacing and no other indication for CRT			
In patients who are expected to survive with good functional status for >1 year:			
• CRT should be considered in those in NYHA functional class III or IV with an EF ≤35%, irrespective of QRS duration, to reduce the risk of worsening of HF	IIa	C	–
• CRT may be considered in those in NYHA functional class II with an EF ≤35%, irrespective of QRS duration, to reduce the risk of worsening of HF.	IIb	C	–

5.2) Published data

CRT was developed as an electrical treatment for heart failure symptoms in patients with severe left ventricular impairment and impaired synchronisation of left ventricular contraction. Early studies confirmed symptomatic benefit in these patients with more recent data demonstrating a mortality benefit and defining groups of patients who are most likely to benefit from this treatment. The data are presented according to the selection criteria of left ventricular function, dyssynchrony and symptoms:

5.2.1) Left ventricular function

CRT trials have been conducted almost exclusively in patients with severely impaired left ventricular systolic function (LVEF ≤35%). Small studies (Chung *et al. Eur J Heart Fail* 2010;**12**:581–87, Fung *et al. J Cardiovasc Electrophysiol* 2006;**17:**1288–92) have shown benefit in selected patients with less severe systolic impairment but at present there are currently insufficient data to recommend CRT in patients with LVEF >35%. There are no data to support the implantation of a CRT device in patients with normal left ventricular systolic function.

5.2.2) Dys-synchrony

CRT is an electrical treatment allowing the stimulation of the right and left ventricles. Its benefit is thought to derive from resynchronisation of cardiac contraction. Initial studies inferred dyssynchrony from prolonged QRS duration (≥120ms) on the standard ECG. Later studies investigated the concept of mechanical dyssynchrony in those with and without QRS prolongation.

5.2.2.1) QRS <120ms

Small single centre studies have suggested benefit from CRT in patients with normal QRS duration selected in a variety of ways. A small randomised clinical trial of CRT in 126 patients with LVEF ≤35%, NYHA III symptoms, QRS <120ms and mechanical dyssynchrony (Beshai *et al. N Engl J Med* 2007;**357**:2461-2471) showed an increase in the proportion of patients improving by one NYHA class (29% versus 48% p=0.04) but there was no significant improvement in other end points, including the quality-of-life, 6-minute walking distance, left ventricular function or peak oxygen consumption. A large on-going trial (EchoCRT, NCT00683696) in patients with QRS <130ms should provide additional information in this important group of patients but at present there are insufficient data to recommend CRT in patients with normal QRS duration.

5.2.2.2) QRS ≥120ms

There are multiple clinical trials demonstrating significant sustained symptomatic benefit in patients with heart failure, LVEF ≤35% and QRS ≥120ms:

Table 1 Inclusion criteria in randomized clinical trials evaluating cardiac resynchronization therapy in heart failure

Trial	Patients	NYHA class	LVEF (%)	LVEDD (mm)	SR/AF	QRS (ms)	ICD
MUSTIC-SR[16]	58	III	≤35	≥60	SR	≥150	No
MIRACLE[5]	453	III, IV	≤35	≥55	SR	≥130	No
MUSTIC AF[35]	43	III	≤35	≥60	AF	≥200	No
PATH CHF[6]	41	III, IV	≤35	NA	SR	≥120	No
MIRACLE ICD[8]	369	III, IV	≤35	≥55	SR	≥130	Yes
CONTAK CD[54]	227	II, IV	≤35	NA	SR	≥120	Yes
MIRACLE ICD II[9]	186	II	≤35	≥55	SR	≥130	Yes
PATH CHF II[55]	89	III, IV	≤35	NA	SR	≥120	Yes/no
COMPANION[10]	1520	III, IV	≤35	NA	SR	≥120	Yes/no
CARE HF[11]	814	III, IV	≤35	≥30	SR	≥120	No
CARE HF[17]	813	III, IV	≤35	≥30	SR	≥120	No
REVERSE[21,22]	610	I, II	≤40	≥55	SR	≥120	Yes/no
MADIT CRT[20]	1800	I, II	≤30	NA	SR	≥130	Yes
RAFT[56]	1800 Canada	II, III	≤30	>60	SR/AF	≥130 ≥200[a]	Yes

The mean improvement in NYHA function class was 0.5 to 0.8, with a 20% increase in 6 minute walk distance and an increase in peak oxygen consumption of 10 to 15%. The trials have also shown improvements in ejection fraction, mitral regurgitation and a reduction in left ventricular dilation:

Table 2 Endpoints, design, and main findings of the randomized clinical trials evaluating cardiac resynchronization therapy in heart failure

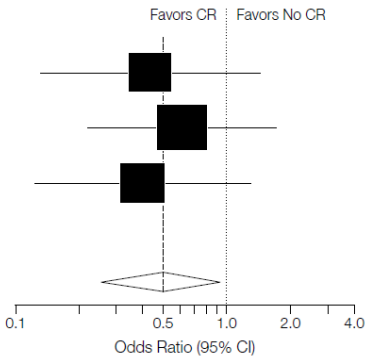
Trial	Endpoints	Design	Main findings
MUSTIC-SR[16]	6MWT, QoL, pVO_2, Hosp	Single-blinded, controlled, crossover, 6 months	CRT-P improved: 6MWT, QOL, pVO_2; reduced Hosp
MIRACLE[8]	NYHA class, QoL, pVO_2	Double-blinded, controlled, 6 months	CRT-P improved: NYHA, pVO_2, 6MWT
MUSTIC AF[35]	6MWT, QoL, pVO_2, Hosp	Single-blinded, controlled, crossover, 6 months	CRT-P improved all; reduction of Hosp
PATH CHF[6]	6MWT, pVO_2	Single-blinded, controlled, crossover, 12 months	CRT-P improved: 6MWT; pVO_2
MIRACLE ICD[8]	6MWT, QoL, Hosp	Double-blinded, ICD vs. CRT-D 6 months	CRT-D improved all from baseline (not ICD)
CONTAK CD[54]	All-cause death + HF Hosp, pVO_2, 6MWT, NYHA class, QoL, LVEDD, LVEF	Double-blinded, ICD vs. CRT-D 6 months	CRT-D improved: pVO_2, 6MWT; reduced LVEDD and increased LVEF
MIRACLE ICD II[9]	VE/CO_2, pVO_2, NYHA, QoL, 6MWT, LV volumes, LVEF	Double-blinded, ICD vs. CRT-D 6 months	CRT-D improved: NYHA, VE/CO_2; volumes, LVEF
COMPANION[10]	(i) All-cause death or Hosp	Double-blinded, controlled, OMT, CRT-D, CRT-P, ~15 months	CRT-P/CRT-D: reduced (i)
CARE-HF[11]	(i) All-cause death or CV event (ii) All-cause death	Double-blinded, controlled, OMT, CRT-P, 29 months	CRT-P reduced (i) and (ii)
REVERSE[21]	(i) % worsened by clinical composite endpoint, (ii) LVESVi, (iii) HF Hosp, (iv) all-cause death	Double-blinded, controlled, OMT, CRT-P ± ICD, 12 months	Primary endpoint NS; CRT-P/CRT-D reduced (ii) and (iii) Hosp but not (iv)
MADIT–CRT[20]	(i) HF event or death, (ii) All-cause death, (iii) LVESV	Controlled, CRTP, CRT-D, 2.4 years	CRT-D reduced (i) and (ii) but not (ii)

A meta-analysis of 4 early trials of CRT in 1634 patients reporting death and hospitalisation for heart failure or arrhythmia (Bradley *et al. JAMA* 2003;**289**:730-740) showed an absolute 1.8% (relative risk reduction 51%, hazard ration 0.49; 0.25-0.93) reduction in heart failure mortality, a significant absolute 4.4% (relative risk reduction 29%, hazard ratio 0.71; 0.53-0.96) reduction in heart failure hospitalisation, but no significant change in non-heart failure mortality although there was a trend to a reduction in all-cause mortality (absolute 1.4%, relative risk reduction 23%, hazard ratio 0.77; 0.51-1.18):

Figure 2. Death Among Patients Randomized to Cardiac Resynchronization vs No Resynchronization

A Progressive Heart Failure Mortality

Study	Cardiac Resynchronization: No. of Patients	Cardiac Resynchronization: No. (%) of Heart Failure Deaths	No Cardiac Resynchronization: No. of Patients	No Cardiac Resynchronization: No. (%) of Heart Failure Deaths	Weight, %	Odds Ratio (95% CI)
CONTAK CD[51]	245	4 (1.6)	245	9 (3.7)	29.6	0.44 (0.13-1.43)
InSync ICD[55]	272	6 (2.2)	282	10 (3.5)	39.9	0.61 (0.22-1.71)
MIRACLE[57]	263	4 (1.5)	269	10 (3.7)	30.6	0.40 (0.12-1.29)
MUSTIC[31]	29	0	29	0	0	
Overall	**809**	**14 (1.7)**	**825**	**29 (3.5)**		0.49 (0.25-0.93)



C All-Cause Mortality

Study	Cardiac Resynchronization: No. of Patients	Cardiac Resynchronization: No. (%) of All-Cause Deaths	No Cardiac Resynchronization: No. of Patients	No Cardiac Resynchronization: No. (%) of All-Cause Deaths	Weight, %	Odds Ratio (95% CI)
CONTAK CD[51]	245	11 (4.5)	245	16 (6.5)	28.9	0.67 (0.31-1.48)
InSync ICD[55]	272	14 (5.1)	282	17 (6.0)	34.0	0.85 (0.41-1.75)
MIRACLE[57]	263	14 (5.3)	269	19 (7.1)	35.4	0.74 (0.36-1.51)
MUSTIC[31]	29	1 (3.4)	29	0	1.7	3.11 (0.12-79.4)
Overall	**809**	**40 (4.9)**	**825**	**52 (6.3)**		0.77 (0.51-1.18)

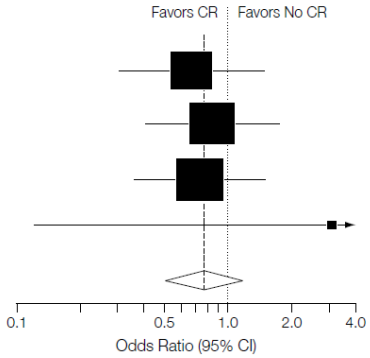
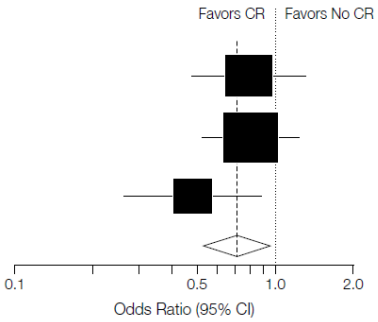


Figure 3. Heart Failure Hospitalization Among Patients Randomized to Cardiac Resynchronization vs No Cardiac Resynchronization

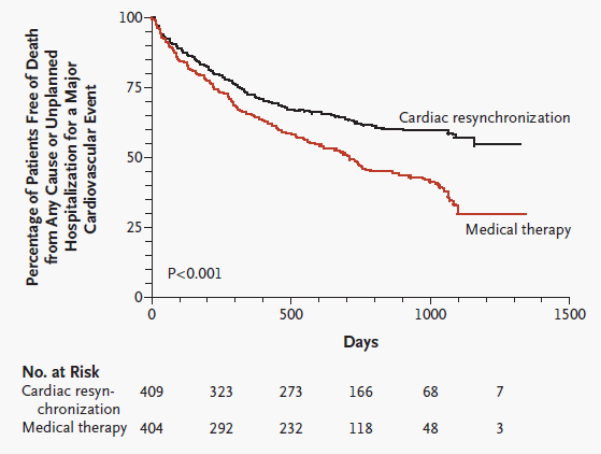
Study	Cardiac Resynchronization: No. of Patients	Cardiac Resynchronization: No. (%) of Patients Hospitalized	No Cardiac Resynchronization: No. of Patients	No Cardiac Resynchronization: No. (%) of Patients Hospitalized	Weight, %	Odds Ratio (95% CI)
CONTAK CD[51]	245	32 (13.1)	245	39 (15.9)	32.4	0.79 (0.48-1.32)
InSync ICD[55]	272	47 (17.3)	282	58 (20.6)	44.5	0.81 (0.53-1.24)
MIRACLE[17]	228	18 (7.9)	225	34 (15.1)	23.1	0.48 (0.26-0.88)
Overall	**745**	**97 (13.0)**	**752**	**131 (17.4)**		0.71 (0.53-0.96)

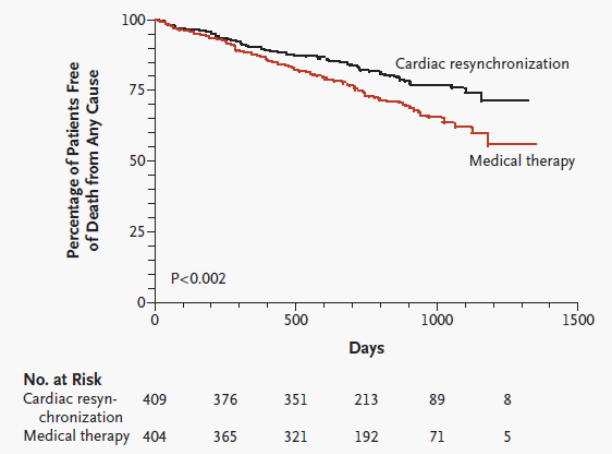


Mechanical dyssynchrony

In an attempt to increase the proportion of patients with QRS ≥120ms who show objective clinical benefit from CRT, trials have assessed a variety of indices of mechanical dyssynchrony and QRS durations:

Multiple small single centre reports described echocardiographic indices correlating with response to CRT and these indices of mechanical dyssynchrony were used as an empirical selection criterion for patients with QRS 120-149ms in the CArdiac REsynchronisation in Heart Failure trial (CARE-HF; Cleland *et al. N Engl J Med* 2005;**352**:1539-49). This randomised 813 patients with NYHA III/IV heart failure symptoms, LVEF ≤35% and QRS ≥150ms or ≥120ms with echocardiographic dyssynchrony (an aortic pre-ejection delay of more than 140ms, an interventricular mechanical delay of more than 40ms, or delayed activation of the posterolateral left ventricular wall) to optimal pharmacological therapy with or without the implantation of a pacemaker capable of CRT (CRT-P). Over a mean follow-up of 29.4 months there was a 16% absolute reduction in the primary end-point of death or heart failure hospitalisation (37% relative risk reduction, hazard ratio, 0.63; 95 percent confidence interval, 0.51 to 0.77; P<0.001), with a highly significant 10% absolute all-cause mortality reduction (36% relative risk reduction, hazard ratio 0.64; 95 percent confidence interval, 0.48 to 0.85; P<0.002):





However, only 92 randomised patients (11.3%) were selected on the basis of a QRS duration 120-149ms and mechanical dyssynchrony. These patients appeared to derive less benefit from CRT (HR 0.74; 0.54-1.02) than those with QRS durations ≥150ms (HR 0.60; 0.46-0.79) (Stavrakis *et al. J Cardiovasc Electrophysiol* 2012;**23**:163-168).

Because of a lack of agreement on the echocardiographic measurements for CRT selection, the PROSPECT trial (Chung *et al. Circulation*. 2008;**117**:2608-2616) assessed 498 patients with standard CRT indications. Twelve echocardiographic parameters of dyssynchrony, using conventional and tissue Doppler– based techniques, were evaluated. The ability of the echocardiographic parameters to predict a clinical composite score response varied widely, with sensitivity ranging from 6% to 74% and specificity ranging from 35% to 91%; for predicting left ventricular end-systolic volume response, sensitivity ranged from 9% to 77% and specificity from 31% to 93%. For all the parameters, the area under the receiver-operating characteristics curve for positive clinical or volume response to CRT was ≤0.62. There was large variability in the analysis of the dyssynchrony parameters.

Currently available measurements of dyssynchrony do not have sufficient sensitivity and specificity to extend or restrict CRT indications based on symptoms, QRS duration and LVEF. It is possible that future research will demonstrate mechanical dyssynchrony criteria which refine CRT selection criteria but at present there is insufficient evidence for their routine clinical use in patient selection for CRT therapy.

QRS duration and morphology

A recent meta-analysis (Stavrakis *et al. J Cardiovasc Electrophysiol* 2012;**23**:163-168) suggests that the majority of benefit from CRT was seen in those with a QRS ≥150ms (HR = 0.58, 95% CI: 0.50–0.68; P < 0.000010):

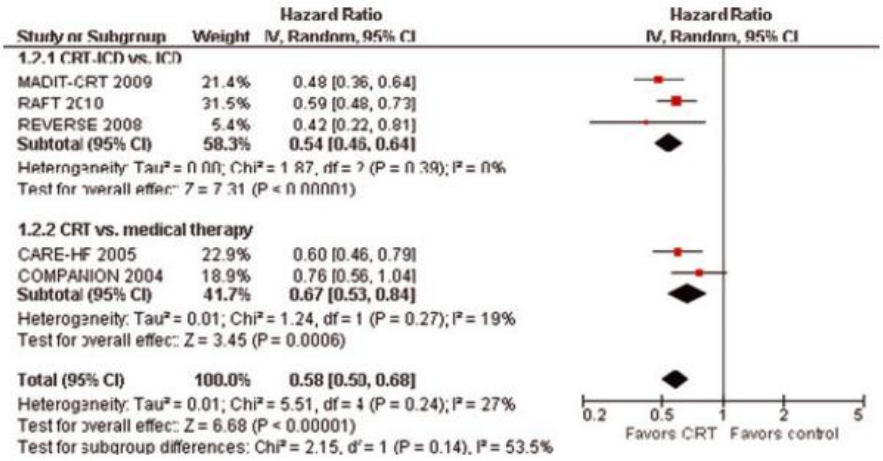


Figure 2. *Forest plot of study-specific and pooled hazard ratio and 95% confidence interval for the primary endpoint among patients with QRS ≥ 150 ms assigned to cardiac resynchronization therapy (CRT) versus control. ICD = implantable cardioverter defibrillator.*

with a non-significant benefit in those with QRS <150ms:

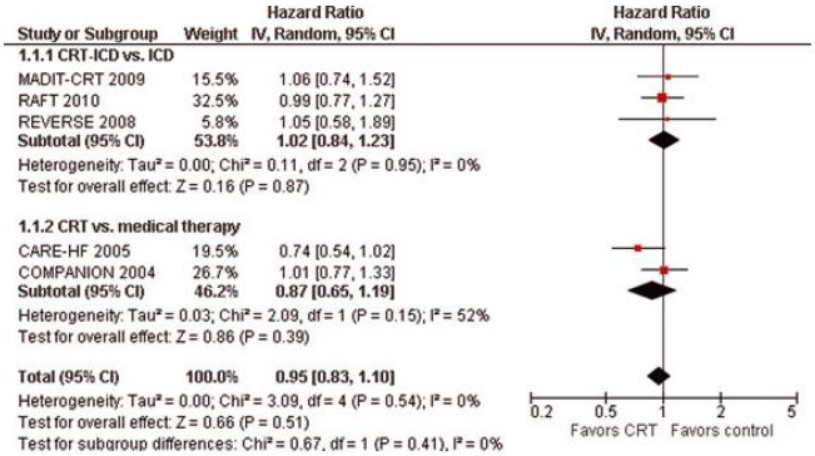
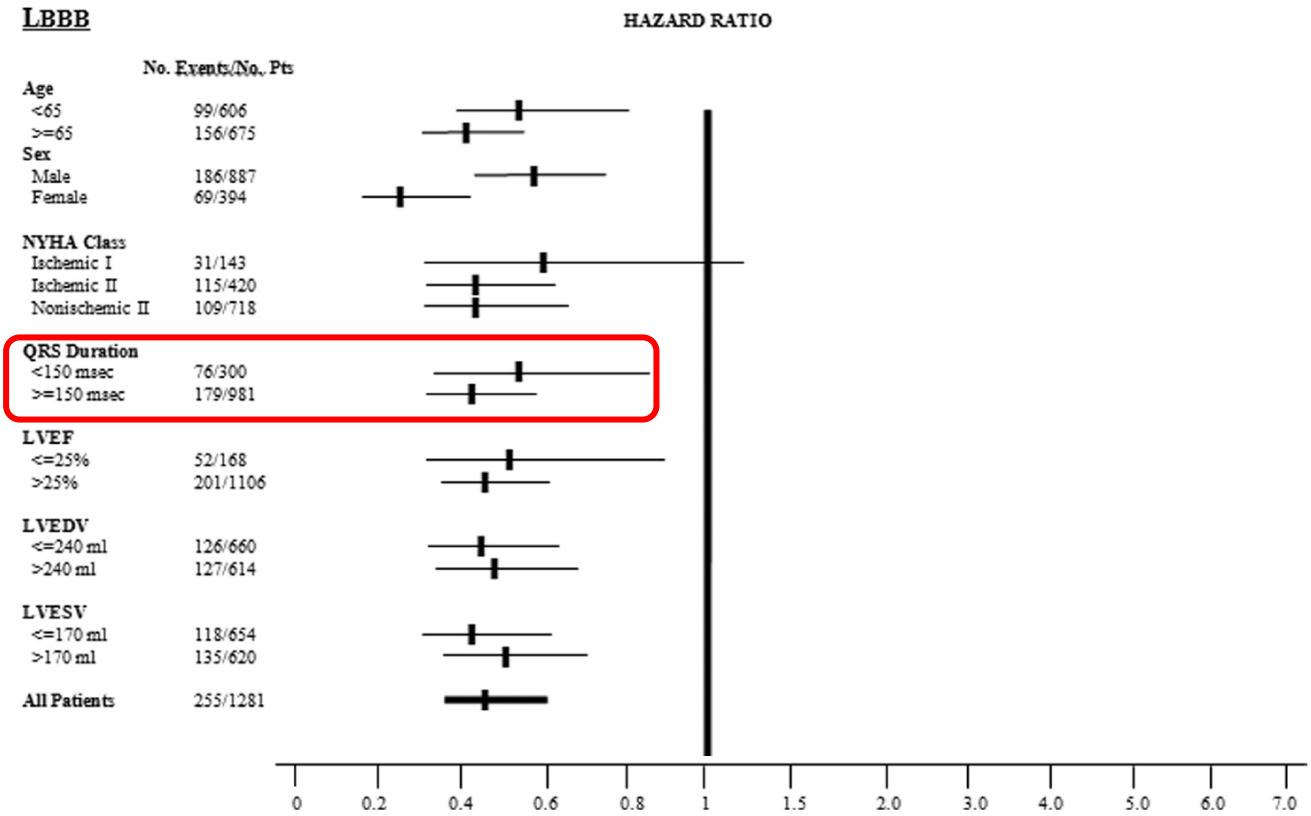


Figure 3. *Forest plot of study-specific and pooled hazard ratio and 95% confidence interval for the primary endpoint among patients with QRS < 150 ms assigned to cardiac resynchronization therapy (CRT) versus control. ICD = implantable cardioverter defibrillator.*

QRS duration can be prolonged by a number of different conduction delays. The commonest in heart failure patients is left bundle branch block (LBBB) but others show right bundle branch block (RBBB) or non-specific conduction delays. There are theoretical reasons why patients with LBBB might benefit more from CRT than patients with other patterns of QRS prolongation as LBBB results in delayed contraction of the left ventricular free wall, the area specifically stimulated in CRT.

Analysis of MADIT-CRT (Zareba *et al. Circulation.* 2011;**123**:1061-1072) in less symptomatic patients, suggests similar benefit in those with QRS prolongation due to left bundle branch block (LBBB) for QRS durations of 120-149ms and >150ms:



It is recognised that QRS ≥150ms is strongly correlated with the presence of left bundle branch block (LBBB). Combining data from MADIT-CRT analysed by Zareba *et al. Circulation* 2011;**123**:1061-1072 and Stavrakis *et al. J Cardiovasc Electrophysiol* 2012;**23**:163-168 shows benefit of CRT in less symptomatic patients with QRS ≥150ms or QRS 120-149ms with LBBB:

	QRS 120-149ms	QRS ≥150ms	ALL patients
LBBB	n=300 HR = 0.54	n=981 HR = 0.43	n= 1281 HR = 0.47
RBBB/IVCD	n=343 HR = 1.5	n=193 HR = 0.98	n=536 HR = 1.24
TOTAL	n=643 HR = 1.06	n=1174 HR = 0.48	

n= number of patients
HR = hazard ratio

5.2.3) Symptoms

Early CRT trials randomised patients with severe heart failure symptoms (NYHA III/IV). More recent trials have tested the technology in less symptomatic patients.

5.2.3.1) NYHA class I

Two trials of CRT randomised patients without heart failure symptoms (NYHA I) REVERSE (Linde *et al. J Am Coll Cardiol* 2008;**52**:1834–43) and MADIT-CRT(Moss *et al. N Engl J Med* 2009;**361**:1329-38). REVERSE included 75 patients in NYHA I with EF <40% and LVEDD >55mm. There was a trend to a reduction in heart failure events (hazard ratio 0.87; 0.37-2.03), but no significant effect on all-cause mortality which was only 2% in both groups.

Clinical Composite Response Detail	CRT-OFF (n = 191)	CRT-ON (n = 419)
Worsened, n (%)	41 (21)	67 (16)
Death	3 (2)	9 (2)
Hospitalization due to or associated with worsening HF	14 (7)	12 (3)
Crossover due to worsening HF	5 (3)	1 (<1)
Worsened patient global assessment and NYHA functional class	0 (0)	2 (<1)
Worsened NYHA functional class only	18 (9)	40 (10)
Worsened patient global assessment only	1 (1)	3 (1)
Improved, n (%)	76 (40)	228 (54)
Improved on patient global assessment and NYHA functional class	11 (6)	69 (16)
Improved NYHA functional class only	28 (15)	59 (14)
Improved patient global assessment only	37 (19)	100 (24)
Unchanged	74 (39)	124 (30)

MADIT-CRT randomised 152 patients in NYHA I with a history of ischaemic heart disease and LVEF ≤30%. There was a trend to reduced heart failure end-points with a non-significant hazard ratio of approximately 0.77.

A recent meta-analysis of these trials (Adabag *et al. J Am Coll Cardiol* 2011;**58**:935–41) has shown statistically significant benefit in heart failure hospitalisation (11.9% versus 20.5%, HR 0.57, NNT 12, p=0.04) and a trend to reduced mortality (6.0% versus 7.1%, HR 0.85, NNT 88, p=0.71).

Table 3 **Pooled Mortality and HF Events/Hospitalizations With CRT Among Asymptomatic or Mildly Symptomatic Patients With HF**

	CRT	ICD	RR	95% CI	p Value	NNT
NYHA functional class I/II						
Mortality	8.0%	11.5%	0.81	0.65–0.99	0.04	29
HF hospitalization	11.6%	18.2%	0.68	0.59–0.79	<0.001	15
Combined	17.5%	26.4%	0.72	0.65–0.81	<0.001	
NYHA functional class II						
Mortality	9.6%	13.1%	0.78	0.65–0.95	0.011	28
HF hospitalization	14.6%	21.5%	0.67	0.57–0.79	<0.001	14
Combined	20.7%	29.3%	0.73	0.64–0.83	<0.001	
NYHA functional class I						
Mortality	6.0%	7.1%	0.85	0.36–2.01	0.71	88
HF hospitalization	11.9%	20.5%	0.57	0.34–0.97	0.04	12
Combined	15.5%	22.1%	0.70	0.44–1.13	0.14	

5.2.3.2) NYHA class II

Five randomised trials included patients with NYHA class II symptoms: CONTAK-CD (Higgins *et al. J Am Coll Cardiol* 2003;**42**:1454–9) , MIRACLE ICD (Young *et al. JAMA* 2003;**289**:2685-2694*)*, REVERSE (Linde *et al. J Am Coll Cardiol* 2008;**52**:1834–43), MADIT-CRT (Moss *et al. N Engl J Med* 2009;**361**:1329-38) and RAFT (Tang *et al. N Engl J Med* 2010;**363**:2385-95). A meta-analysis (Adabag *et al. J Am Coll Cardiol* 2011;**58**:935–41) demonstrates significant reductions in all-cause mortality (absolute 3.5%, hazard ratio 0.78 (0.65-0.95) p=0.011) and heart failure hospitalisation (absolute 6.9%, hazard ratio 0.67 (0.57-0.79) p<0.001) as shown above.

5.2.3.3) NYHA class III

Trials of CRT have consistently shown benefit in morbidity and mortality in patients with severe left ventricular impairment (LVEF≤35%) prolonged QRS duration (≥120ms) and moderate or severe heart failure symptoms (NYHA III/IV). The data are reviewed above.

5.2.3.4) NYHA class IV

Although clinical benefit has been seen from CRT in patients with NYHA class IV symptoms, only 10% of those randomised in the clinical trials were in NYHA IV and those were ambulatory out-patients on oral medication without recent hospital admission. These patients have high heart failure mortality and have been regarded as having a contraindication to ICD therapy.

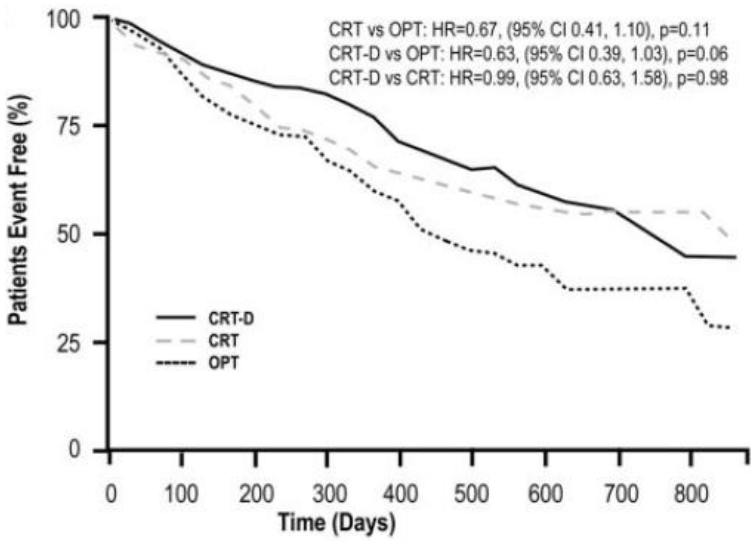
In NYHA IV patients randomised in the COMPANION trial (Lindenfeld *et al. Circulation* 2007;**115**:204-212), the primary end point of time to death or hospitalisation for any cause was significantly prolonged by both CRT-P (HR, 0.64; P=0.02) and by CRT-D (HR, 0.62; P=0.01) compared with optimal medical therapy (OPT). There were significant improvements in quality of life and NYHA function class with 67% of the 217 NYHA IV patients improving their symptoms to NYHA III. This is the same proportion of patients improving as in other NYHA functional classes:

TABLE 4. Functional Capacity in NYHA Class IV Patients: Change From Baseline to 6 Months

Indicator	Number	Median (Q1, Q3)	% Improved	*P*
6-Minute walk				
CRT/CRT-D	69	45.6 (−15.2, 106.4)	...	0.55
OPT	12	45.6 (−22.3, 60.9)	...	...
Quality of life				
CRT/CRT-D	109	−25.0 (−44.0, −8.0)	...	<0.01
OPT	29	−4.0 (−20, 9.0)	...	...
NYHA				
CRT/CRT-D	119	...	78	<0.01
OPT	27	...	52	...

Q indicates quartile.

44% of NYHA IV patients receiving OPT patients died in the first year, compared with 36% of CRT-P and 30% of CRT-D patients. Their 2-year mortality was non-significantly reduced with a hazard ratio of 0.67 for CRT-P and 0.63 for CRT-D compared to OPT:



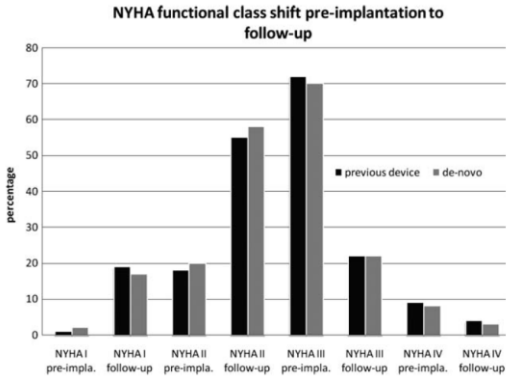
NYHA IV symptoms are not a contraindication to CRT therapy but the incremental benefit of CRT-D over CRT-P may be smaller than in less symptomatic patients because of the high risk of heart failure death.

5.2.4) QRS prolongation due to right ventricular pacing

The adverse acute and chronic haemodynamic effects of right ventricular pacing have been described in many publications over the past century. In patients with preserved LV function, RV pacing increased the risk for heart failure hospitalization (MOST, Sweeney *et al. Circulation* 2003;**107**:2932-7) while in patients with LV dysfunction, the detrimental effect of RV stimulation was even more marked with a 60%increase in the combined endpoint of heart failure hospitalization or death (DAVID, Wilkoff *et al. JAMA* 2002;**288**:3115–23). An analysis of heart failure patients in the MADIT II trial (Barsheshet *et al. Heart Rhythm* 2011;**8**:212-8) showed reduced survival benefit in those with >50% RV pacing (HR = 0.89, P = 0.45) compared to those with ≤50% RV pacing (HR = 0.60, P <0.001).

Some patients with a requirement for ventricular bradycardia pacing experience severe heart failure symptoms and are found to have severe left ventricular impairment. Their QRS duration is prolonged by right ventricular pacing for bradycardia. There are no randomised controlled trials of upgrade to a CRT device but observational studies have shown similar benefits to those seen in *de novo* CRT implantation (Witte *et al. J Card Fail* 2006;**12**:199-204, Nägele *et al. Pacing Clin Electrophysiol* 2008;**31**:1265-1271, Wokhlu *et al. Heart Rhythm* 2009;**6**:1439-1447, Fröhlich *et al. Eur Heart J* 2010;**31**:1477-1485).

The European CRT Survey (Bogale *et al. European Journal of Heart Failure* 2011;**13**:974–983) included 2367 CRT implant procedures of which 692 (29.2%) were upgrades to CRT from standard right ventricular pacemakers or ICDs. Procedural complications were not increased in upgrade procedures and patients' NYHA class improvements and other outcomes were similar between the groups during 1 year follow-up:



Upgraded patients have comparable symptom and mortality outcomes at 1 year to those receiving *de novo* CRT implants, and implant procedural complications are not significantly higher in upgraded patients.

5.2.5) Patients with heart failure and an indication for bradycardia pacing

Given the detrimental haemodynamic effects of RV pacing and the demonstrated benefits of upgrade to CRT, the Homburg Biventricular Pacing Evaluation (HOBIPACE, Kindermann *et al. J Am Coll Cardiol* 2006;**47**:1927–37) randomised 30 patients with a standard indication for permanent ventricular pacing, an LV end-diastolic diameter ≥60 mm and an ejection fraction ≤40%. Statistically significant benefit from CRT compared to RV pacing was demonstrated for symptoms (The Minnesota Heart Failure score was six points lower with CRT versus RV pacing (p < 0.010), NYHA functional class was an average of 0.6 lower with CRT versus RV pacing (p < 0.015)) and left ventricular function (LVEF was 6.3% higher with CRT and RV pacing (p<0.001).

5.2.6) Atrial fibrillation

Atrial fibrillation is common in patients with heart failure, affecting 25-50% of patients with NYHA class III/IV symptoms. Thus, approximately 20% of patients undergoing CRT implantation in Europe are in permanent atrial fibrillation.

A meta-analysis (Upadhyay *et al. J Am Coll Cardiol* 2008;**52**:1239-1246) of 1164 patients in the 5 prospective cohort studies which included both patients in sinus rhythm and those in atrial fibrillation showed that patients in atrial fibrillation had clinically and statistically significant improvements with CRT: a mean 8.6%, increase in LVEF (7.1% - 10.1%, $p < 0.0001$) a mean improvement of 0.8 NYHA functional class (0.7 - 1.0, $p < 0.0001$), a mean 11.6m increase in 6-minute walk distance (13.51 to 19.59m, $p < 0.005$) and a 9.4 points improvement in self-perceived quality of life score (MLWHF, 13.38 -5.37 points, $p < 0.0001$).

NYHA class improved similarly for patients in atrial fibrillation and sinus rhythm (0.90 for SR patients, 0.84 for AF patients) and all-cause mortality was not significantly different at 1 year (relative risk ratio: 1.57, 95% confidence interval 0.87-2.81). Those in sinus rhythm showed a mean 11.6m greater improvement in the 6-min walk distance than those in AF (11.6 (CI: 10.4 to 12.8 m) and Minnesota score (3.9 points less, 95% CI: 3.4 to 4.5 points) than AF patients. AF patients showed a statistically significant greater increase in ejection fraction (0.39% greater increase in ejection fraction, 95% CI: 0.22% to 0.55%).

The available data show that patients in AF benefit similarly to those in sinus rhythm when a high proportion of ventricular beats are biventricularly paced. Koplan *et al.* (*JACC* 2009;**53**:355-360) found patients with 93-100% pacing dependence had a 44% reduction in mortality and hospitalisation for heart failure compared to subjects paced 0% to 92% (HR 0.56, $p <0.00001$). This may be achieved with conventional heart failure treatment with β-blockade but may require AV node ablation. This was performed in 56% of patients in these trials:

Table 2 Use of AVJ Ablation in AF Patients

	AF Patients		
Study	Total AF Patients	No. of Received AVJ Ablation	% Received AVJ Ablation
Delnoy et al. (22), 2007	96	21	22%
Gasparini et al. (21), 2006	162	114	70%
Molhoek et al. (20), 2004	30	17	57%
Linde et al. (18), 2002	64	40	63%
Leclercq et al. (19), 2000	15	15	100%

5.2.7) Conclusions

1) CRT is indicated in patients with severely impaired LV systolic function (LVEF ≤35%) and ECG evidence of dyssynchrony (QRS duration ≥120ms)
2) The greatest benefits are seen in the most symptomatic patients (NYHA III/IV)
3) Less information is available on the benefits of CRT in patients with mild heart failure symptoms. Meta-analysis of NYHA I patients has shown statistically significant benefit in heart failure hospitalisation and a trend to reduced mortality. In NYHA II patients in the same meta-analysis demonstrated highly significant reductions in heart failure hospitalisation and mortality.

4) In those with mild to moderate symptoms (NYHA I/II), a greater likelihood of clinical response is seen in those with left bundle branch block and/or QRS duration ≥150ms
5) Current indices of mechanical dyssynchrony derived by echocardiographic imaging have insufficient sensitivity and specificity to be clinically useful in patient selection
6) Patients with QRS prolongation caused by right ventricular pacing benefit from upgrade to a CRT device
7) Patients with a requirement for ventricular bradycardia pacing and severe left ventricular impairment (LVEF ≤35%) should be considered from implantation of a CRT device regardless of native QRS duration
8) Patients in atrial fibrillation show similar benefit from CRT providing a high proportion of biventricular stimulation is achieved by pharmacological or ablation therapy

6) Contraindications to device therapy

Unlike pacing for bradycardia where emergency treatment may be life-saving, CRT and ICD implantation is usually an elective or semi-elective procedure before which modifiable risks can be minimised. An exception occurs when a patient with a CRT and/or ICD indication has an urgent requirement for bradycardia pacing. In this situation the competing risks of temporary pacing and complications from the implantation of a permanent device have to be weighed.

6.1) sepsis

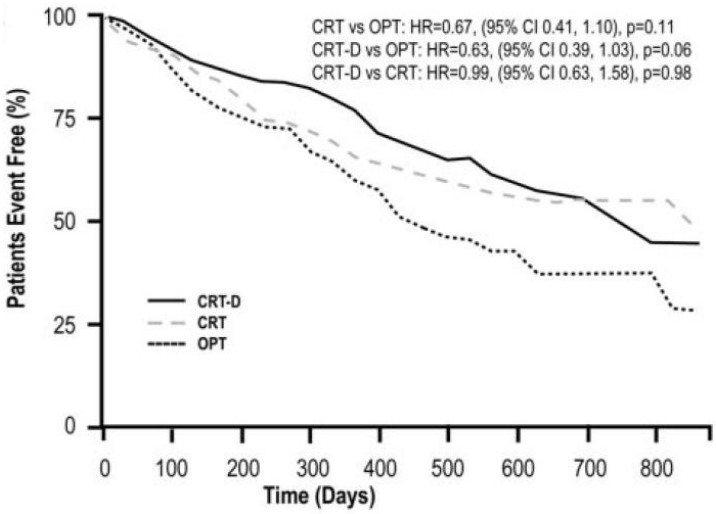
a) active bacterial infection or colonisation such that the risks of device implantation outweigh the expected benefits
b) temporary pacing may be indicated while the infection is treated

6.2) coagulopathy

a) iatrogenic anti-coagulation and/or anti-platelet therapy increase the risks of haematoma and device-related infection
b) the risks of reversing anticoagulation must be weighed against the risks of thrombosis

6.3) life-expectancy

a) mortality is unpredictable for the majority of the population
b) age alone is a poor predictor as life expectancy. US government actuarial statistics (http://www.ssa.gov/oact/STATS/table4c6.html) show that life expectancy is more than one year for males up to the age of 112, and in females 113 years. At the age of 80, life expectancy is 7.9 years in men and 9.4 years in women.
c) cancer is the only disease type where robust data exist on life expectancy and this must be carefully individualised
d) significant co-morbidities may limit both life expectancy and potential benefit received from an ICD. These co morbidities include but are not confined to severe renal impairment and severe chronic obstructive lung disease.
e) patients with NYHA IV symptoms have a life expectancy of significantly more than 1 year as demonstrated in an analysis of the COMPANION study (Lindenfeld *et al. Circulation* 2007;**115**:204-212) where at 1-year 44% of OPT, 36% of CRT-P and 30% of CRT-D treated patients had died:



This is consistent with a published series (Castel *et al. Europace* 2010;**12**:1136–1140) of 40 patients in NYHA IV receiving CRT matched to 40 managed with OPT alone where 1-year mortality was 30.5% in the CRT group and 27% in the OPT group:

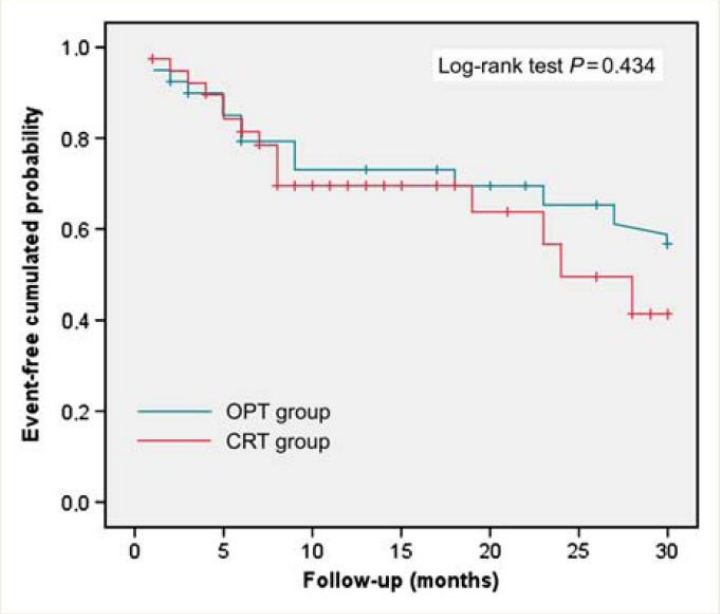


Figure 1 Time to all-cause mortality or urgent heart transplantation.

6.4) NYHA IV for ICD

It is generally accepted that ICD therapy should not be offered to patients with persistent NYHA IV symptoms because of their poor quality of life and limited life expectancy. Current North American device guidance (Epstein *et al. JACC* 2008;**51**:e1-62) states that "Once patients have persistent or frequently recurrent Class IV symptoms despite optimal management, life expectancy is less than 12 months, and ICD implantation is not indicated, regardless of patient and family preferences." although there are no recent published data to support this assessment. There is, however, clear benefit from CRT in patients with NYHA IV symptoms and most of these patients will improve to NYHA III functional class.

Whilst ICD implantation is therefore relatively contraindicated in patients with NYHA IV symptoms, it is reasonable to offer those with a life expectancy of at least 1 year, implantation of a CRT-D device if they have a CRT indication while those with a worse prognosis can be offered CRT-P. Those without a CRT indication should be managed with optimal pharmacological therapy and reassessed as an out-patient after 1 month.

6.5) Incessant or frequent ventricular tachycardia or ventricular fibrillation

ICDs do not prevent ventricular arrhythmias, they simply treat those that occur with anti-tachycardia pacing and/or defibrillation shocks. Incessant or frequently occurring VT or VF requires urgent pharmacological and/or ablation therapy. Only if the arrhythmia can be satisfactorily controlled can an ICD provide acceptable treatment as frequent shocks are extremely unpleasant and poorly tolerated, causing significant and sometimes severe psychological morbidity.

6.6) Ventricular tachycardia in the presence of normal cardiac function

Patients with episodes of VT (not VF) in the presence of normal or near normal ventricular function require careful electrophysiology assessment as these tachycardias can often be cured by radiofrequency ablation, avoiding the need for ICD therapy.

7) Other sections

7.1) Patient choice

While a patient may have a recognised cost-effective indication for an ICD and/or a CRT device, they may have carefully considered reasons why they do not want to undergo such a procedure. The advantages and disadvantages of the treatment options must be clearly and honestly discussed and, as far as possible, individualised for that patient in order for them to come to a fully informed decision. Patient literature and decision aids should be developed to help in this discussion and decision making. The patient's wishes must be respected.

7.2) End of life care

Defibrillators can be deactivated by simple non-invasive re-programming, and this is appropriate in a patient receiving terminal care for heart failure cancer or any other reason. Deactivation of defibrillator therapy will prevent the patient receiving painful and futile shocks at the end of their life. It is both legal and ethical to deactivate implanted devices after full discussion and agreement with a competent patient. Advice is provided in a British Heart Foundation booklet written by Dr James Beattie in 2009, Implantable cardioverter defibrillators in patients who are reaching the end of life" which is available from the BHF website (http://publications.bhf.org.uk/publications.aspx M105 ICDs end of life booklet).

Deactivation of CRT and/or bradycardia pacing is not required in this situation as pacing stimulation is asymptomatic. ICD therapy can be deactivated with affecting pacing.

The depletion of a device battery should always allow reassessment of the continuing need for device therapy.

7.3) National data collection

National audit data collected by the national pacemaker and ICD database (www.devicesurvey.com) has demonstrated significant disparity in ICD and CRT implantation rates across the UK which cannot be explained by disease prevalence. The cause of this apparent inequality of access is unknown and requires further research.

We suggest that NICE guidance should require each implanting centre to submit complete and timely audit data to the national database with a minimum data set including aetiology, NYHA functional class, left ventricular ejection fraction, QRS duration, history of ventricular arrhythmias (primary or secondary prevention) and complication rates.

Expected implant rates for ICD and CRT have been very helpful in planning services and we would welcome revised rates in the new guidance.

7.4) Reassessment

When a patient is assessed and found not to fulfil NICE guidance criteria for device implantation, we recommend reassessment at annual review or when there is a clinical event or other change in symptoms or treatment.

7.6) Implantation and follow-up

The implantation of ICD and CRT devices is complex and can be time consuming. The complication rates are significantly higher than for bradycardia pacemakers. Device follow-up is complex and time consuming with a requirement for individualisation of programming to optimise response and minimise the risk of inappropriate therapy. This includes the requirement for optimisation of programming in CRT devices with echocardiographic assessments, particularly in those who do not initially improve following implantation. In addition, patients with indications for ICD and CRT are complex and most have heart failure and other co-morbidity. They require frequent and expert clinical review to optimise symptoms and prevent decompensation and sudden death. Because of the effects of their underlying disease and treatment, many patients require psychological assessment and support. Implant and follow-up centres also need robust databases and protocols to deal with device complications and advisories with 24-hour cover for emergencies.

It is Heart Rhythm UK's view that to maintain clinical the cost-effectiveness seen in the clinical trials, these devices should be implanted by high-volume operators in high-volume centres.

8) Conclusions

8.1) Evolution of guidance on the use of ICD and CRT

1) Clinical guidance has evolved in its format and content
2) Whilst guidance could never encompass every conceivable situation, nor will there ever be complete evidence on which to base such guidance, nevertheless this formal process of evaluating evidence is important in setting standards of clinical practice
3) Guidance will always follow trial evidence so requires periodic re-evaluation
4) The inclusion and exclusion criteria adopted in clinical trials are always a compromise between generalisability and power calculations required to achieve statistical significance
5) Meta-analyses have been very helpful in defining treatment effects in subgroups
6) Whilst guidance can be written which reproduces trial inclusion and exclusion criteria, this can result in long, complex and potentially contradictory recommendations
7) Heart Rhythm UK's goal is to offer device therapy to all patients for whom there is evidence that they are likely to benefit
8) Device implantation in the UK is far lower than in other developed countries
9) The complexity of guidance may be contributing to under provision because of lack of knowledge and the perceived time and financial costs of screening tests
10) We recommend a pragmatic approach with simple, clear, easily memorable guidance which identifies areas where the evidence is clear and others where there is uncertainty. In small groups of patients with complex cardiovascular diseases, guidance should defer to the best evidence available at the time.

8.2) Key points in the current analysis

1) All patients should receive optimal pharmacological and other therapies.
2) All patients with cardiovascular disease should be fully assessed in order to identify patients who would benefit from device therapy.
3) Patients who are found not to have a device indication should be reassessed annually or sooner if there is a change in their clinical status.
4) The advantages and disadvantages of device therapy should be discussed with all patients to allow them to come to a fully informed decision.
5) ICD implantation reduces the risk of sudden cardiac death in patients resuscitated from cardiac arrest or haemodynamic compromise due to ventricular tachycardia.
6) Patients with a high risk cardiac condition and a history of syncope are at similar risk of sudden cardiac death as those resuscitated from cardiac arrest and benefit from ICD implantation.
7) Patients with severe left ventricular impairment (LVEF ≤35%), whether this is due to ischaemic or non-ischaemic heart disease, are at high risk of sudden death and benefit from ICD implantation.
8) There are no large randomised controlled trials of primary prevention ICD therapy in patients with rare high risk cardiac conditions. The best available contemporary evidence of risk factors should be used to guide therapy.
9) CRT implantation improves heart failure symptoms and reduces hospitalisation and mortality in patients with LVEF ≤35% and QRS duration ≥120ms.
10) Benefit from CRT is seen in patients from all NYHA functional classes. There is less evidence of long-term benefit in those with mild symptoms (NYHA I and II) but improvements in symptoms and mortality are consistent and statistically significant.

11) Currently available indices of mechanical dyssynchrony derived from imaging are insufficiently sensitive and specific to be clinically useful.
12) Further stratification of benefit in patients with QRS 120-150ms can be derived from the presence of left bundle branch block.
13) Patients with QRS prolongation caused by necessary right ventricular pacing benefit from up-grade to a CRT device.
14) Patients with a bradycardia pacing indication and impaired ventricular function benefit from CRT.
15) The benefit of CRT shown in patients in atrial fibrillation is similar to sinus rhythm providing a high proportion of beats are biventricularly paced. This may require pharmacological treatment or ablation.

8.2) Summary recommendations

These key points can be summarised in the recommendations below. The over-lap in the criteria for ICD and CRT appear complex, but this combination would improve clinical utility.

1) All patients should undergo appropriate diagnostic tests to establish the aetiology and optimal management of their heart condition. It is essential to identify patients with conditions which can be cured with ablation therapy such as fascicular tachycardia or right ventricular outflow tract tachycardia.
2) All patients should receive optimal pharmacological therapy for their condition.
3) Patients should undergo revascularisation when indicated (NICE clinical guideline 126 – Management of Stable Angina. July 2011. http://guidance.nice.org.uk/CG126).
4) All patients should be assessed for relative and absolute contraindications to device therapy and co-morbidity which increases the risk of treatment or reduces its efficacy. These include myocardial infarction or revascularisation within 4 weeks unless the patient has had a secondary prevention ICD indication. This should be explained to the patient and weighed in decision making.
5) All patients should have their condition and its management options discussed with them to make a fully informed decision.
6) If a decision is made not to implant a device, this should be reviewed at least annually or when there is a significant change in the patient's condition.

Based on the currently available data, we recommend that in the absence of a fully reversible cause (including an arrhythmia which can be prevented by ablation therapy), patients on optimal pharmacological therapy, with expectation of life expectancy of ≥1 year and with a quality of life acceptable to the patient:

Patients with LVEF ≤35% (regardless of aetiology) should routinely be considered for a device based on their symptoms (NYHA functional class) and QRS duration:

	NYHA I	NYHA II	NYHA III	ambulant NYHA IV
QRS <120ms	ICD	ICD	ICD	OPT
120-149 no LBBB	ICD	ICD	CRT-D	CRT-D
120-149 + LBBB	CRT-D	CRT-D	CRT-D	CRT-D
≥150ms	CRT-D	CRT-D	CRT-D	CRT-D

CRT-P (pacemaker) implantation should be offered in place of CRT-D (defibrillator) when ICD therapy is contraindicated or declined by the patient.

3) **Patients with LVEF >35%** (without NYHA IV symptoms):
   - with spontaneous sustained ventricular arrhythmias
     or
   - with inherited conditions with high risk features for sudden cardiac death according to the best available evidence

     should routinely be considered for: ICD

4) ICD implantation should not be performed within 4 weeks of a myocardial infarction or revascularisation unless the patient has a secondary prevention indication.

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