

**THE CLEARING HOUSE FOR HEALTH OUTCOMES AND  
HEALTH TECHNOLOGY ASSESSMENT**

Department of Public Health and General Practice  
Christchurch School of Medicine

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Outcomes from the use of the  
Implantable Cardiac Defibrillator

*A critical appraisal of the literature*

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## Executive Summary

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Sudden cardiac death (SCD) is a major public health problem that accounts for more than half of all cardiovascular deaths in western nations. Most cases of sudden cardiac death are due to a ventricular arrhythmia and often there is an element of underlying ischaemic heart disease.

Current attempts to improve out-of-hospital resuscitation services to reduce the high fatality rate from ventricular arrhythmia have largely proven to be ineffective. Survival rates for patients sustaining a cardiac arrest outside of hospital remain at below 25%. Attention has now turned to the implantable cardiac defibrillator (ICD) that can remove a life threatening arrhythmia.

The risk of sudden cardiac death in the general population is small (estimated annual rate of 2 deaths per 1,000 people), epidemiological studies have clearly identified a number of high risk groups. Patient groups most at risk include: survivors of cardiac arrest, patients with an acute or chronic myocardial infarction and patients with cardiomyopathy (especially related to congestive heart failure). Unfortunately currently available investigations that are aimed at determining the risk of sudden cardiac death for an individual appear to be of only limited value.

Modern ICDs are able to have their leads inserted transvenously and are secured to an endocardial position; while the generator is placed in a subpectoral pocket. The devices are fully programmable and include pacing as well as low and high energy cardioversion capabilities.

Complications from the insertion of these devices are common, although most are not serious and peri-operative mortality is now rare. Most complications relate to lead dislodgment, bleeding problems and erosions, and occasionally more serious occurrences such as thromboembolic events or infection. Inappropriate shocks are also common and can significantly impinge on the recipient's quality of life.

The ICD has been consistently shown to be effective at terminating ventricular arrhythmias and therefore at reducing the incidence of sudden cardiac death for recipients. The incidence of sudden cardiac death in recipients has been consistently shown to be less than 1% annually. However, some uncertainty still exists about whether overall survival is enhanced by the device. This uncertainty is due to the lack of evidence from randomised controlled trials. In the absence of these trials a range of other studies have been used to estimate the benefit of the ICD on total survival. These studies have included retrospective case control trials using a control group from the same, or other institutions, who have either received an ICD or an alternative (usually drug) treatment, unmatched but concurrent cohort studies, hypothetical mortality trials based upon the first appropriate shock from the device, and episodes of documented arrhythmia recorded on new devices. Most of these studies have found that the ICD has been associated with a reduction in overall mortality. However, these studies are associated with marked limitations, in particular, they are all prone to significant problems with selection bias and difficulty with the effects of confounding. Patient populations have varied and have introduced bias in their definitions of sudden death and inappropriate shock. Further areas of bias for the studies include their temporal disparity in patient recruitment, and questionable validity of using an appropriate shock as a valid endpoint.

A few trials have examined the effect of the ICD on the recipient's quality of life. Apart from being limited by their small sample size these trials have also been confounded by examining the effects of a device on quality of life among patients with a serious underlying illness. Generally these studies have suggested that quality of life can be preserved amongst recipients although often there is some initial impairment just after implantation. Most recipients remain grateful for receiving their device and, adapt to the major changes in their functioning, work ability and psychological state that result from suffering a cardiac arrest and receiving an ICD.

Despite the concerns associated with the ICD, alternative therapeutic options appear to have a limited ability to improve survival. Although several large trials have found a beneficial effect from the use of amiodarone, a high proportion of patients have needed to withdraw from this therapy due to its side effects (typically around 25%). Only a small number of patients are eligible for surgery or catheter ablation treatment.

A number of studies have examined the cost effectiveness of the device. These have generally concluded that ICD treatment is associated with increased cost to the funding organisation. Nevertheless most have tentatively concluded that the device is a cost-effective intervention for treating arrhythmias compared to other options. For example, Kupersmith (1995) found that the marginal cost benefit per year of life saved was a favourable US \$25,700 using 1993 as a base. The ICDs particular advantage in these studies is through its assumed ability to increase the years of life for recipients and likelihood of reducing their need for hospital based care. In addition, some authors have further suggested that the cost effectiveness of the device does compare favourably with many other established treatments for other conditions.

Indications for ICD insertion are difficult to derive from the literature. The main problem is that no definitive evidence is yet available to state categorically that the device can improve overall survival amongst any group of patients. This problem is further compounded by the inconsistency in the research surrounding patients selected for the intervention as well as the relative inability of current investigations to identify individuals most at risk of SCD. There is some general recognition in the literature that the ICD is most appropriate for patients who are in one of two groups that are at high risk of sudden cardiac death. The two groups are:

- cardiac arrest survivors (principally on the basis of a number of cohort and case control studies and one small randomised controlled trial- which found that only 4.8 patients needed to be treated in order to save one life)
- people at high risk of a malignant tachyarrhythmia on the basis of either a previous arrhythmia and/or an induced arrhythmia on testing, without an arrest, who are either not eligible or have failed other medical or surgical treatments and usually have underlying ischaemic heart disease and/or a low ejection fraction (principally case control studies and one randomised controlled trial- MADIT Trial which had narrow inclusion criteria but a very favourable result indicating that only 4.4 patients needed to be treated in order to save one life)

The remaining uncertainty about the ability of the device to improve overall survival and the defined indications for the device seem likely to be resolved when the results of several large multi-centre randomised controlled trials are available in 1998.

The following table presents a number of summary statements based on the findings of this review along with their evidence gradings.

## Health outcomes from the use of cardiac defibrillators

### Summary statements

Statement	Evidence grading of main studies providing key information	Conclusion from this review
Implantable cardiac defibrillators are effective at interrupting malignant ventricular arrhythmias	Level 2  RCTS- (it is unethical to assess absolute efficacy by randomising people to no treatment)	Overwhelming evidence exists from a large number of mainly cohort studies, amassing sample of over 4,000 patients, based in a variety of organisations and countries
The ability of the ICD to interrupt a malignant ventricular arrhythmia has translated into proven efficacy for the device at reducing the incidence of sudden cardiac death amongst recipients	Level 2	As above Overwhelming evidence exists of effectiveness, either using mortality rates or recorded shocks as an endpoint
The ICD is preferable to drugs at reducing the incidence of sudden cardiac death	Level 2	Some evidence from case control/cohort studies but mitigated by selection bias and confounding. Definitive answer will soon be available from the results of current RCTs
Recipients of the ICD have an overall survival advantage compared to patients treated with drugs	Level 2,3	Uncertainty exists due to deficiencies in level 2 evidence In particular there may be higher rates of non-sudden cardiac death amongst recipients that nullify antiarrhythmia advantage. Results of large RCTs will soon provide more definitive answer
The most appropriate people to receive a device are the survivors of a cardiac arrest	Level 2,3	RCT evidence awaited Exception: small group of patients defined in inclusion criteria of MADIT level 1 trial
The ICD is cost effective relative to drug treatment	Cost effectiveness studies	General consistency in studies for this statement - within the assumptions necessary to complete these studies
Implantation of an ICD has a marked impact on the quality of life of the recipient	Level 3	Limited evidence from small studies confounded by underlying illness

Evidence grading:

Level 1= randomised controlled trials, level 2 = case control/cohort studies, level 3= descriptive studies.

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# 1 Methodology

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## 1.1 SEARCH STRATEGY

This review was undertaken by searching Medline and Embase (Pharmacology version) from 1993 using the following strategy:

*implant\$.tw.*

*defib\$.tw.*

Selected articles prior to 1993 were also retrieved.

Current Contents was searched between 1995 and week 42 1997 using the following strategy:

*implant:.ab,ti,kw,kp.*

*defibril:.ab,ti,kw,kp.*

*1 and 2*

*implantable defril:.ab,ti.kw,kp.*

The Cochrane Library database of completed reviews, protocols and trials was searched using the terms: defib, arrhythmia, implant. The database of the International Network of Agencies for Health Technology Assessment was examined for projects using the terms; implant, defib, arrhythmia. Several search vehicles on the Internet (Excite, Yahoo, Infoseek) were used to locate any relevant sites using the same terms.

In total over 4,000 abstracts were assessed from the preceding databases and from them over 500 relevant articles were located, assessed and summarised.

## 1.2 EVIDENCE GRADING

Collected articles were grouped according to their content (eg cost effectiveness, efficacy etc.) and graded according to their individual study design (eg randomised controlled trial etc). Three grading categories have been used (see Table 1):

**Table 1: Evidence gradings used in this review**

<b>Grading category</b>	<b>Study design</b>
Level one	Meta analyses Randomised controlled trials
Level two	Comparative studies ie. case control or studies
Level three	Descriptive studies ie case series, expert opinion

All studies were read and reviewed from each of these categories, however, only studies meeting certain criteria were formally appraised.

### **1.3 CRITICAL APPRAISAL STRATEGY**

The following criteria were used to select articles for formal appraisal:

- Descriptive, comparative (either case control or cohort type studies) and randomised controlled trials reviewing the efficacy, cost effectiveness, indications or complications related to the use of implantable defibrillators.
- Sample size was > 50 patients.
- Follow up period was > 3 months
- The trial gave an explicit description of study design, methods, results and analysis
- Intention to treat analysis was undertaken (RCT)
- English language
- All articles examining the indications or prioritisation for the devices were reviewed.

Articles were formally appraised using the schedule developed by the Group Health Cooperative of Puget Sound (1996) and adapted by the New Zealand Guidelines Group of the National Health Committee (1997). Summaries of appraisal results have usually been shown in tabular form and conclusions from the literature have mostly been presented with reference to the evidence grades. Where possible efficacy has

been described in terms of all cause survival after 1 year. Respective p values are shown along with absolute risk reductions and NNT (number needed to treat) has been calculated and presented.

Specific comments on the methodology used in this review are made at the beginning of some sections.

#### **1.4 LIMITATIONS OF THIS REVIEW**

Evidence grades have been applied to all of the literature based upon the study design of each article. The formal critical appraisal process systematically reviewed the methods and analysis of the studies in each of the three grades.

This study has used a structured approach to review the literature. However there are some potential limitations inherent in this process

Although, in general, grade one evidence (randomised controlled trials and meta analyses) is usually best able to reduce the effects of bias and confounding (through the use of randomisation) the most important determinant of the validity of a study is the rigour applied to it's design and subsequent analysis and not necessarily the type of study design that has been used. In addition, certain types of study are more appropriate for particular issues. For example a cohort study can usually best describe the prognosis of a group of patients with a particular illness and a randomised controlled trial is well suited to evaluate the effects of a treatment. The reader is referred to the original study for full clarification of the methods and results used in any particular study.

This review has been limited by the need to restrict the analysis to English language studies and references presented in the databases cited above. All web sites on the Internet could not be assessed.

Although this review has greatly benefited from advice provided by consultants, it has not been exposed to wide peer review. In addition, the work has been based only upon

the published academic literature and has not reviewed unpublished work. It is notable that there were no New Zealand articles present in the literature, therefore it is uncertain if the conclusions presented from the literature can be generalised to a New Zealand population and context.

While most of the articles cited in the databases were obtained (>85%) a small proportion were not available from overseas in sufficient time to be included in this review.

This review was conducted over a limited period of time (2 months).

## 2 Introduction

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Sudden cardiac death (SCD) has often been defined as death that occurs unexpectedly within 1 hour of the onset of acute symptoms (Myerburg 1987, Roberts 1986, Greene 1990, Goldstein 1990).

Sudden cardiac death is usually due to a ventricular tachyarrhythmia (Volpi et al 1988, Luu et al 1989, Gilman et al 1994, Wilber et al 1997). Most episodes (about 80%) occur in patients with ischaemic heart disease (Koch et al 1993, Reichenbach 1977, Kolettis and Saksena 1994) although SCD does not usually occur at the same time as ischaemia or an acute myocardial infarction (Myerburg 1993). Several studies have shown that less than 15-20% of patients with SCD have post-mortem evidence of an acute infarction (Koch et al 1993).

Sudden cardiac death is a major public health problem in western countries and it accounts for more than half of all cardiac deaths (Yusuf 1993). In the United States this amounts to more than 350,000 deaths annually from SCD (Myerburg 1993). In New Zealand the figure is around 3600 (Ministry of Health 1997). Furthermore the outlook for survivors from near-miss SCD (a cardiac arrest) is bleak. Around 40%, (Kochs et al 1993) will die from an arrhythmia within the first two years of their near-miss episode. Many will also experience significant ongoing morbidity and more than 50 % will be rehospitalised within a year (Maynard 1993).

In contrast to the reduction in coronary artery disease mortality achieved over recent years in many western countries (Myerburg 1997) including New Zealand (Jackson 1995), the number of SCDs has remained relatively stable (Rosenberg 1972).

In part this persistently high mortality rate is due to the continuing poor survival from out-of-hospital cardiac arrest in most countries (2-25%, ~10% in most communities; Wilber et al 1997). Survival from out-of-hospital arrest remains dismal despite recent improvements in pre-hospital care such as the introduction of helicopter evacuation

and well trained paramedic services (Valenzuela 1992). Given this poor outcome from attempts to improve pre hospital resuscitation services, increasing attention has been paid to the feasibility of other treatments which may prevent or abort potentially fatal ventricular tachyarrhythmia. The implantable cardiac defibrillator (ICD) is a recent development designed to interrupt an otherwise fatal ventricular arrhythmia.

A number of prognostic indicators can identify patients at increased risk of potentially life threatening cardiac arrhythmia. The problem is that the subgroups with the highest case fatality rate (such as patients with low ejection fraction and survivors of out-of-hospital cardiac arrest) do not generate most cases of sudden cardiac arrest (Myerburg 1992). That is, the group with highest relative risk for SCD actually has the lowest population attributable risk (Wilber et al 1997). In contrast, the larger populations, with lower relative fatality rates generate more cases (in absolute numbers) of SCD. This problem indicates the need to develop more sensitive markers to stratify the risk of large segments of the population (Myerburg 1997). The challenge therefore is not only to focus on very high-risk subgroups but also to develop methods of identifying high-risk clusters within the general population.

In recent years a distinction has been made between the preconditions underlying a fatal arrhythmia and the acute functional events that initiate the fatal event. It is now generally understood that the etiological basis of an arrhythmia provides the foundation for an episode of ventricular tachycardia/ventricular fibrillation while transient risk factors act as triggering events. This model provides an essential understanding of the determinants of risk for a fatal arrhythmia.

## **2.1 MODEL FOR THE DEVELOPMENT OF AN ARRHYTHMIA**

### **2.1.1 Etiological determinants of sudden cardiac death**

- Coronary heart disease (80% of people with sudden cardiac death )  
Determined by cholesterol, exercise, hypertension, diabetes, smoking, genetic factors etc (these risk factors are closely correlated with coronary heart disease

mortality AND the risk of sudden cardiac death (Kannel et al. 1975, Kuller 1980, Myerburg 1997).

- Cardiomyopathies (10 –15% of SCDs)
- Other heart structural defects ( +/-5% of SCDs)
- Lesions of molecular structure (eg long QT syndrome)? amount of contribution

### **2.1.2 Transient risk factors for SCD**

- Ischaemia
- systemic effects eg electrolyte imbalances
- neurophysiologic interactions eg local cardiac factors
- toxic cardiac effects eg drugs

Triggering factors act upon the etiological substrate to result in a:

**FATAL ARRHYTHMIA (SUDDEN CARDIAC DEATH)**

(Adapted from Myerburg 1997)

## **2.2 CARDIAC ARRHYTHMIA**

Normal cardiac rhythm is initiated at the sinus node. The sinus node spontaneously generates a regular number of electrical impulses, which are then propagated throughout the heart muscle. An arrhythmia occurs when the rate or regularity of impulses produced by the sinus node are abnormal or when impulses are generated from outside of the sinus node. Symptoms of cardiac arrhythmia vary greatly; the most common are palpitations, dizziness or collapse. Many patients with life threatening arrhythmia will be asymptomatic (at least until physiological compromise occurs). Clinically important arrhythmias result from the interaction of several factors. Short arrhythmias are present in every person, although their prevalence increases with age and some environmental factors (De Backer 1984). These short arrhythmias can initiate life threatening events when a “substrate”, or abnormal ventricular tissue capable of carrying impulses, is present (Jordaens 1996). A common substrate is scar tissue from ischaemic heart disease (Jordaens 1996).

### **2.2.1 Ventricular Tachycardia (VT)**

A tachycardia is an accelerated heart rate, and ventricular tachycardia is a rapid rate that is arising from abnormal impulses generated in the ventricles rather than the sinus node, as in the normal situation. In the majority of cases it occurs because of an underlying structural abnormality of the heart; in nearly 75% of patients defect will result from myocardial infarction (Willems 1990). Although some patients can tolerate VT without haemodynamic compromise, VT can easily lead to ventricular fibrillation and become life threatening (Bayes 1989).

### **2.2.2 Ventricular Fibrillation (VF)**

VF is characterised by rapid, chaotic electrical activity of the ventricles resulting in loss of the pumping action of the heart which leads to circulatory arrest (Health Council of the Netherlands 1993). Irreparable brain damage ensues if the circulation is not restored within 3–4 minutes and death results soon after. Immediate resuscitation and DC shock are the only remedies. As with VT there is usually an underlying structural abnormality, most commonly coronary heart disease. In a small percentage of young people the heart has no apparent defect (Knilans 1992).

## **2.3 DIAGNOSTIC TECHNIQUES FOR ARRHYTHMIAS**

Before therapy can be chosen the presence, type and origin of the arrhythmia must be established.

### **2.3.1 General diagnostic techniques**

Documentation of an arrhythmia by means of an ECG is the first important investigation undertaken to achieve a diagnosis. If necessary a 24 hour ambulatory ECG can then be used to increase the chance of recording an abnormal rhythm. Alternatively an exercise test can be used in an attempt to provoke the abnormal rhythm. The following additional tests are routinely undertaken to detect any underlying structural abnormality (particularly coronary heart disease) or to find a

correctable defect that may be the cause of the arrhythmia such as an electrolyte imbalance:

- biochemical examination of the blood
- chest X-rays
- echocardiography
- radionucleotide imaging of the heart
- cardiac catheterisation and coronary angiography

These tests may also furnish some prognostic information about the arrhythmia.

### **2.3.2 Electrophysiological study (EPS)**

EPS is used to locate the origin of an arrhythmia and identify the pathway, or mechanism propagating the abnormal rhythm through programmed electrical stimulation of the heart (PES). PES involves advancing a catheter to the heart via an artery or vein, under fluoroscopic guidance. Electrical equipment is then used to stimulate the heart and induce the arrhythmia. The electrical equipment can terminate the arrhythmia. Drugs can then be tested to gauge whether they are able to suppress or control the arrhythmia (Wellens 1971).

Once the arrhythmia has been induced the sequence of electrical activation of the heart can be mapped in order to pinpoint the origin of the electrical activity and thereby define the origin of the arrhythmia (Health Council of the Netherlands 1993).

EPS carries some risks, including those associated with catheterisation (bleeding, infection) and others relating to the induction of an arrhythmia (Ruskin 1992). Extensive training of personnel and a well equipped laboratory are required in order to maximise the safety of the procedure and enhance the accuracy of the investigation (Zipes 1989).

EPS is a common precursor for ICD implantation; either as part of the diagnostic work up to define the presence and type of arrhythmia, or as part of the

implantation procedure to confirm the effectiveness of the device. However, evidence around the use of EPS is incomplete and only a few statements can be made based on an analysis of the literature. A significant problem has been variability in patient selection, along with discrepancies in the methods used to perform the procedure (Bocker 1997, Steinbeck and Greene 1996). Much of the early evidence was based upon non-randomised comparative studies (ie cohort and case control studies) and descriptive studies (ie expert opinion, or case series). Recently, though, some large randomised controlled trials have challenged the efficacy of EPS (eg CASCADE 1993, Mason 1993). Table 2 illustrates some of the possible indications for EPS.

The most significant problem associated with EPS appears to be its poor positive predictive value (ACC/AHA 1995). Although EPS is commonly used to select appropriate treatment for patients with ventricular tachyarrhythmias, there is no clear evidence that invasive investigation is superior to holter monitoring (ESVEM 1993, Steinbeck and Green 1996, Daubert and Kimm 1997, Steinbeck et al. 1997). Supporters of EPS claim this research is flawed by the investigator's inability to follow up their patients for a sufficiently long period. These supporters point to a small (57 patients) randomised trial based in Calgary which found the invasive approach to be superior when examined over a follow up of at least 6.5 years. In addition, ESVEM is criticised because of possible bias in patient selection for the trial (ESVEM selected a number of patients already found to be intolerant of some of the medication used; Mitchell et al 1996).

To date no trial has had sufficient statistical power to answer the outstanding critical question - whether EPS can define the patients most likely to receive survival benefit from the insertion of an ICD (Mason 1993, ESVEM 1993). A number of current trials (including the Multi-centre UnSustained Tachycardia trial, see Buxton et al. 1993) may help clarify this central issue.

**Table 2: Overview of conditions for which electrophysiological testing has been used**

Condition	Key Reference	Level of evidence
Premature Ventricular complexes,	ACC/AHA 1995.	Multiple
Non-sustained VT.	ACC/AHA,1995	Multiple
Unexplained syncope	ACC/AHA 1995 Gulamhusein et al. 1982	Multiple
Survivors of cardiac arrest	Wilber et al,1988	2
Unexplained palpitations	ACC/AHA,1995	Multiple
Used to guide drug therapy	Steinbeck et al. 1992	1
In patients who are candidates for an ICD	Moss et al,1996	1
Hypertrophic cardiomyopathy	Fananapazir et al. 1992	2
Combinations of several conditions eg drug testing in survivors of cardiac arrest	CASCADE,1993	1

References have been selected as key examples of the use of EPS for each of the conditions.

## **2.4 RISK ASSESSMENT OF PATIENTS FOR SUDDEN DEATH FROM A CARDIAC ARRHYTHMIA**

The risk of sudden cardiac death in the general population is low and is estimated to be 2 per 1000 persons per year (Kligfield 1987). This makes general population screening for any risk factors for SCD impractical. Risk stratification has therefore been undertaken in patients largely after they have sustained a myocardial infarction (heart attack). Typically it has used the following methods:

**Table 3: Risk stratification methods and their usefulness at identifying individuals at high risk for sudden cardiac death**

Risk stratification method	Usefulness for risk stratifying individuals according to their likelihood of sudden cardiac death
Ambulatory holter monitoring electrocardiogram (ECG)	Identifies post MI patients with ventricular premature beats who may be at increased risk of sudden cardiac death. The usefulness of holter monitoring to detect patients at increased risk is otherwise debated. Holter monitoring may be able to define those patients who have a low risk of a fatal arrhythmia. There is uncertainty about relative benefits of holter monitoring and invasive studies (Mason 1993, Review: Steinbach and Nurnberg 1997)
Signal averaged ECGs	Can detect slowed conduction which is the substrate for ventricular arrhythmias but interpretation problems exist, especially with patients with some ECG abnormalities such as bundle branch block (Borggefe et al. 1997)
Invasive electrophysiological studies	EPS reviews have yielded conflicting results, although it seems likely that patients who do not have an inducible arrhythmia with EPS do have a good prognosis (Wellens 1997)
Estimates of left ventricular function (LVF)	LVF is a powerful, general indicator of mortality risk from all cardiac causes (Gomes et al 1997; Kober 1997)
Heart rate variability	These tests may have a useful role in combination with other tests, especially the estimation of LVF (Kober 1997)
Measurements of reflex baroreceptor sensitivity	
The identification of repolarisation alternans	

Note: All of the studies referred to in Table 2 are level three evidence (expert reviews). However, the authors have often cited supporting evidence from level 1 and 2 studies.

Risk stratification for individual patients using the currently available range of investigations remains poor. In general, either non-invasive or invasive methods of risk stratification do a reasonable job of identifying patients whose risk of SCD is low and thereby enables these people to be spared potentially hazardous therapies (Gilman et al 1994). However, a considerable amount of work is still required in order to enable the specific identification of those individuals who are at greatest risk of a fatal arrhythmia (Breithardt 1997, Steinbeck et al 1997, Kober 1997).

## 2.5 POPULATION RISK STRATIFICATION

Although it is difficult to reliably define individual SCD risk, certain population groups have been found to have an increased epidemiological risk of a fatal arrhythmia:

- Patients who have already experienced a malignant ventricular arrhythmia (Furukawa et al 1989, Kannel et al. 1984, Bigger and Fleiss 1984, Jordaens 1996). Their survival rate is less than 50% over 3 years (Goldstein 1981).
- Patients with a recent myocardial infarction (Moss 1980, Bigger and Fleiss 1984) particularly if they are subject to a number of ventricular premature beats (Coronary Drug Project Research Group 1973, Ruberman et al 1977, Bikkina et al 1992, Rabkin et al 1981, Chiang et al 1969). However, only about 10 – 15% of patients dying from SCD have any evidence of acute ischaemia. Patients with past ischaemic heart disease are at high risk of any form of cardiac fatality. Most patients with SCD will have a previous history (known or unknown) of ischaemic heart disease. Sometimes SCD may be the only indication of past ischaemic heart disease.
- Patients with any form of cardiomyopathy. The most common cause of cardiomyopathy is congestive heart failure. These patients have a 30-45 % risk of death from arrhythmia (Massie 1987, Dorian et al. 1994). In particular, depressed left ventricular function is emerging as a very potent predictor of overall cardiac death, including sudden cardiac death. Mortality appears to increase exponentially as left ventricular function declines (Volpi 1993, Maggioni 1993).
- Patients with certain miscellaneous cardiac abnormalities eg long QT syndrome.
- A small number of people with no apparent cardiac abnormality. However, some authors have suggested that many of these people may have subtle abnormalities on more extensive testing (Jordaens 1996).

## 2.6 CONCLUSION

EPS and other investigations currently have limited ability to define individuals most likely to benefit from an ICD. Several major trials nearing completion may assist in this task. For example, the large multi-centre randomised controlled MUSTT trial will help define the use of EPS in patients with ventricular arrhythmias who have a previous history of myocardial infarction and who have an ejection fraction of less than 40% (Buxton et al. 1993, Estes 1996). Similarly the PORT Project at Stanford University (USA) is a series of five trials designed to determine a reliable method to stratify patients with ischaemic heart disease for their risk of malignant arrhythmia. The Project also aims to determine the most accurate clinical predictors of individual risk of sudden death (<http://preferences.stanford.edu/PORT/portoview>).

Enrolment from several large ongoing trials (AVID, CASH, CIDS; see Section 6.2) is sufficiently (>2,400 patients) to permit sub-analysis of patients with varying risk factors, and hence determination of the ability of investigations to identify sub-groups most likely to benefit from a device.

### **3 Description of the implantable cardiac defibrillator**

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Contemporary fourth generation ICDs are multi-programmable pulse generators which have facilities for anti-tachycardia pacing, low energy cardioversion, telemetry and electrocardiogram storage in addition to high energy defibrillation. A second look feature now allows the device to abort therapy for any arrhythmia that has terminated spontaneously while the device is charging.

Modern devices are usually implanted transvenously in a manner analogous to the insertion of a pacemaker (usually via the subclavian or cephalic vein) and the generator is placed in muscular pouch in the subpectoral position. The ICD consists of a pulse generator and lead system, and weighs about 140gms. The device can deliver a defibrillation shock of up to 40 joules from energy stored in a capacitor within the generator. Modern devices can last up to 5–8 years before they require replacement (ANDEM 1997). New devices allow diagnostic information to be retrieved and the device to be reprogrammed to intervene in different rhythms by either pacing (electrical overriding of the rhythm) or the delivery of either low or high energy cardioversion.

Implantation requires programmed electrical stimulation, firstly to gauge the defibrillation threshold (the energy required to correct, or cardiovert, an arrhythmia) and then, after placement, to check that the device is effective. Most current devices use a tiered approach to therapy, particularly the treatment of VT. Pacing is used as the first line therapy, followed by low-energy shocks if pacing is unsuccessful, and then high energy shocks as a last resort (AHTAC 1995). Transvenous Implantation requires a hospital stay of approximately 5 days although this period is diminishing. Follow-up is usually undertaken after one month and then three monthly thereafter, with telemetric interrogation of stored information from the ICD providing important information about its functioning.

### 3.1 HISTORY OF THE ICD

The ICD has evolved rapidly since Mirowski inserted the first device in 1980. Significant technological developments since then have rapidly reduced the size of the ICD generator and leads, which in turn has permitted changes to the placement of the device and the way it is inserted. The evolution of ICD technology has been characterised by five significant steps (see Table 4)

**Table 4: Steps in the technological evolution of the ICD**

Approximate year of introduction	Programmable possibilities	Detection method	Available treatment modalities
1980	No	Probability based on rhythm density	Defibrillation only
1982	No	Frequency of complexes	+ Cardioversion
1988	4 parameters	Frequency	+ Cardioversion
1989	Programming for several myocardial zones	Frequency and stability	+ Antitachycardia pacing and demand ventricular stimulation
1995	Programming for several myocardial zones	Atrium and ventricular detection as well as frequency and stability of tracings	+ Atrioventricular 'universal' stimulation

After Block 1996 and ANDEM 1997

The latest devices weigh 100 gms and are capable of sensing the cardiac rhythm in the atrium and the ventricles as well as independently administering pacing or cardioversion to either parts of the heart. This latest development could significantly improve the specificity of arrhythmia detection and reduce the number of inappropriate ICD generated treatments (Lavergne et al. 1997).

Significant reductions in the volume of the device (from approximately 150ml to the current size of 60mls) have enabled surgical approaches to the insertion of the device to dramatically change over the last 17 years (see Table 5).

**Table 5: Significant steps in the surgical implantation of ICDs**

Year	Thoracotomy	Leads	Placement of Generator
1980	Thoracotomy via Sternotomy	Epicardial	Abdominal
1982	Thoracotomy under xyphysternum	Epicardial	Abdominal
1986/9	No	Transvenous	Abdominal
1991	No	Transvenous	Abdominal
1993	No	Transvenous	Pectoral

After: Block 1996, ANDEM 1997

Today's transvenous ICDs are significantly safer to insert than previous models, which required a thoracotomy. They are also potentially more widely available to patients who previously may not have been considered fit enough for the operation (Frame 1993, Zipes 1995, Lawton 1996). The technology is now generally regarded as being on a plateau, with further reductions in size expected to be modest only (Saksena et al. 1996, Block et al 1995, Block 1995, Jung 1994, Reddy and Bardy 1997).

The battery life of the ICD generator has markedly increased over the last 17 years. New generation devices have an average life of between 5–8 years. It is noted that there is a tension between the ability to reduce size to facilitate easy implantation and the need to maintain a reasonable size to ensure adequate battery capacity (Saksena 1996, Block et al 1995, Block and Breithardt 1995, Alt et al 1997). While pacing has reduced the need to defibrillate all ventricular arrhythmias (Block and Breithardt 1995) and a biphasic waveform has reduced the defibrillation threshold (Lerman and Cannom 1996, Hammil et al 1995) the device must still carry sufficient capacitance to deliver a number of appropriate strength shocks.

Currently a number of lead systems exist which can be implanted in a variety of locations. With the introduction of biphasic waveforms, tripolar lead systems have become uncommon (Lerman and Cannom 1996). Modern bipolar configurations include the following arrangements:

- right ventricular lead and active pectoral can (Bardy et al. 1993)
- single right ventricular lead with two electrodes (Neuzner 1994)

- combination of right ventricular and right atrial leads with a single defib electrode for each lead (Luceri et al. 1995)

### 3.2 Distribution of ICD implantation

The use of ICDs worldwide has increased markedly over the last decade. From the first implantation in 1980 (Mirowski 1980) it is now estimated that over 36,000 people have already received a device (Porterfield 1993). In excess of 20,000 cardiac defibrillators are now being inserted each year (Saksena 1994). Although an estimated 80% of ICDs are implanted in the United States (Anderson and Camm 1993) a significant number of devices are now inserted in most other western countries.

**Table 6: Estimates of the number of ICDs inserted in different countries (region)**

Region/ Country	Estimated Number of ICDs inserted	Year of estimate, and reference	Estimated Population (millions)	Approximate ratio of number of ICDs inserted to population
Quebec, Canada	336	1992 (Conseil d'évaluation des technologies de la santé du Québec 1992)	7	4.8 per 100,000
United States	20000	1992 (Anderson 1992)	250	8 per 100,000
Australia	350	1995 (Cowley 1990, AHTAC 1995)	18	2 per 100,000
Netherlands	200	1993 (Health Council of the Netherlands 1993)	15	1.3 per 100,000
New Zealand	40	1997 (Crozier, personal comm 1997)	3.6	1 per 100,000

Population estimates based upon: United Nations Demographic Yearbook (1995), NY.

#### 3.2.1 Implantation of ICDs in New Zealand

New Zealand has a relatively small ratio of devices implanted per 100,000 population (1:100,000), although considerable caution must be exercised when comparing countries using estimates calculated by different methods and in different years.

Most implants in New Zealand are inserted in Auckland and, unlike Australia, all insertions are carried out in public hospitals.

**Table 7: Implantation of ICDs in New Zealand**

City	Number of ICD implants (1997)
Auckland	25
Hamilton	8
Christchurch	12
TOTAL	40

Based upon Crozier, personal communication 1997

### 3.2.2 Distribution of units inserting ICDs in Australia

By comparison with New Zealand, Australia has 11 units inserting ICDs.

**Table 8: Distribution of ICD units in Australia**

State	Diagnostic studies	Radio frequency ablation	ICD insertion (1995)
New South Wales	5 public 2 private	3 public 1 private	3 public 2 private
Victoria	5 public 1 private	5 public	3 public
Queensland	1 public	1 public	1 public
Western Australia	2 public	1 public	1 public
South Australia	2 public	1 public	1 public
TOTAL	18 units	12 units	11 units

After: AHTAC 1995

## 3.3 RESOURCE REQUIREMENTS

### 3.3.1 Workforce requirements

Naccarelli and Morgan (1996) suggested that the United States has an appropriate ratio of electrophysiology cardiologists to population size (1:274,410 people). Recently Naccarelli (1997) has observed a ratio of 1:913,333 in a large health maintenance organisation, Kaiser California. Noting ratios of 1:750,000 in Canada and 1:2,800,000 in the UK, Naccarelli concluded that the US had a surplus of electrophysiology cardiologists. The New Zealand ratio is approximately 1:1,200,000 (assuming that 3 cardiologists in New Zealand are undertaking this work). This ratio is clearly a flawed estimate of workforce requirements because it is so heavily influenced by the effects of the small numbers involved.

Rather than focusing on the number of practitioners, a more suitable approach to describing workforce requirements for ICD implantation is to examine their requirements for provision of a high quality service. A number of authors have

suggested that all electrophysiology cardiologists need a minimum annual number of procedures to maintain their skills (typically about 10 ICD insertions per year) although there is no evident consensus on a suitable annual minimum volume (Flowers et al 1991, Hayes et al 1994, Scheinman 1992, Naccarelli 1997). In addition there is clearly a need for adequate knowledge, skills, and support, and possibly some requirement for access to competing methods of arrhythmia management (Breithardt et al 1992).

### **3.3.2 Hospital requirements**

Australian data suggests that the average length of stay for patients receiving cardiac mapping in an electrophysiology unit is 5.6 days (AHTAC 1995). Patients stay for an average of 4.5 days for radio-frequency ablation or 19 days for ICD insertion (AHTAC 1995). It should be noted that these figures could include time taken for other diagnostic or therapeutic interventions. AHTAC (1995) reports that the average bed requirement for the procedure alone is 1-2 days for serial electrophysiological testing or radio-frequency ablation and 5 days for ICD insertion. The report notes that 50–70 % of ablation is now undertaken as a day case procedure. After ICD insertion approximately 1 day in intensive care and 2 days in a telemetry bed are needed (AHTAC 1995).

Because most of the procedures are undertaken on an outpatient basis, it is estimated that a cardiology unit undertaking 50 EPS studies per year could expect to add only 0.2 beds to their general ward requirements, with no requirement to increase the number of cardiac intensive care beds or telemetry beds (AHTAC 1995). Similarly a unit undertaking 50 RF ablations a year could expect to need an additional 0.2 telemetry and general beds per year.

### **3.3.3 Technical resource requirements for ICD insertion**

The following are required for ICD insertion:

- EPS laboratory (often included in cardiac catheterisation laboratory) - transvenous ICDs can be safely inserted in the electrophysiology laboratory instead of the operating theatre (Strickberger et al. 1995, Tung 1995)

- permanently installed standard fluoroscopy equipment with a C arm
- programmable stimulators for generating electrical impulses
- computerised equipment for storing, recording, and analysing stimuli delivery and ECG data
- capacity to monitor haemodynamic data.
- radio-frequency generator is required for RF ablation.
- defibrillator, pulse oximeter and resuscitation equipment
- trained electrophysiology cardiologist(s), cardiac technician(s) and nurse(s).
- transvenously inserted ICDs can be inserted in the EPS laboratory

Many procedures could be outpatient delivered eg tilt table testing, ICD generator replacement and some electrophysiology investigations.



## **4 Adverse outcomes from ICDs**

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The studies included in this review did not use consistent definitions of the complications associated with ICDs and they did not always comprehensively report complications that either occurred or were absent in their series. For this reason, this review has not assumed that if a complication was not listed it did not occur and only events specifically cited have been included.

Similarly, averages have not been given for the tables, as it has not been assumed that the studies that did not specify the occurrence of a complication actually did not have any. In addition, the reader is advised that publication bias may be operating, such that the studies available in the literature may not be representative of the general experience of most patients receiving a device. It may be; for example, that the operators who are more likely to have their work published may actually experience fewer complications than most operators.

### **4.1 TYPES OF ICD COMPLICATIONS**

ICD complications fall into two categories:

- complications associated with the implantation surgery
- complications associated with the fallibility of the device

### **4.2 COMPLICATIONS RELATED TO THE SURGICAL PROCEDURE**

#### **4.2.1 Peri-operative mortality**

The development of transvenous implantation has reduced the mortality risk associated with the insertion of current ICDs to less than 1%, compared to 3 % associated with earlier devices requiring a thoracotomy (Lerman and Cannon 1996, Block et al. 1995, Hauser et al. 1993, Saksena 1994, Sra 1994).

#### **4.2.2 Failure to insert a device**

Most series have reported that over 90% of patients have been able to receive a transvenously implanted device successfully (Bardy et al 1993, Strickberger 1995, Zipes 1995, Bardy et al. 1996). Recent trials have generally reported higher success rates than earlier trials describing the first experiences with transvenous ICD insertion (Brooks 1994). Reduction in size, transvenous insertion, and the development of biphasic waveform have virtually eliminated any restriction on the patients who can receive an ICD successfully (Bardy et al. 1993, Lerman and Cannom 1996, Brooks 1994, Neuzner 1994, Natale 1995).

Complications associated with ICD implantation are common and occur in 20-60 % of recipients. This incidence depends on the number of patients included in the review (published studies have ranged between 7-1138), length of follow-up (studies have varied between 3 days to nearly 4 years), and definitions used for including a complication (Grimm 1993, Pfeiffer 1994). In addition, a given series may have included implantation methods (ie both transvenous and transthoracic), devices with varying numbers of leads, or differing implantation sites (abdominal and pectoral). Although the results are presented in tabular form, the reader is advised to be cautious in making any direct comparisons between study results.

#### **4.2.3 Lead dislodgements**

Lead dislodgement is the most common complication associated with ICD implantation, occurring in up to 10% of recipients. It is important because it can increase the defibrillation threshold, which in turn can lower the effectiveness of the device. In general, the frequency of lead dislodgment seems related to the lead type and position, and the experience of the doctor implanting the device.

**Table 9: Frequency of lead dislodgment**

Reference	No of patients	No patients with lead displacements	Percentage of patients with lead displacement
Hauser 1993	302	4	1%
Frame 1993	105	2	1%
Bardy 1993	80	8	10%
Grimm 1993	241	9	4%
Sra 1994	95	8	8%
Gielchinsky 1994	51	3	6%
Brooks 1994	149	6	4%
Fahy 1995	150	4	2.7%
Zipes, 1995	1349	121	9%
Nunain 1995	54	5	10%
Jones 1995	159	11	6.9%
Korte 1995	79	5	5%
Roelke 1995	131	2	1.5%
Drucker 1995	256	6	2.7%
Schwartzman 1995	170	6	3.5%
Raviele 1995	306	11	3.6%
Strickberger 1995	172	3	1.7%
Bardy et al 1996	464	10	2.2%
Gold 1997	1000	17	1.7%
Gupta 1997	437	8	1.8%

After: ANDEM 1997, Lawton 1996

The overall incidence of lead dislodgment has been reported as 6.8% in a large review of published case series (Lawton et al 1996). Small numbers, variations in insertion site and length of follow-up largely account for interstudy variation. In general, the literature suggests that leads associated with pectorally placed devices are superior to those of abdominal site devices (Kelly et al. 1988, Schwartzman et al. 1995, Saksena 1994). In addition, lead dislodgment seems to be more common when the operator is less experienced. Jones (1995), for example, found that the dislodgment rate in his first 46 patients (17.4%) far exceeded that in his final 109 patients (2.7 %).

#### 4.2.4 Infection

Infection is now a relatively rare complication (<4%) with the use of modern transvenous implantation techniques. Infection was previously more common with transthoracic procedures, which required major open-chest surgery. The majority of infections are still due to bacteria typically resident on the skin (from either the patient or the operating team) and the pathogens are usually staphylococci.

Infection is usually clinically apparent within 60 days of implantation and it is still considered a potentially life threatening complication (Kennergren 1996).

**Table 10: The frequency of reported infection after ICD insertion**

Reference	Total number of patients	No of patients with infection	% of patients with infection
Bardy 1993	84	1	1.2%
Shiahan 1993	64	2	1.2%
Hauser et al. 1993	302	1	0.3%
Hammel 1993	43	1	2.3%
Schwartzman 1995	170	7	4%
Jones 1995	159	2	1.3%
Lawton 1995	100	1	1%
Shiahan 1995	57	2	3.5%
Zipes, 1995	1349	36	2.7%
Strickberger 1995	172	1	0.8%
Gold 1997	1000	2	0.2%
Gupta 1997	437	8	1.8%

After: Kennergren (1996) and ANDEM (1997)

Again the effects of small numbers are apparent in the above figures, along with some variation due to inclusion in some individual studies of different types of devices and implantation procedures. Infection rates do not appear to be significantly higher when implantation is undertaken in the electrophysiological laboratory rather than the operating theatre (Fitzpatrick et al. 1994, Singer et al. 1997).

#### **4.2.5 Haematomas, bleeding and wound problems**

Wide variation is evident in the reported frequency of wound related complications after ICD implantation (range 0-16%). Most of the variation relates to differences in definitions used by different authors for categorising the presence (or absence) of a wound-related complication. Many authors have included the number of all haematomas that have occurred in their case series while others have only specified the number of clots that have needed surgical evacuation (Block 1992, Frame 1993). In general, most studies have found that wound problems are usually related to: the muscular pocket used for the devices, the use of subcutaneous leads in certain devices, and concurrent anticoagulation of some patients for other medical reasons (Kennergren 1996).

**Table 11: The frequency of reported wound/bleeding problems**

Reference	Number of patients	Number of haematomas or bleeding problems	Percentage of patients with haematomas or bleeding problems
Bardy et al. 1993	84	4	4.8%
Frame 1993	105	2	1%
Jones 1995	159	1	0.6%
Shiahan 1995	57	4	7%
Zipes, 1995	1349	17	1.3%
Strickberger 1995	172	5	2.9%
Bardy et al. 1996	464	5	1.1%
Gold 1997	1000	18	1.8%
Gupta 1997	437	2	0.4%

After: ANDEM 1997, Kennergren 1996

#### 4.2.6 Thromboembolic events

ICD implantation can lead thrombosis formation around the device, and this material can subsequently become dislodged and form an embolus. The reported incidence of thrombotic vegetations on transvenous leads has varied markedly. This variation seems related to the different definitions of these events that have been used by a variety of researchers. The highest rate of thrombosis formation (15.7% - Jung et al. 1993) was recorded in a series that specifically examined the incidence of thrombotic growth around transvenous leads. By contrast other authors who found lower rates of thrombosis formation only included the complication when they were associated with a clinically significant embolic event (eg Jones 1995). The consensus from the literature is that while these growths are probably common, they appear to embolise relatively infrequently. Consequently their clinical significance remains undetermined (Saksena et al. 1996).

**Table 12: The reported frequency of thromboembolic events after ICD implantation**

Reference	Total number of patients in series	Number of patients with thromboembolic event	Percentage of patients with event
Block 1992	64	2	3.1%
Grimm 1993	241	4	1.7%
Bardy et al. 1993	84	2	2.4%
Hammel 1993	43	1	2.3%
Brooks 1994	149	2	1.3%
Nunain 1995	54	1	1.9%
Zipes 1995	1349	6	0.4%
Roelke 1995	131	1	0.8%
Schwartzman 1995	170	3	1.8%
Raviele 1995	306	3	1.0%
Jones 1995	159	1	0.6%
Bardy et al. 1996	464	2	0.4%
Jung et al. 1993	51	8	15.7%

After: ANDEM 1997, Kennergren 1996

#### **4.2.7 Perforation of the heart or lungs**

The use of a subclavian approach to gain venous access for the procedure allows for the possibility that the operator will perforate a lung and cause a pneumothorax. Similarly the insertion of an endocardial lead via the superior (or inferior) vena cava means that the procedure may accidentally result in perforation of the right ventricle of the heart. In the few studies that have commented on these potential problems the incidence of either complication appears to be very low, and usually below 1%.

**Table 13: The reported frequency of heart/lung perforations after insertion of the ICD**

Reference	Pneumothorax or haemothorax	Perforation of the heart
Hauser 1993	0	1% (0.3%)
Grimm 1993	--	1.2% (3/241)
Fahy 1995	0% (0/150)	0.6%
Jones 1995	0.6% (1/159)	0.6%
Zipes 1995	0.1% (2/1349)	0.4% (5/1349)
Shiahan 1995	0.6% (1/159)	0
Strickberger 1995	2.3% (4/172)	0
Lawton 1995	2% (2/100)	0
O'Nuinan 1995	0	1% (1.9%)
Bardy et al. 1996	0.4% (2/464)	0
Molina 1996	--	5.1% (4/78)*

After: ANDEM 1997, Kennergren 1996

Note: 0= no patients with complication, --- = not stated

\* Note Molina used a unique type of stiff catheter, incorporating active fixation, which might be predisposed to a higher rate of cardiac perforation.

Transvenous leads do not cause the problems associated with epicardial leads, which have included: epicarditis, erosion of coronary arteries, cardiac tamponade, mediastinitis and phrenic nerve injuries. Several studies have previously documented these complications in 9-32 % of patients receiving an epicardial ICD device (Kelly 1988, Saksena 1994, Zipes 1995, Grimm et al. 1993, Winkle et al. 1989, Manolis 1989).

#### 4.2.8 Rare complications

The following complications are unquantified but they have occasionally been described in reports of large series of ICD implantations. The events are therefore assumed to be rare.

- Pacemaker migration (Mancini and Grubb 1990, Shandling et al. 1991).
- Subclavian crush syndrome (Parsonnet et al. 1989, Magney et al. 1993, Fink et al. 1992, Magney et al. 1995).
- Air embolisation (Kennergren 1996).

- One review article has examined the possibility that radio-frequency signals from portable telephones may interfere with ICD functioning (Hayes et al. 1996).
- Prolonged defibrillation testing can lead to deterioration of cardiopulmonary function in patients with a poor ejection fraction (Hachenberg et al. 1991, Antunes et al. 1988, Bakker et al. 1994, Frame 1992).
- Replacements present an additional challenge due to the presence of fibrotic tissue. ICD replacements are associated with a substantially increased risk of insulation damage and infection (Kennergen 1996, Block and Breithardt 1996).

### **4.3 COMPLICATIONS RELATED TO FAILURE OF THE DEVICES**

#### **4.3.1 Proarrhythmia**

Another complication associated with the device is its paradoxical ability to provoke arrhythmia. In theory any of the therapies delivered by an ICD has the potential to do this. A number of studies have reviewed the incidence of induced VT as a result of anti-tachycardia pacing delivered by an ICD. Their results have ranged from 0–43% per episode of pacing (Fisher 1978, Waspe 1983, Saksena 1985, Bardy 1993, Gillis 1993, Ip 1991). Similarly the incidence of acceleration of induced or spontaneous VT by cardioversion therapy has been reported as being between 4% and 30% per episode (Saksena 1985, Bardy 1993, Lauer 1994, Zipes 1984, Ciccone 1985). A considerable amount of the variation in these reports is probably due to the effect of small patient numbers (range 8-40). A number of reports describe (usually single cases) of an ICD delivering an inappropriate treatment which in turn has induced arrhythmia (Pinski 1994, Callans 1993, Grimm 1992, Schmitt 1994). Although many of these have resolved by the device functioning appropriately to terminate the iatrogenic rhythm, at least 3 fatalities have been documented (Birgetsdotter-Green 1992, Cohen 1991, Fromer 1992). In addition, several researchers have noted that patient discomfort can be markedly increased by delivery of a number of additional shocks after the device itself has induced arrhythmia (Schmitt 1994, Pinski and Fahy 1995, Callans 1993).

### **4.3.2 Failure to prevent or detect an arrhythmia**

A crucial limitation of the implantable defibrillator is its inability to alter the underlying substrate, which is responsible for the arrhythmia. The device is therefore palliative in that it intervenes after an event has occurred and does not prevent or inhibit the generation of arrhythmia.

The ICD has an arrhythmia detection algorithm, which is usually programmed to have high sensitivity but lower specificity for an arrhythmia. As a result it is rare for a device not to respond to a ventricular tachyarrhythmia (Jordeans 1996). However, the trade off is that ICDs often have difficulty distinguishing some supraventricular arrhythmias from those with a ventricular origin (Nunain et al. 1995, Grimm et al. 1993, Bocker et al. 1993). Research suggests that 10 – 30% of patients per year receive inappropriate shocks mostly due to the device's unnecessary response to a supraventricular arrhythmia (Reddy and Bardy 1997, Zipes 1995, Nuinan 1995). Inappropriate shocks are important because they cause discomfort, contribute to psychological discomfort, drain the battery and may precipitate an arrhythmia (Dunbar et al. 1993, Keimel and Abeyratne 1995). This problem will be substantially ameliorated and the number of inappropriate shocks reduced in future by use of better algorithms based on information gained from memory recorders now present in current ICDs and by the recent development of dual chamber sensing capabilities (Schugger et al. 1988, Kaemmerer and Olson 1995, Ayers et al. 1997, Lavergne 1997).

### **4.3.3 Lead fractures, damage to insulation, lead erosions**

These complications often occur some time after ICD insertion and although not life threatening they reduce the efficacy of the device and sometimes the recipient's quality of life. The incidence of lead fractures and erosion also depends on the length of follow-up and the definitions used in the different studies. However, it is usually infrequent, occurring in less than 5% of all implantations.

**Table 14: The reported frequency of ICD lead damage/erosion or fracture**

Reference	Number of patients in series	Number of patients with lead damage, erosions, lead fracture	Percentage of patients
Bardy 1993	84	1	1.2%
Grimm 1993	241	10	2.4%
Sra 1994	95	1	1.1%
Fahy 1995	150	4	2.7%
Roelke 1995	131	3	2.2%
Fahy 1995	150	4	2.7%
Zipes 1995	1349	20	1.5%
Drucker 1995	256	4	1.6%
Schwartzman 1995	170	5	2.9%
Jones 1995	159	9	5.1%
Korte 1995	79	4	5%
Strickberger 1995	172	2	1.1%
Raviele 1995	306	6	2%
Bardy et al. 1996	464	2	0.4%
Lawton 1996	348	10	2.9%
Gold 1997	1000	4	0.4%
Gupta 1997	437	17	3.9%

After: ANDEM 1997, Kennergren 1997

#### **4.3.4 Factors that may reduce the incidence of complications**

Rates of pneumothorax and haemothorax (Parsonnet 1995, Parsonnet et al. 1989) and lead dislodgment (Bardy et al. 1993) have been shown to decrease as the operator gains more experience in ICD implantation.

The incidence of complications does not appear to be related to whether the insertion is conducted by cardiologists in catheter laboratories or surgeons in operating theatres (Saksena et al. 1993, Fitzpatrick et al. 1994, Molina 1995, Paul et al. 1991, Stamato et al. 1992, Strickberger et al. 1994, Strickberger 1995, Singer 1997). More important is the use of aseptic technique and the quality of equipment and supporting staff (Kennergren 1996).

## 5 Beneficial outcomes - the efficacy of the ICD

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The efficacy of the ICD can be measured against any of the four goals for the insertion of the device, which are to:

- terminate tachyarrhythmias, prevent cardiac arrest and reduce the incidence of sudden cardiac death
- prolong life
- improve the quality of life
- assist with understanding the mechanisms of sudden cardiac death

This review will examine the effectiveness of the ICD with respect to each of the first three goals. The first question is whether the ICD can do what they are made for; can it treat tachyarrhythmias and thereby prevent SCD? The most important overriding question to consider at the same time is whether it can actually improve overall survival. Do ICDs guarantee that people will actually live longer, as opposed to ensuring only that they will die as prematurely but from another cause apart from SCD? Finally, if they are effective at prolonging life, can they improve the quality of this extra life?

The goal of increasing the understanding of the mechanisms underlying SCD is regarded as an intermediate step towards achieving the other three goals and it is not specifically addressed by this review.

### 5.1 EFFICACY OF THE ICD TO TERMINATE FATAL ARRHYTHMIA AND PREVENT SCD

The ICD is fundamentally designed to terminate a fatal arrhythmia and thereby prevent SCD. However an inherent problem exists with research that has attempted to validate this property. The problem is that ultimately nearly all deaths are arrhythmic sudden deaths, but obviously not everyone can use an ICD. This means the definition

of SCD should be expanded to include only those people who die from an unexpected, arrhythmic death that could have been prevented had the arrhythmia been terminated (Torp-Pederson 1997). Instead of this definition, trials examining the efficacy of the ICD to prevent arrhythmic death have used highly variable classifications of SCD (see Table 15). For example the trial by Kim et al. (1996) failed to provide any clear and objective definition for SCD while the study by Moss et al. (1996) detailed rigorous criteria. Nearly half of the studies have not clearly defined the term SCD (16/35 studies). Where a definition has been provided it has usually been based on either the time between onset of symptoms and death (17/35; usually death less than one hour after symptoms), death that is unwitnessed (11/35) or simply any unexpected death (4/35). Most trials have not required validation of arrhythmic death by electrocardiographic tracing and fewer (33/35) have used autopsy evidence to exclude other causes of death. Therefore, most often the classification of SCD has been surmised to have occurred if the patient died without witness, unexpectedly, or within one hour.

Table 15 presents an assessment of the 35 completed studies which have examined the incidence of SCD in an evaluation of the ICD efficacy.

**Table 15: Classifications of sudden cardiac death in the literature**

<b>Definition of sudden Cardiac death</b>	<b>Randomised controlled trials Evidence grade 1</b>	<b>Comparative studies Evidence grade 2</b>	<b>Descriptive studies Evidence grade 3</b>	<b>Total</b>
Death within one hour of symptoms	Wever 1995		Gomes 1997	2
Death within one hour of symptoms, or unwitnessed (ie during sleep)		Lawton 1996 Zipes 1995	Bardy 1996 Li 1996 Lessmeier 1994 Grimm 1993 Panagiotis 1997 Kim 1995 Kim 1996 Bocker 1993	10
Death within one hour of symptoms or unexpected		Crandall 1993		1
Death within one hour of symptoms or unwitnessed or unexpected		Bocker 1996		1
Instantaneous death ie within five minutes of Symptoms		Choue 1994	Raviele 1995	2
Death within one hour Of symptoms,unwitnessed, unexpected and validated by hospital records, Interviews, and autopsy		Sweeney 1995		1
Hinkle and Thale Criteria	Moss 1996			1
Not stated	Siebels 1994	Haffajee 1997 Jafar 1997 Shiahan 1995 Powell 1993 Ector 1996 Newman 1992	Bardy et al 1996 Bocker 1995 Levine 1996 Trappe 1997 Brooks 1994 Pacifico1997 Fogoros 1990 Fromer 1992 Palatianos 1991	16

The variability and vagueness surrounding the term SCD present two main problems:

- it allows for the possibility of significant classification bias in the studies that have examined the efficacy of the ICD to prevent arrhythmic death
- it obscures the ability of the trial to show convincingly that a death classified as SCD is preventable by means this intervention

Pratt (1996) and Britton (1974) studied the discrepancies between ICD efficacy studies and concluded there was 40% variation among investigator's ability to reliably define the cause of death. These variations become particularly problematic when the literature is being searched to determine people at highest risk who warrant intervention to reduce their chances of SCD. A classification tool has been proposed to assist with classification of the literature (and to encourage the use of more robust definitions in the future)(See Table 16).

**Table 16: Classification schedule for studies examining sudden cardiac death**

Strata	Definition
Documented arrhythmic death	Death occurring within 5 minutes of symptoms and documented VT/VF within 10 minutes prior to death
Arrhythmic death by exclusion	Observed abrupt death or circumstances compatible with instant death where history does not indicate severe disease incompatible with life for some time, and where autopsy does not indicate a non-arrhythmic cause
Arrhythmia by default	Abrupt loss of consciousness and disappearance of the pulse with no prior collapse of circulation and no other data

(After: Torp-Pedersen 1997, Epstein et al. 1996)

Most of the studies examined in this review classify arrhythmic death by default. The two principal exceptions are Moss (1996) and Sweeney (1995). It is notable that both of these evaluated ICD efficacy in highly selected populations (myocardial infarction, low ejection fraction and inducible tachyarrhythmias in Moss; patients prior to transplant in Sweeney).

With the limitations noted about the classification of SCDs, consistent evidence is now available to show that ICDs can reliably terminate an otherwise fatal arrhythmia

(Maloney et al. 1991, Saksena 1992, Kim 1996). Furthermore this benefit has been translated into the almost total elimination of the possibility of SCD (however SCD has been defined among recipients of the device. The consistency of results presented in the literature, despite the use of varying methods and settings, suggests that the ICD has been conclusively proven to reduce the incidence of SCD to less than 1% annually among recipients (Bardy et al. 1992, Winkle et al. 1989, Manolis et al. 1989, Echt et al. 1985, Lehmann et al. 1988, Tchou et al. 1988, Fogoros et al. 1990, Sweeney 1994, Zipes 1995, Block et al. 1995, Schlepper et al. 1995, Akhtar et al. 1992, Raviele 1996, Steinbeck 1997).

## **5.2 THE EFFICACY OF ICDS TO IMPROVE OVERALL SURVIVAL**

Although ICD therapy has been shown to be extremely successful at terminating an arrhythmia and preventing sudden death, its efficacy in prolonging overall survival remains controversial. Three types of studies (descriptive, comparative, and randomised controlled trials) have been used to evaluate this issue.

Table 17 provides a summary of the different types of studies that have been used to examine the efficacy of the ICD to improve overall survival along with typical results from these studies and some of the main limitations associated with the study design.

**Table 17: Summary of studies evaluating the efficacy of the implantable cardiac defibrillator on survival**

Type of study and evidence grade	Results	Limitations
<p>C omparison of ICD patient series with historical controls</p> <p>Evidence grade 2-3</p>	<p>Authors generally find reduced sudden cardiac death, but lower non-sudden cardiac death rates in the ICD group imply selection of low risk patients (Winkle et al. 1989)</p>	<p>Differences in patient selection and confounders, eg. EF, medications, past ischaemic heart disease etc</p> <p>Biases in delay to receive therapy. Longer duration to receive ICD results in only fitter surviving</p>
<p>Comparison of actual death rates with “deaths” from “appropriate shocks”</p> <p>Evidence grade 2-3</p>	<p>Usually reduced sudden cardiac death (Levine et al. 1991)</p>	<p>Validity of appropriate shocks questionable</p> <p>Some shocks may be inappropriate eg. for an SVT</p> <p>Episodes that may spontaneously revert will receive shock</p>
<p>Comparison of ICD patients with historical matched control group or concurrent unmatched and non-randomised group.</p> <p>Evidence grade 2</p>	<p>Usually reduced sudden cardiac death, but either no effect or an increase in non-sudden cardiac death rates. (Newman et al. 1992, Crandall et al. 1991)</p>	<p>Incomplete matching of confounders between groups</p> <p>Uncertain if concomitant treatments are similar between the groups</p> <p>Biases due to differences between the groups in the delay between cardiac arrest and therapy</p> <p>Concurrent subject groups less are likely to have differences in concomitant therapy</p>
<p>Concurrent randomised control subjects with devices that preferably can also record the rhythm when a device discharges</p> <p>Evidence grade 1</p>	<p>Results suggest benefit in highly selected patient groups (Moss 1996)</p>	<p>Primary endpoint should be total mortality to avoid classification biases</p> <p>Still need to avoid referral biases to participant centres and bias in which centres participate</p>

### **5.3 EVALUATION OF THE ENDPOINTS USED BY STUDIES TO DETERMINE THE EFFICACY OF THE ICD**

Studies evaluating ICD efficacy have used two endpoints to examine the effect of the device on survival. The two available endpoints are:

- a comparison of the actual incidence of death between two groups OR
- a comparison between the time to first recorded “appropriate shock” for an arrhythmia - which is presumed to have been otherwise fatal, and the mortality rate of a group without the device.

#### **5.3.1 Comparison of the actual incidence of death**

In this method an estimate of the effectiveness of the device is gained by comparing the mortality rate of a group of recipients with another group who have not received the device. However, a significant problem has occurred when researchers have used the SCD mortality rate as their only endpoint. Several early studies found that there was a low incidence of sudden cardiac death amongst ICD recipients (Echt et al. 1985, Lehmann et al. 1988). More recent studies have also included the death rates from other causes and found that when overall mortality is used as the endpoint ICD recipients do not gain any significant survival advantage (Kim et al 1993, Siebels 1994). Several authors have concluded that the ICD saves people from SCD only for them to soon die from another cause (Kim et al. 1993, Siebels 1994).

Measurement bias is another important potential problem with studies that have used mortality rates as their endpoint. For example, misassigning a patient who dies with an ICD to a non-sudden death would favour the efficacy of the device. Numerous researchers have pointed to the possibility of measurement bias when mortality rates have been used as the endpoint of a trial examining ICD efficacy, and have noted that this potential is increased by the wide variety of definitions applied to SCD in the literature (Saksena 1992, Green et al. 1989, CASCADE Group 1991, Kim 1993). To eliminate this bias it is important that these trials use total mortality as their endpoint.

Another problem in the use of SCD mortality rates as the endpoint is the concept of “competing risks” among the study population. Many trials have recruited patients who are gravely ill from underlying cardiac pathology. These subjects have a high risk not only of SCD but also of death from other causes. The problem then becomes whether the competing risk of death from other causes can nullify any advantage an ICD may give in protecting these patients from sudden death (Sweeney and Ruskin 1994, Nisam 1997, Fogoros 1996).

### **5.3.2 Comparisons using time before first “appropriate shock”**

The second type of comparison made in studies assessing ICD efficacy is average time before the occurrence of an “appropriate shock” in a subject group compared to observed mortality in a similar group without ICDs. Appropriate shocks are episodes where the device has discharged and terminated what is considered to have been a fatal arrhythmia had the device not intervened. It seems likely that these studies overestimate ICD efficacy because many shocks may be incorrectly defined as a ventricular tachyarrhythmia, while some ventricular events might have been haemodynamically tolerated whilst they terminated spontaneously. Recent trials have defined “fatal” arrhythmia more rigorously and have applied these tighter definitions to the data available from the device’s memory (Bocker et al 1996). Even these more stringent definitions cannot fully eliminate the possibility of measurement bias.

## **5.4 DESCRIPTIVE STUDIES OF ICD EFFICACY IN IMPROVEMENT OF OVERALL SURVIVAL**

In total 7 studies were located that matched our criteria (see section 1). A further 19 studies were reviewed, but lacked adequate detail in their methods to enable inclusion. The following descriptive studies were reviewed but not tabled due to deficiencies in study design, presentation or analysis: Former et al. 1992, Porterfield et al. 1993, Trappe et al. 1995, Kim et al. 1996, Panagiotis et al. 1997, Fogoros et al. 1990, Lessmeier et al 1994, Mahmoud et al. 1995, Shahian et al. 1995, Daoud et al. 1995, Levine et al. 1996, Kim et al. 1995, Link et al. 1997, Li et al. 1996, Sakena et al. 1992, Brooks et al. 1994, Bocker et al. 1995, Palatianos et al. 1991, Jafar et al. 1997,

Bocker et al. 1993. Usually these trials lacked a clear description of their indications for ICD implantation. The trials that were not included were often conducted in population subgroups (eg. Levine et al. 1996 used only patients with asymptomatic non-sustained VT and Panagiotis et al. 1997 examined the use of ICDs in the elderly) or comparisons between devices (eg. use or not of a subcutaneous catheter in Jafar et al. 1997) or surgical implantation methods (eg transvenous vs transthoracic insertion in Shahian et al.1995).

The results of the 7 descriptive studies are presented in Table 18.

**Table 18: Descriptive studies examining the efficacy of the ICD to improve survival**

Reference	No. of patients	Average Follow up period	% with coronary heart disease	Mean Ejection Fraction	Result Actuarial survival from Sudden death and overall (total ) survival
Raviele et al. 1995	307	14.5 months	99%	33%	Sudden death survival at 1 year (98%) and 3 years (96%) and Total survival was 90% at 1 year and 80% at 3 years
Zipes et al. 1995	1356	11 months	76%	34%	Sudden death survival 99.4 % a 1 year and Total survival was 93 % At 1 year
Lawton et al. 1995	102	9 months	75%	31%	Sudden death survival: 100% at 1 year and Total survival was 87% at 1 year
Pacifico et al. 1997	231	15 months	84%	34%	Sudden cardiac death survival 99% at 1 year and 99 % at 2 years. Total survival was: 97% at 1 year and 95% at 2 years
Bardy et al. 1996	473	5.8 months	67%	36%	Sudden death survival 99% at 1 year Total survival 94.4% at 1 year
Neuzner et al. 1994	136	10.8 months	63.6%	36%	Total survival 96.3% at 1 year
PCD 1994 Saksena	605	5.9 months	76%	35%	Sudden cardiac death survival 98.7% at 2 years. Total survival 87.6% at 2 years.l:

## 5.5 DISCUSSION ON DESCRIPTIVE STUDIES

These descriptive studies simply present the survival of a cohort of ICD recipients followed up over time but do not include a comparison group.

The two principal weaknesses of this methodology are:

- uncertainty that the study group and their outcome are representative of the total population and
- significant uncertainty that the outcome is due only to the intervention and is not the result of bias or confounding.

Despite the lack of a control group comparisons are often made with results obtained from other descriptive studies. For example, Raviele et al. (1995) found a relatively low mortality rate amongst his 307 patients and commented on their favourable outcome relative to other similar published series. These comparisons must be regarded with considerable caution as Raviele et al. (1995) are unable to determine the possible role that bias or confounding may have had in the favourable outcome of their patients.

Another methodological problem with these descriptive studies is wide variation in indications for ICD implantation. Some studies have included patients with VT that has been found to be inducible on EPS while others have excluded these patients. This variation in patient selection makes it difficult to know which group the device is most appropriate for. The studies therefore include groups of patients that are not homogeneous for SCD risk (Sarter 1996, Steinbeck 1997). The outcome of the intervention will therefore depend on the relative proportion of low risk patients included in the trial. Therefore, selection bias may have significantly contributed to the results.

The studies may also have a significant amount of confounding from the effects of other risk factors for SCD. For example, prevalence of coronary heart disease varies by 30% between participants in studies by Neuzner (1994) and Raviele (1995).

Finally, all of the studies had short follow-up times (only 5.9 months in the case of Bardy et al. 1996). Despite this short duration researchers have presented their results as Kaplan Meier survival curves and extrapolated their data over at least one year.

## **5.6 COMPARATIVE STUDIES REVIEWING THE EFFICACY OF THE ICD TO REDUCE SUDDEN CARDIAC DEATH**

The efficacy of the ICD for improving survival has largely been evaluated by comparison with medication, which is the other main treatment option for SCD prevention. Several of these studies have compared ICD recipients with patients in the same institution treated with medication alone. These studies have chosen either an historical comparative group or a concurrent group of patients receiving treatment at the same time as the ICD recipients.

## **5.7 COMPARATIVE STUDIES WITH AN HISTORICAL (MATCHED) CONTROL GROUP**

The study by Newman et al. (1992) is a rare example of this type. Newman found that the ICD was associated with higher efficacy than medication. However, potential problems include the study's inability to control for non-matched confounders and for the time difference between the recipients and the control group. During this period of nearly three years several beneficial advances in cardiology became more widely used in the host institution of the study (including aspirin and revascularisation for coronary heart disease patients) (Newman et al. 1992).

## **5.8 COMPARATIVE STUDIES USING A CONCURRENT CONTROL GROUP**

The two examples of this type of study (Pinski et al. 1991 and Lawton 1995) both report the comparison of small recipient groups with concurrent groups treated with medication only. Both studies showed no significant difference in overall survival after 1 year, although survival from SCD alone favoured the ICD group. In general, these studies are flawed by the possibility of substantial biases in patient selection. Patients at a lower risk of sudden death may have received the devices. In addition

recipients seem generally to have had increased risk from other causes (eg. the use of ICDs in patients awaiting a heart transplant in Sweeney et al. 1995).

A small number of prospective, randomised controlled trials have recently been completed and several others are currently underway. The outcome from these trials will provide definitive evidence of the ICD efficacy compared to medical therapy at reducing the incidence of SCD.

## 6 Comparison of the efficacy of ICD vs drugs

A number of studies have compared the ICD efficacy with pharmaceutical based treatment. This review has assessed these studies according to whether subjects were randomised or not to receive either treatment option. Table 18 presents a summary of studies that did not randomise patients to receive either the device or primarily medication

### 6.1 NON-RANDOMISED TRIALS COMPARING THE EFFECTIVENESS OF ICD VS DRUGS

**Table 19: Summary of (non-randomised) studies comparing the efficacy of the ICD with drug treatment to reduce sudden cardiac death and improve survival**

	Type of study and evidence grade	Compare ICD vs	No in ICD group	No in other group	Number of ICD patients x average number of month's follow-up.	Number in comparison group x average number of months follow up.	Was ICD group matched to control group	Results, Including all causes of death
Newman et al. (1992)	Case Control Grade 2	drugs especially amiodarone	60	120	1110	2820	Yes for 5 variables	Probability of surviving 3 years: 65% in ICD group, 49% in drugs group
Powell et al. (1993)	Cohort Grade 2	drugs	150	181	4650	8869	No, ICD group had significantly lower average ejection fraction (EF)	Percentage of deaths in ICD group: 19% vs 34% in drug group
Crandall et al. (1993)	Retro-spective case control Grade 2	drugs	99	95	2178	3420	No, differences in age, EF, Ischaemic heart disease	No significant difference total mortality but significantly less cardiac death in ICD gp
Choue et al. (1994)	Retro-spective case control Grade 2	drugs	68	214	2244	6848	no	Probability of survival 3 years 76% ICD gp, 70% drugs gp.

Table 19 continued on next page.

Table 19 continued.

	Type of study and evidence grade	Compare ICD vs	No in ICD group	No in other group	Number of ICD patients x average number of month's follow-up.	Number in comparison group x average number of months follow up	Was ICD group matched to control group	Results, Including all causes of death
Sweeney et al. (1995)	Case Control Grade 2	drugs while all waiting for transplant	59	53	932	837	Yes in analysis, clear description of variables	No significant difference ICD vs drugs
Bocker et al. (1996)	Retro spective case control Grade 2	sotalol	50	50	1200	1550	Yes, 6 variables	Probability of 3 year survival: 84% in ICD gp, 74% in drugs gp
Ector et al. (1996)	Retro spective case control Grade 2	Amiodarone or transplant	103	129 (amio) 163 (Trans)	2101	5444 (A) 5528 (T)	Yes adjusted in calculation for age, sex, follow-up length, but not ejection fraction	SMR <sup>1</sup> ICD gp: 3.46 SMR amiod group: 2.46 Transplant gp SMR: 5.45 NO Significant differences, though.

### 6.1.1 Results of non-randomised trials

Non randomised efficacy comparison studies of SCD reduction and improvement in overall survival have found either a benefit for ICD treated patients or no significant difference. Several authors have concluded that although the ICD indisputably reduces mortality from SCD this may be at the expense of increasing fatality from other causes such that overall recipient survival is not increased (Anderson1996).

A number of problems exist with these non-randomised comparisons studies:

- The studies compare the ICD to a heterogeneous range of drug treatments. In the case of Ector et al. (1996), the ICD is also compared with a surgical

<sup>1</sup> SMR = standardised mortality ratio, which is the ratio of the observed and the expected number of deaths where the expected number of deaths is the sum of the expected deaths in the general population of the same age and sex and with a similar follow up duration (Ector 1996).

treatment, ie. heart transplantation). The range and doses of the medication prescribed to patients varied markedly between the studies. For example, Bocker et al. (1996) compared the relative survival of ICD recipients with that of patients treated primarily with sotalol, while Newman et al. (1992) undertook a comparison with patients receiving mainly amiodarone. In addition, Saksena et al. (1996) makes the important point that any single drug may exert its protective effect by a number of different mechanisms that may act on either the substrate or the triggers for an arrhythmia. By contrast, the ICD has just one action, which can only occur after the arrhythmia has started. Saksena et al. (1996) therefore suggests that it may be inappropriate to compare the effect of the ICD with that of drugs because their effects are best understood as complementary and not comparative.

- The studies show marked differences in their concomitant use of medication among ICD implant recipients. For example, ICD recipients in the study by Sweeney et al. (1995) had a significantly higher percentage of beta-blocker usage (24%) than those in the trial by Crandall et al. (1993) (7%). Beta-blockers are one of the few medications with a clearly proven antiarrhythmic effect (see Section 7.1). It is therefore difficult to know whether the effect found in the ICD treated group is due to the device or confounding from the associated use of medication.
- The trials exhibit varying amounts of selection bias. Some studies selected patients for the ICD group on the basis of failure to respond to medication. These patients may be associated with a worse prognosis. For example, patients in the trial by Powell et al. (1993) were selected because they had been unable to tolerate amiodarone. Amiodarone appears to be one of the best antiarrhythmic drugs available, so these patients may be at a survival disadvantage. Alternatively, it is possible that patients failing to respond to medication represent a group with a survival advantage because they have already lived for a significant period during their drug trials.
- The different studies are not easily comparable because they have used heterogeneous types of patients at varying risk of SCD. For example, Ector (1996) studied patients with low ejection fraction awaiting transplant who were at high risk of sudden death while Newman (1992) utilised patients with

VT whose risk was considerably lower. The studies also involve different study methods. Ector utilised differences in standardised mortality rates while Powell (1993) compared Kaplan Meier survival curves. Follow-up length varies markedly between the studies. The study base (ie. the number of patients multiplied by the follow-up duration) is notably smaller for the ICD recipient group in most of the studies. This discrepancy may result in a possible bias because Newman (1992) found that when ICD recipients were followed up for a longer duration the total survival difference between ICD recipients and medication recipients rapidly disappeared.

- Several of the trials have not been able to adjust for important confounders between the study group and their controls. None of the studies have been able to ensure that the case group is sufficiently close to the control group in all other respects except for the interventions being examined. Crandall (1993) at least recognised the significant differences between his patient and control groups in their average age and past history of ischaemic heart disease and ejection fraction. However he failed to adjust for these differences in his analysis. Although Newman (1992) matched comparison groups for 5 important variables, matching does not accommodate for unrecognised variables, and only randomisation reliably adjusts for all known or unknown confounders.
- An inherent problem with any comparison between studies of ICDs undertaken in different years is the rapidly evolving technology used in the devices. Earlier studies involved transthoracically implanted ICDs while later ones have utilised the transvenously implanted device. The ICD treatment group in earlier studies would be relatively disadvantaged by the higher mortality associated with major open chest surgery (see Section 4). A related confounder is the different use of out-dated medications amongst the control groups. The drug-treatment group in some trials (Sweeney et al. 1995) included a significant number of people who received outdated class 1 antiarrhythmic drugs. These drugs have been proven conclusively to be harmful (see Section 7.1) and may have confounded the results of these trials.
- Several of the studies noted the difficulty of studying patients at high risk of death from a number of causes. Sweeney et al. (1995) reviewed cases that

were waiting for cardiac transplant. There was, not surprisingly, a high mortality rate among these patients (37.4%, during the mean follow-up period of 15 months). This effect of a high background mortality rate makes it difficult to avoid the number of SCDs being overwhelmed by the other causes of death.

- Another possible selection bias was the use of electrophysiological testing to determine which patients were eligible to receive an ICD. There is some evidence that EPS is able to provide information on an individual's risk of fatal arrhythmia (see Section: 2.3.2). The patients who received a device on the basis of poor outcome predicted by EPS, for example, might be less likely to have the survival advantage of the group who were given medication.
- A final problem is that most of the trials are based in a single institution and are therefore subject to possible bias from the beliefs of individual clinicians about the relative merits of ICD implantation. A clinician who believes an ICD offers relatively little survival advantage may be less likely to offer implantation to patients with a poor prognosis. The assignment of patients to ICD implantation may therefore have been biased. This possibility is borne out by the use of the intervention in some studies as last resort therapy for patients in an extremely perilous situation (eg patients awaiting transplant in Sweeney et al. 1995) or among patients who have already failed drug therapy (Bocker et al. 1996).

## **6.2 RANDOMISED COMPARATIVE STUDIES**

A small number of completed randomised controlled trials have examined ICD efficacy in comparison to medication at reducing the rate of sudden cardiac death and improving overall survival.

**Table 20: Randomised comparative studies evaluating the efficacy of the ICD versus medication to reduce sudden cardiac death and improve survival**

Reference And evidence grade	n	Intervention	Follow up duration	ICD type	Result	NNT <sup>2</sup>
<b>Studies only conducted in cardiac arrest survivors</b>						
Wever 1995 Evidence grade 1	60	First intention ICD implantation vs tiered drug treatment	27 months	Transthoracic, except 3 transvenous insertions amongst drug treatment group	All cause RR <sup>3</sup> of death for ICD group = 0.27 (C.I. <sup>4</sup> 0.09 – 0.85) p=0.02	4.8
Siebels 1993 (early CASH trial) Evidence grade 1	230	Propafenone	11 months (other arms of trial are on-going)	Transthoracic	All cause mortality 13.56 in ICD group, 16% in propafenone. (not stat.sig). But 0 sudden deaths in ICD group and 10.7% in propafenone	-
<b>Studies conducted amongst cardiac arrest survivors and/or those with syncope secondary to a tachyarrhythmia</b>						
McCarthy AVID 1997 Evidence grade 1	1016	Empirical amiodarone and / or sotalol vs ICD	45 months Ongoing	transvenous	(Preliminary result) Relative reduction in total mortality by 38% in 1 year, 26% over 2 years, 30% over three years	-
<b>Studies conducted upon those with tachyarrhythmias but excluded survivors of cardiac arrest</b>						
MOSS 1996 Evidence grade 1	196	Prophylactic insertion of an ICD vs conventional tiered therapy	27 months	45 transthoracic. 50 transvenous.	ICD RR 0.46 (C.I 0.26-0.82) p= 0.0009 RRR= 0.59, ARR= 0.228	4.4

### 6.2.1 Discussion of randomised controlled trials

All four studies found a favourable survival advantage for patients treated with an ICD. However, despite the inherent ability of the randomised controlled trial to reduce the effects of bias and confounding a number of problems still exist.

<sup>2</sup> NNT = number needed to treat, which is the number calculated as the reciprocal of the absolute risk reduction and indicates the number that would need to be treated in order to save one life.

<sup>3</sup> RR = relative risk, ie the the ratio of the risk in the treated group compared to the risk in the untreated sample.

<sup>4</sup> CI = confidence intervals= the interval within which there is a 95% statistical probability that the actual value lies.

- The small trial by Wever (1995) can be criticised for significant use of class 1 antiarrhythmics among the group receiving medication. In addition, this group had a relatively small number of patients receiving beta-blockers. Both of these factors could have increased the mortality risk amongst this group and confounded the study's main finding of a survival advantage for ICD recipients.
- The CASH study is ongoing and final results are not expected until 1998. However, the propafenone arm was terminated due an excessive number of sudden deaths, although this was not statistically significant. Consequently, the relative effect of the ICD compared to propafenone on total mortality is unknown.
- The study by Moss (MADIT)(1996) is a landmark trial as it exclusively recruited patients who had not suffered a cardiac arrest and excluded patients with a past history of malignant ventricular tachyarrhythmia. It is therefore the first major randomised controlled trial to assess the prophylactic use of the ICD in-patients at risk of sudden death but asymptomatic from arrhythmia. This means it has the potential to expand the indications for ICD use, but it does have a number of problems. Firstly it had tight selection criteria (past myocardial infarction, poor ejection fraction, asymptomatic non-sustained VT) and required over five years to recruit the mere 196 participants. Concern therefore exists about the generalisability of its findings from the small, tightly defined patient group to the larger group at risk of arrhythmia ie. those who have already experienced a malignant ventricular arrhythmia (Nisam 1997, Higgins et al. 1997, Moss 1997). Furthermore MADIT has also been criticised because it may have introduced several possible biases:
  - ❖ Patients were selected for randomisation if they had not responded to procainamide. The selection of a group of patients because they had failed antiarrhythmic therapy may have introduced a bias against the medication treated group (Friedman 1996).
  - ❖ The group who were allocated to receive medication contained a significant number of patients who received a class I anti-

arrhythmic. These drugs have been shown to be harmful (see Section: 7.1) and may have reduced survival in that group

- ❖ Beta-blocker therapy (which has a favourable effect upon outcome) was three times more common in the ICD -treated group.
- The authors of the study have at least in part, addressed the effect(s) of these potential biases. They have recently presented a mathematical model which can adjust for the effect(s) of these biases on their results. Moss (1996) concluded from this model that bias did not have a significant effect on their results. However, even if the result from MADIT is accepted it is still difficult to generalise beyond the narrowly defined post infarction population used in the trial (Moss 1996). Even the authors have maintained that only a small number of people would be eligible for device implantation on the basis of their results. Furthermore, the total number of potentially preventable deaths would be small, probably at most 1-2% of the post-myocardial infarction population. This would only account for fewer than 10 % of all cardiac related deaths (Maggioni 1993, Bigger et al. 1984, Wilber et al. 1997).
- Finally there is an underlying problem with evaluating the ICD efficacy by comparing it to drug treatment. Many studies have found that a significant number of patients with an ICD (40 – 70 %) still require medication with antiarrhythmic effects (Dougherty 1996). This medication is often needed to suppress SVTs or to treat an underlying cardiac disorder, especially ischaemic heart disease (Jordaens 1996, Dougherty 1996). However, antiarrhythmic drugs can also interfere with the proper functioning of ICDs by raising defibrillator thresholds or adversely affecting the ability of the ICD to detect VT or VF (Dougherty 1996). Although this problem should be recognised it is probably unavoidable because most authorities would now regard it as unethical to use a placebo treated group in any study evaluating the efficacy of either the ICD or medication for improving survival.

## **6.3 FUTURE PROSPECTS**

Three ongoing, prospective, multi-centre randomised controlled trials will provide a more definitive answer to the outstanding issue of whether ICDs can improve overall survival for patients with malignant ventricular tachyarrhythmias.

### **6.3.1 Canadian Implantable Defibrillators (CIDS) study**

This trial compares ICD implantation with amiodarone. To be included: Patients must have one of the following: a documented VF cardiac arrest, sustained VT with syncope, VT without syncope but associated with symptoms, or syncope that is likely to be cardiac in origin and where inducible sustained VT is found during an electrophysiological study for patients with an ejection fraction of less than 35% (Connolly et al. 1993). The study is enrolling 650 patients and uses total mortality as its primary outcome. The results are expected in late 1998.

### **6.3.2 Antiarrhythmics Versus Implantable Defibrillators (AVID)**

AVID is an intention to treat comparison of the ICD with sotalol or amiodarone (AVID Investigators 1995) using patients with an ejection fraction of less than 40% who have experienced prior episodes of haemodynamically compromising VT or VF. The primary endpoint is all cause mortality with several secondary endpoints, including cost. The trial aims to recruit 1,000 patients before 1998 and results are expected soon after, although preliminary results have already been released (McCarthy 1997, see Table 20).

Already AVID has been the subject of some controversy. Critics point to the large number of descriptive studies and the two randomised controlled trials that have found a survival advantage among ICD recipients and argue that it is unethical to randomise patients to inferior medical care (Josephson and Nisam 1997, Saksena 1996, Singer 1996, Estes 1996). In contrast, supporters express concern at the potential for bias that may be occur if some physicians selectively refer patients away from participating centres because they fear these patients will be randomised away from their preferred treatment option (AVID Trial Executive Committee 1997, Anderson 1996, Connolly and Yusuf 1992). This issue has been

further compounded by the unwillingness of some large and prestigious cardiology centres to become involved in the trial. It also appears that some participating may be crossing over significant numbers of patients from drug treatment to the ICD limb, and thereby reducing the power of the study (Fogoros 1994, Singer 1994, Epstein 1993).

### **6.3.3 CABG patch study**

This trial examines all cause survival amongst 900 people scheduled to undergo coronary revascularisation with LVEF less than 35% and randomised to receive the surgery with or without ICD insertion (CABG Investigators 1993). Although this trial does not primarily examine the ICD in relation to drug treatment it will be large enough to permit subgroup analysis to assess this issue.

## **6.4 CONCLUSION**

Although non-randomised comparisons between ICD and drug therapy are informative about clinical practice, and about the outcomes associated with different institutional settings, they do not provide a reliable and robust comparison of the relative effectiveness of the two treatment options. Some studies have conceptualised the ICD as a palliative procedure reserved for people with a dismal prognosis and for those who have already failed medication. These studies do not permit an appropriate comparison between two treatment options in which there is uncertainty about the more efficacious treatment and for which the study is designed to determine the preferable treatment.

Non randomised trials are also significantly flawed by their inability to counter possible biases or confounders. Few of the studies were adequately able to address the issue of confounding by other indicators of poor survival, such as impaired left ventricular function, and many trials were subject to possible biases associated with their selection of patients for ICD or drug treatment.

In short, non-randomised trials of the effectiveness of the ICD versus drugs are not homogeneous and they are difficult to compare. Furthermore, they have been unable to resolve significant design limitations relating to bias, confounding and chance.

Randomisation in several large trials nearing completion will help overcome the problems associated with confounding and bias that have plagued earlier studies attempting to define the efficacy of the ICD for prolonging life. These studies will provide objective data on the relative risks and benefits of the ICD versus drug treatment. However it is notable that because none of these trials includes a no-treatment arm, no study will be able to determine the absolute efficacy of the device. It is possible that if none of the 3 studies (CIDS, AVID, CASH) can find a significant difference between the ICD and medication, then the beneficial and harmful effects of the 2 treatments may be of similar magnitude (Connolly et al. 1993, Siebels and Kuck 1994).



## **7 Review of the effectiveness of ICD alternatives**

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### **7.1 EFFICACY OF DRUGS**

In marked contrast to the very low annual mortality rates (<2%) associated with ICDs, antiarrhythmic drugs have a reported annual sudden death rate of about 10% (Dicarlo et al. 1985, Herre et al. 1989, Weinberg et al. 1993, Singh et al. 1995, Moss et al. 1996).

Each of the four classes of antiarrhythmic drugs has its own mechanism of action and therefore its own efficacy to improve survival.

#### **7.1.1 Class I**

Class 1 antiarrhythmics play a minimal role in improving overall survival for patients at risk of SCD as the results of two recent meta-analyses suggest that they may be proarrhythmic (Echt et al. 1991, Teo 1993). Both meta-analyses found that class 1 drugs are associated with an increase in overall mortality (RR 1.13, C.I.: 1.01-1.27,  $p = 0.04$ ; CAST trial 1991, Obiasmanno et al. 1996, Greenberg et al. 1995, Akiyama et al. 1991).

#### **7.1.2 Class II**

A number of randomised controlled trials have consistently found that post myocardial infarction use of beta blockers either short-term or long-term reduces overall mortality and SCD (McAlister and Teo 1997, Yusuf et al 1985). Beta blockers appear to be an important treatment for arrhythmia although there is some uncertainty about their therapeutic action. It is possible that aside from beta-blockade, either their ability to reduce the heart rate or decrease the blood pressure may be their therapeutic modality (Yusuf 1985).

### 7.1.3 Class III

#### *Sotalol*

Though Sotalol is a non-selective beta-blocker it has class III anti-arrhythmic properties at higher doses. A number of small retrospective cohort and case control trials support the use of sotalol as therapy for ventricular arrhythmias (Bocker et al 1996, Kehoe et al. 1993, Rankin et al. 1991, Anastasiou-Nana 1991, Ruder et al. 1989, Anderson 1990). These trials have generally shown a reduction in the number of sudden deaths (and sometimes total mortality) in the sotalol treated group. However, their small size, retrospective approach, and inability to eliminate bias limit their usefulness.

Randomised controlled trials have found inconsistent results, with some concluding that sotalol offers a survival advantage at least comparable to that of beta-blockers (eg Julian et al. 1983, Mason 1993). However other trials have found contrasting results such as the Survival With Oral Sotalol (SWORD) trial which was terminated early when an excess mortality was found in the group receiving sotalol (Waldo et al. 1996). Some researchers have recently questioned the proarrhythmic potential of the drug, with some series reporting an incidence of arrhythmia in the treated group of nearly 5% (Fiton and Sorkin 1993, Waldo et al. 1996). The exact role of sotalol in the treatment of ventricular arrhythmia therefore remains undetermined.

#### *Amiodarone*

Although classed as a Class III agent, amiodarone also has some Class I and II properties. Randomised controlled trials have found it to have an inconsistent ability to reduce the incidence of SCD and improve overall survival when used in patients with either CHF (Singh et al. 1995, Hamer 1989), recent MI (Cairns 1997, EMIAT 1997), or survival from a cardiac arrest (CASCADE 1993). A recent meta-analysis of all trials involving amiodarone therapy for arrhythmia concluded that it reduced the risk of sudden death by 17% (Teo et al. 1993). The meta-analysis found that amiodarone therapy had an absolute risk reduction of 0.025, which suggested that 40 patients would need treatment to prevent one sudden cardiac fatality. The authors note that with a total of only 5713 patients

among all trials the results of the meta-analysis should be regarded with some caution. In particular, the authors point to the markedly discordant results obtained in the GESICIA (Dovall et al. 1994) and STATCHF (Singh et al. 1995) trials, which enrolled patients with a similar underlying, risk for arrhythmic death. Therefore the benefit from amiodarone remains to be firmly established. However it is one of the few drug options that does not seem to have any proarrhythmic potential and it does not increase the risk of SCD. This makes it an appropriate choice for patients at high risk of arrhythmic death.

The main limitation of the drug appears to be its side effects. Most trials have noted that around one third of patients are withdrawn from therapy because of adverse effects (McAlister and Teo 1997). Despite this high withdrawal rate the incidence of serious side effects (particularly pulmonary fibrosis) are relatively rare over the duration of the studies (usually less than 7 years) and they may be less common with the current trend towards lower doses (ie less than 250 mg per day; Teo 1993). For example, Dunsman et al. (1990) found that only 6% of patients developed pulmonary complications and no cases occurred at doses below 310mg per day.

#### **7.1.4 Class IV**

The results of 26 trials suggest that calcium channel blockers lead to a small, non-significant increase in overall mortality risk (Teo 1993). Furberg (1995) found a similar statistically insignificant increase in deaths in a meta-analysis of the use of nifedipine in patients with ischaemic heart disease. The INTERCEPT trial (1995) is a large randomised controlled trial which may help resolve the role of the newer long acting calcium channel blockers, and in particular verapamil, which has shown some beneficial effects in trials to date (Yusuf 1996).

## 7.2 SUMMARY OF THE EFFICACY OF DRUGS TO REDUCE THE INCIDENCE OF SUDDEN CARDIAC DEATH AND IMPROVE SURVIVAL

The efficacy of each of the four classes of drugs to reduce sudden cardiac death and improve survival can be summarised according to the number of trials completed for each class and the overall odds ratio from the studies (see table 20).

**Table 21: Summary of trials examining the efficacy of drugs to reduce sudden cardiac death and improve survival**

Class of drug	Number of trials	Overall odds ratio <sup>5</sup> for mortality	Confidence intervals and p value <sup>6</sup>
I	61	1.13	1.01- 1.27 p=0.04
II	56	0.81	0.78-0.87 p=<0.00001
III	14	0.83	0.72-0.95 p=0.01
IV	26	1.03	0.94-1.13 p=ns

After: McAlister and Teo 1997

With studies evaluating the efficacy of drug treatment for survival improvement in patients at high risk of an arrhythmia, an important issue is the widespread, and inappropriate use of the suppression of ventricular ectopic beats as a proxy indicator of the suppression of ventricular tachyarrhythmias (McAlister and Teo 1997). Ample evidence exists to confirm that ventricular ectopic beats are a marker of excess risk of SCD for patients with underlying heart disease (Bigger and Fleiss 1984, Ruberman et al. 1977, Rabkin et al. 1981, Chiang et al. 1969). However, recent research indicates that ventricular ectopic beats are actually the electrical byproducts of a complex process that involves important trigger factors acting on the underlying aetiological determinants of a malignant arrhythmia (see Section 2). This new understanding of the causation of ventricular tachyarrhythmia and of the delineation of individuals at risk means that studies evaluating the efficacy of drugs to reduce of SCD risk must use (total) mortality as their endpoint. However as yet this has only been inconsistently used in large trials (Teo et al. 1993, McAlister and Teo 1997).

<sup>5</sup> Odds ratio= describes the odds of a patient in an experimental group having an outcome event relative to a patient in a control group.

<sup>6</sup> Confidence intervals= quantifies uncertainty. The 95% CI is the range of values within which we can be 95% sure that the true value lies for all patients from whom the study sample were selected.

### **7.3 EFFICACY OF SURGERY**

Revascularisation and coronary artery bypass reduce the mortality from SCD as well as ischaemic death (Yusuf 1994). Boubolis et al. (1995) and Geha et al. (1992) reviewed their own experience, along with the literature, and found that some surgical treatments (such as ablative surgery) could improve survival for patients at risk of SCD. However, evidence from large randomised trials is not yet available to support this contention. In addition, it is generally recognised that few people have a localised lesion that could be treated by surgical intervention (AHTAC 1995)

In particular, a very small number of people have a ventricular aneurysm that is amenable to surgical intervention (Andem 1997).

### **7.4 EFFICACY OF CATHETER ABLATION**

The development of EPS, which permits the accurate determination of the origin of an arrhythmia, has permitted the introduction of surgical techniques to eliminate these sites and effectively to offer a cure for some patient's arrhythmia.

Catheter ablation involves the application of energy to the site generating the arrhythmia, thereby destroying it. Although DC current was originally used as the energy source, this treatment was not without serious risks (Evans et al. 1991). Modern treatment usually now utilises radio frequency (RF) energy (Health Council of the Netherlands 1993). RF catheter ablation is largely free of complications, painless and the operator can control the size of the intervention (Witkamp 1989). Catheter ablation is usually undertaken at the same time as EPS to restrict the need to catheterise the patient more than once and reduce radiation exposure to patient and staff (Klein 1992).

The technique is regarded as primary treatment for a small number of patients with specific indications, such as those with an accessory pathway where there is often an atrial focus and a rapid ventricular response (ACC/AHA Task Force 1995). In these cases literature results are consistent and clearly favour surgery (Williamson et al. 1994, Scheinman et al. 1992). RF ablation has previously been widely used with

varying degrees of success for patients with ischaemic heart disease (Klein 1992), cardiomyopathy (Scheinmann 1994) and idiopathic VT (Klein 1992). Ablation has largely replaced open heart techniques and freezing, which were associated with a significant intra-operative mortality of nearly 15%, although this figure also reflects the high risk of the selected population who often underwent the surgery as a last resort (Health Council of the Netherlands 1993). Today the technique has limited value in the treatment of ventricular tachyarrhythmias which have a ventricular origin, because the cause (such as cardiac damage from ischaemia or cardiomyopathy) often involves a large or diffuse area which is not amenable to a localised treatment (Morady 1993, ACC/AHA Task Force 1995). Among the few eligible patients success rates have varied between 45% and 85%, although complication rates have typically been low (around 3%; NASPE Scheinman 1994).

#### 7.4.1 Use of RF ablation

Although there are few randomised controlled trials the ACC/AHA Task Force (1995) has attempted to present the consensus from the literature for the use of RF ablation. This is presented in Table 22.

**Table 22: The use of RF ablation**

Consensus agreement that RF is appropriate	No consensus evident or uncertainty about the use of RF	Consensus suggests that RF is inappropriate
<ul style="list-style-type: none"> <li>• Patients with re-entrant ventricular tachycardia</li> <li>• Patients with asymptomatic sustained monomorphic VT when the tachycardia is drug resistant or the patient cannot tolerate medication.</li> </ul>	<ul style="list-style-type: none"> <li>• Non-sustained VT that is symptomatic and the tachycardia is drug resistant or the patient is drug tolerant or does not want drug therapy.</li> </ul>	<ul style="list-style-type: none"> <li>• Patients with VT that is better managed by drug, surgical, or ICD treatment.</li> <li>• Unusual rapid or polymorphic VT that cannot be localised by PES.</li> <li>• Asymptomatic and clinically benign non-sustained VT</li> </ul>

After: ACC/AHA 1995, Fisher 1994. Evidence grades = mainly 2 and 3.

## 7.5 REDUCTION OF SCD BY OTHER THERAPIES

### 7.5.1 Treatment of ischaemia

Treatment of ischaemic heart disease (eg aspirin; ISIS-2 Group 1988) has also been found to reduce the incidence of sudden cardiac death (Yusuf and Teo 1991).

Prevention of heart disease (eg cholesterol lowering, smoking cessation) has also been suggested as effective (Hunink et al. 1997).

### **7.5.2 Physical therapy and the reduction of sympathetic tone**

Physical therapy has been postulated to operate through reducing sympathetic tone (akin to beta blockers). Some limited evidence suggests that it may reduce the risk of SCD among patients recovering from a myocardial infarction (Schwartz et al. 1985).

### **7.5.3 Electrolyte supplements**

Although ample evidence shows that certain electrolyte imbalances can precipitate a malignant arrhythmia, various electrolyte supplements may also be associated with reduced risk of sudden death (Wester and Dyckner 1986). Magnesium, in particular, has attracted significant research interest. Although a definitive answer has not been found, a recent large review has concluded that magnesium treatment for patients at risk of SCD is probably not effective (Teo et al 1996).

### **7.5.4 Increased use of beta blockers**

Conclusive evidence shows that beta blockers improve survival after myocardial infarction at least in part through a reduction in arrhythmia related deaths (Kendall et al. 1995). However they appear to be underutilised by many physicians (Kennedy and Rosenson 1995).



## 8 Cost effectiveness of ICD therapy

ICD therapy is expensive, being associated with a high initial cost (typically around \$50,000 in New Zealand). However, this expense must be viewed in light of the relative cost of other treatment options over a reasonable period of time. Cost effectiveness studies attempt to make this comparison. Most ICD cost effectiveness studies have presented their final analysis as a series of ratios:

$$\frac{\text{Change cost}}{\text{Change in effectiveness}} = \frac{\text{Total cost (defib)} - \text{Total cost drug treatment}}{\text{Life expectancy from defib} - \text{Life expectancy for drug treatment}}$$

That is, these studies have evaluated the relative benefits of ICDs and drug treatments in terms of improved life expectancy and reduction in total cost. The results have typically been expressed in units of cost (dollars) per year of life gained.

**Table 23: Summary of studies examining the cost effectiveness of the ICD**

Author	Country	Comparison	ICD implantation technique	Patient selection	Method of evaluation
Kupperman 1990	United States	ICD vs anti-arrhythmics	Transthoracic	Cardiac arrest survivors	Markov model
Larsen 1992	United States	ICD vs amiodarone vs conventional antiarrhythmics	Transthoracic	Population high risk of VT VF from past history of recurring arrhythmia	Modelisation
O'Brien 1992	UK	ICD vs amiodarone	Transthoracic	Cardiac arrest survivors	Markov model
Kupersmith 1995	United States	ICD vs anti-arrhythmics	Transthoracic mainly, few transvenous	Cardiac arrest survivor	Markov model
Wever 1996	Netherlands	ICD vs anti-arrhythmics (distinction of a first line therapy ICD vs not)	Transthoracic	Cardiac arrest survivor	Clinical trial with simultaneous costs
Owens 1997	United States	ICD vs amiodarone (distinction if first intention ICD and those inserted as other treatments have failed)	Transveous	Cardiac arrest survivor	Markov model
Mushlin 1997	United States	ICD vs anti-arrhythmic	Transthoarcic and transvenous	Documented un-sustained VT and inducible VT unsuppressed by class I drugs.	Clinical trial with simultaneous costs

After: ANDEM 1997, Mushlin 1997

## **8.1 COST EFFECTIVENESS STUDIES - SIMILARITIES AND DIFFERENCES**

Studies evaluating the cost effectiveness of the ICD have a number of important similarities and differences.

### **8.1.1 Similarities between studies**

All studies have used standard hospital costs, although different methods have been used to obtain or estimate these amounts. All have consistently taken the viewpoint of the funder, with none attempting to include indirect costs and adopt a social viewpoint. In all studies it was noted that the intervention cost is dominated by the cost of the device itself (Anderson and Camm 1993).

While most trials collected data retrospectively, both Wever (1996) and Mushlin (1997) gathered cost information prospectively as part of a clinical trial. Furthermore, in the retrospective studies the two study populations are not necessarily comparable.

None of the studies adequately integrated into their costs the added expense of complications (Ferguson et al. 1996). This omission seems significant given that some studies found complication rates of up to 36% of all implantations (Nunain et al. 1995).

None of the research was completed in New Zealand, using local costs and survival data. Caution must be taken when generalising from any conclusions to the New Zealand context.

### **8.1.2 Differences between reviews of the cost effectiveness of the ICD**

The trials include ICD groups treated by either transthoracic or transvenous implantation. It is important to recognise that costs and peri-operative mortality vary markedly between the two methods. Transvenous implantation is more favourable in cost effectiveness studies as it is associated with lower insertion costs, a longer battery life and reduced peri-operative mortality. However, countering this is the possibility that ICDs can now be implanted in patients

whose surgical risk would have previously precluded it, but who still have a poor prognosis.

Some studies have evaluated the use of the ICD as primary therapy for people at high risk of malignant arrhythmia, whereas others have used the device as second line treatment.

Although the intention of all studies was to define the cost effectiveness of the ICD, Owens (1996) (and to a lesser extent Larsen,1992) have also attempted a cost utility analysis and measurement of cost per year of quality adjusted life.

**Table 24: Results of studies evaluating the cost effectiveness of the ICD**

	Marginal effectiveness of ICD (years of life saved)	Marginal cost benefit per year of life saved
Kuppermann 1990	+1.9 years	\$17,400 (base 1986)
Larsen 1992	+2.2 years	\$29200 (base 1989)
O'Brien 1992	+1.7 years	Pounds 15,400 (base not stated)
Kupersmith 1995	+1.72 years	\$25,700 (base 1993)
Wever 1996		\$11,315 (base 1992)
Owens 1996	+0.5	37,300-\$74400 per QALY (base 1995)
Mushlin 1997	+0.5	\$23,000 (base 1995)

After: ANDEM 1997

## 8.2 RESULTS OF ICD COST EFFECTIVENESS STUDIES

All of the studies results showed similar results. Kupersmith (1995) further emphasised the comparable nature of the results by using his model to present data from some preceding studies (Kupperman 1990 and Larsen 1992). His cost effectiveness ratio findings (\$31,100 per year of life saved for the ICD) were identical to those of Kupperman (\$32,900) and Larsen (\$31,500)

Six of the seven studies found a higher cost with ICD use. Wever (1996) is the exception but it is noteworthy that this trial involved only 60 patients.

Despite extra cost generated by the ICDs, the marginal cost effectiveness ratio is considered favourable by all authors for the populations considered in the studies (ie cardiac arrest survivors and patients subject to ventricular arrhythmia).

Five studies (Kuppermann 1990, Larsen 1992, O'Brien 1992, Kupersmith 1995, Wever 1996) found ICD cost effectiveness compared favourably with that of other routine interventions for other conditions (hypertension treatment, dialysis, pacemaker implantation, coronary bypass). Kupperman integrated the ICD into a league table prepared by Drummond (1987). These comparisons, particularly Kupperman's, must be regarded with some caution. Studies of the cost effectiveness of other interventions (presented in a league tables, for instance) have often used different methodologies and made differing assumptions, among heterogeneous populations (Mason et al. 1993). Several authors conclude that ICDs appear to fall within the range of \$20,000 - \$40,000 cost per year of life saved which is widely regarded as representing an acceptable cost effectiveness ratio (Goldman et al. 1992)

**Table 25: Kupperman's comparison of the cost effectiveness of ICD with other interventions**

<b>Procedure</b>	<b>Cost efficacy (\$ per life year )</b>
Hospital haemodialysis	59,500
Coronary artery bypass grafting (single vessel disease) for severe angina	44,200
Oestrogen therapy for post-menopausal symptoms in women without hysterectomy	32,900
Heart transplantation	26,900
Treatment of mild hypertension	23,200
<b>ICD (1986)</b>	<b>17,400</b>
Treatment for severe hypertension	11,100
<b>ICD (1991)</b>	<b>7,400</b>
Coronary grafting (3 vessel disease)	7,200

After Kupperman et al. 1990 (1986 prices)

The selection of the patients for the intervention is obviously important in determining the effectiveness of the intervention and hence the cost effectiveness of the device. Most of the studies examine ICD use in people who have survived a cardiac arrest and are therefore at high risk of sudden death. While the ratio improves when the denominator of the fraction (ie the number of years of life saved) is increased it becomes more difficult to ascertain benefit when the two comparison treatments are susceptible to high death rates from the underlying disease. Thus Kupersmith found

that it more cost effective to implant ICDs in a group of patients who had better left ventricular function because more people would die in the poor ejection fraction group regardless of the intervention (Kupersmith 1995). By contrast, Owens argues that the cost effectiveness ratio varies little when a population with a lower mortality risk is chosen for the analysis. Owens found that when the occurrence of sudden death was lower the costs were higher and consequently the ratio remained relatively similar.

Wever's study is interesting because it concludes that the ICD is more cost effective as first line therapy than when it is used after medication has failed. An older Australian report (Cowley 1990) concluded that the cost effectiveness of ICDs ranged from A\$ 17,840 to 35,800 per year of life saved, but only when the devices were used after EPS testing had failed to find an effective antiarrhythmic agent (AHTAC 1990). Wever concluded that use of the ICD as second intention therapy allows for a greater number of patients to die who would have survived if they had received the device initially. A similar result was found by O'Donoghue et al. (1990) in an even smaller study than Wevers (40 patients, only 8 of whom actually received the ICD as first line therapy). If this result is accepted the important question becomes: how can the population be screened to ensure that the most appropriate people receive first line therapy? Wever reviewed the use of EPS in order to improve the selection of patients for initial ICD insertion. While this study did find that this selection method improved the cost effectiveness of ICDs, its conclusions may not be generalisable and further research would seem to be indicated.

Recent work has suggested that a major part of the cost effectiveness of ICD therapy is the device's ability to comparatively reduce rehospitalisation rates among recipients. In a simple comparison of pre-insertion and post-implantation hospitalisation rates based on twelve month periods in each direction, Valenti (1996) concluded that after receiving an ICD, patients had markedly fewer admissions and hence the cost of their medical care was significantly reduced.

A crucial issue in these studies is whether ICDs reduce global mortality or just SCDs. As the literature did not allow a reliable indication of the ICD's effect on total mortality, Owens illustrated the effect of different values graphically. Owens found

that reductions in global mortality from insertion of the ICD gave an exponential increase in the marginal cost effectiveness ratio.

Finally, an interesting perspective comes from the study by Hauer et al. (1996). This paper presented an assessment of ICD cost-effectiveness in a hypothetical scenario in the years 1996-2000, using Wever's (1996) data as a baseline. Hauer's study population was based on patients resuscitated from cardiac arrest. The authors found that new ICD technology (transvenous insertion, longer battery life, pectoral implantation in an EPS lab) realised the more favourable cost effectiveness ratio of \$18,615 per year of life saved in the 1996-2000 scenario. They concluded that the ICD could be justified as first choice therapy for all patients resuscitated from cardiac arrest. Although the study's assumptions are debatable it seems likely that recent (and future) innovations for ICDs are likely to make the device more cost effective. For example, transvenous implantation is certainly cheaper than transthoracic, and it is also associated with lower peri-operative mortality (Williamson 1994). Both of these factors improve the cost effectiveness ratio

### **8.3 CONCLUSION**

Overseas studies have generally found that ICD therapy is more expensive than its medication based alternative, but shows a favourable cost effectiveness ratio per year of life saved. However, these economic evaluations rely on the quality of underlying epidemiological data. While uncertainty remains about the efficacy of ICD therapy versus drug treatment in reducing total mortality a reliable economic analysis cannot be undertaken. Until the results of several large ongoing randomised controlled trials become available cost effectiveness studies can only provide a range of estimates based upon their assumed values for ICD efficacy. Little work has yet been done that also integrates post-implantation quality of life measures. Research that examines cost effectiveness of an intervention only will favour any intervention that reduces mortality irrespective of the quality of the extra years of life gained. It is therefore essential that further work should address the cost utility of the ICD. It is noted that the Canadian Implantable Defibrillators study includes such an analysis in its assessment.

## 8.4 REVIEW OF OTHER COST RELATED ANALYSES

Other studies have examined ICD cost. Although these studies have not adopted a specific methodology they present some interesting points. DiMarco (1996) has presented methods for reduction in each of the major areas of cost associated with the ICD. These findings are summarised below:

**Table 26: Cost effective strategies for the use of ICDs**

Target costs	Strategy
Hardware (generator and leads)	<ul style="list-style-type: none"> <li>• Increase market competition</li> <li>• Lessen need for manufacturer support</li> <li>• Maximise battery life</li> </ul>
Implantation	<ul style="list-style-type: none"> <li>• Insert in the EPS laboratory with intravenous technique</li> <li>• Early decision if ICD is primary therapy</li> <li>• Selective anti-arrhythmic drug use</li> </ul>
Ancillary testing	All follow up should use device-based testing and diagnostics

After: DiMarco 1996.

Anderson and Camm (1993) comment that in the United States the cost of ICD implantation when any complication occurs now exceeds the allowance currently provided under Medicare. The authors conclude that ICD implantation carries too high a financial liability for small units because their complication rate may be too high (Mansfield et al. 1994) preventing financial viability (Ferguson et al. 1996).



## 9 The influence of ICD insertion on quality of life

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Larsen (1992) and Owens (1996) both attempted to include a consideration of ICD recipient's quality of life of in their analyses. Both modeled how the cost effectiveness of ICDs would be significantly reduced if ICD treatment impaired recipient's quality of life (in relation to pharmacological treatment). Despite the importance of this measure, no large, prospective trial has been found which has directly compared quality of life in risk-stratified ICD recipients and patients who elect drug treatment. It is noted that several large current trials are gathering this data (CIDS Trial –Connolly 1992, CARDPORT Project 1997).

In the (current) absence of results from large trials, the influence of the ICD on quality of life must be obtained from a review of the four studies which have assessed quality of life in samples of more than 50 patients.

**Table 27: Major trials examining the quality of life of ICD recipients**

Reference and Evidence level	Area of study	Number of patients	Study design	Results
Kalbfleisch et al. 1989 Evidence level: 3	Return to work	101	Retrospective questionnaire	62% of previously employed resume work
Pycha et al. 1990 Evidence level: 3	Quality of life and anxiety/ Depression in patients and spouses	80 (includes 38 spouses)	Retrospective questionnaire (Cleveland Clinic AICD, Self Assessment Anxiety Scale, Beck Depression Inventory)	Low anxiety and depression most patients (76%) and spouses (82%) value extra life from ICD
Luderitz et al. 1993 Evidence level: 3	Quality of life, psychological profile and patient acceptance	57	Retrospective longitudinal questionnaire (own questionnaire, and Spielberger State Trait Anxiety Inventory)	98% recommended ICD to other patients, 56% returned to work, 53 % returned to active life
Bainger and Fernsler 1995 Evidence level: 3	QOL	70	Retrospective questionnaire (Ferraro and Powers Quality of Life Index)	ICD- Overall no effect on QOL, although psychological and spiritual domains declined early after implantation.

After: Gallagher 1997.

Like May et al. (1995), Bainger and Fernsler (1995) examined quality of life as scores on a quality of life index. Both studies found that quality of life declined for recipients during the first 6 months after implantation but this was restored by the end of one year of follow-up. Aside from the obvious problems with the short follow-up and possible selection bias, it is likely that measurement bias may have occurred because baseline quality of life values were gathered just prior to surgery during a time of exceptional stress.

Most authors examining the effect of the ICD on the psychological state have found that recipients are principally happy to have the device (eg 55 of 57 patients in a study by Luderitz et al. 1993). Most patients are positive about the treatment because they believe that it will prolong their life (Keren et al. 1991, Sneed and Finch 1992, Cooper 1986). Most also successfully incorporate the device into their body image (May 1995). Two case reports also noted that the shocks actually generate relief and a renewed sense of “life being special” for some patients (Cooper et al. 1986, Gallagher 1997).

However, some recipients suffer significant psychological morbidity after implantation. In particular, several small studies have reported that many experience considerable fear and anxiety related to the unpredictable occurrence of the shocks (Kelly et al. 1988, Marchlinski et al. 1986, Vlay et al. 1989). Dougherty (1994) found that ICD implantation appeared to result in a significant loss of psychological function for many patients. However, like the findings of another small case series (Morris et al. 1991) that reported high rates of psychiatric illness in ICD recipients, Dougherty’s results are confounded by the subjects’ reactions to suffering a major illness and a near death experience. In general, ICD recipients appear to have levels of psychiatric illness similar to those in other patients after sudden cardiac arrest (Gallagher 1997).

Most recipients who were working prior to implantation return to work and other normal activities after implantation (Bainger and Fernsler 1995, Luderitz 1993, Vlay 1989, Kalbfleisch et al. 1989). However, in keeping with the limitations of research in this area, no accurate figures are available. This makes it difficult to know whether the

small case series reported in the literature are representative of most recipients' experience.

Whatever the cause or the actual percentage of patients, it is generally evident in the literature that many SCD survivors who receive an ICD do experience a significant, although possibly transient, reduction in their quality of life. Many felt increased psychological distress after ICD insertion, sometimes related to a drop in employment or a reduction in their health status. Finally, a number of patients do adapt to these changes and manage to retain an overall positive view of their quality of life (Bainger and Fernsler 1995, Arteaga and Windle 1995).

The results of the large PORT project now being undertaken at Stanford University may help clarify the effects of ICD implantation on the intellectual and emotional wellbeing of recipients. This study of more than 1,000 recipients will undertake regular functional, psychological and quality of life analyses and will document patient preferences for the device and other treatment options. (<http://preferences.stanford.edu/PORT/portoview.html>).



## 10 Indications for ICD use

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The indications for ICD implantation should be based on findings from trials that have examined efficacy in different populations. Indications for ICD use are determined by the external validity of each of these studies. In turn, the external validity is dependent upon the internal validity of the research.

Unfortunately there is uncertainty about the efficacy of the ICD for prolonging life among different patient groups. This difficulty arises because of a lack of evidence from large, well constructed, randomised controlled trials, which would be able to increase the internal validity of current research. Results from the only two randomised controlled trials completed to date (Wever 1995, Moss 1996) have limited generalisability. While the Wever trial had a small sample size, both studies utilised narrow inclusion criteria, putting severe limitations on the generalisability of their findings. Although several large trials will soon be completed, the definition of who should receive the devices in the meantime must largely rest on the findings from non-randomised comparisons and a large number of descriptive studies. Tables 28 – 34 summarise the indications for implantation from each of the 40 major studies assessed in this review.

It is difficult to reach any conclusions about which patients are the most appropriate to receive an ICD. Aside from inherent problems associated with study designs used in these trials, many authors have further complicated the identification of indications for ICD implantation by a lack of clear and consistent definition of the conditions treated by the devices. For example, several authors have examined ICD use in patients with sustained ventricular tachycardia that is not suppressed by medication (Saksena 1992, Saksena 1994, Bardy 1996). However, few have defined sustained VT, stated explicitly which drugs were used, or indicated how the medication was found to be inadequate. Some studies have not even clearly stated the parameters used to select patients for ICD therapy (Siebel 1994, Shahian 1995, Kim 1996, Mahmoud 1995, Brooks 1994). While evidence from cost effectiveness studies tentatively suggest that ICD implantation is cost-effective, the calculations on which these

studies are based crucially require an accurate definition of patients in whom the ICD has proven effective.

Another crucial issue, also poorly addressed by the state of current knowledge, is the evidence relating to identification of patients at highest risk for a ventricular tachyarrhythmia, ideally before they have suffered their first cardiac arrest and been fortunate enough to survive. Current risk stratification techniques can reasonably identify populations at increased risk of arrhythmia but are less able to predict which individuals will be most likely to sustain a malignant arrhythmia. A further outstanding problem is the need to identify the ideal time for patients at high risk of an arrhythmia to receive their device. Answering this question will require that the natural history of the underlying causes of SCD be determined. Although progress is being made in understanding the pathophysiology and natural history of SCD significant gaps still exist in the research (Myerburg et al. 1997).

Recognising these difficulties in the literature, some consistency is evident for considering ICD implantation in a patient who:

*has survived a documented episode of circulatory arrest due to sustained VF or VT and in whom all other treatments (drugs, surgery and catheter ablation) are inappropriate, contraindicated or have been proven to be ineffective*

Guidelines presented by the United States Committee for Cardiothoracic Surgical Practice (Kaiser et al. 1995) and The European Society of Cardiology (Breithardt et al. 1992) both include indications for ICD use based on the results of electrophysiological testing. These indications are contentious because recent findings have suggested that EPS has a doubtful ability to predict SCD and assist with planning the treatment of cardiac arrest survivors either with drugs or devices (see Section 2.3.2, Reiter 1997). A major problem in using EPS to stratify a patient's risk while also determining their most effective treatment is the confounding that can occur when these tasks are undertaken simultaneously (Caruso et al. 1997). That is, patients found by EPS to have a better outcome from testing may actually benefit not from the EPS but simply from the provision of medication from EPS testing

(Steinbeck 1997). The findings from the CASCADE Trial (1993) and Weinberg et al. (1993) and the indifferent performance of EPS (and holter monitoring) in the ESVEM Trial (Mason 1993) all indicate that empirical medication (amiodarone) for ventricular tachyarrhythmia treatment may be as useful as EPS.

Accepting these reservations there is some agreement in the literature on the following criteria:

*persistent inducibility (or spontaneous recurrences after testing) of poorly tolerated sustained ventricular tachycardia or ventricular fibrillation at EPS despite drug treatment with an appropriate (usually class III agent) pharmacological regimen predicted to be effective during EPS serial drug testing (Raviele 1996, Cardiothoracic Surgical Practice Guidelines Kaiser et al 1995, ACC/AHA NASPE Indications 1991).*

An additional indication for implantation, which also uses the results of EPS testing, is the inclusion criteria of the MADIT trial, namely those patients with:

*Q wave MI, and LVEF <35%, spontaneous non-sustained VT and having an inducible sustained VT not suppressed by intravenous procainamide*

Although these patients are acknowledged to be at high risk of SCD (Anderson et al. 1978, Kadish et al. 1993, Wilber et al. 1990, Buxton 1984) it is generally agreed that only a small number of patients will fit these inclusion criteria (Moss 1996, Moss 1997, Higgins et al. 1997, Waldo and Weisfeldt 1997). Although some authors have attempted to show that the clinical characteristics of patients fitting MADIT's inclusion criteria are similar to the majority of cardiac arrest survivors (Nisam 1997), most reviewers (including the authors themselves, Moss 1996), have concluded that the MADIT trial result can be generalised to indicate that only a small and distinct group of patients are eligible for an ICD.

Other possible indications for ICD implantation based upon SPE are more controversial and include:

- *non-inducibility of sustained ventricular arrhythmia at baseline EPS in a patient with spontaneous episodes of poorly tolerated sustained VT or VF and markedly reduced left ventricular function (<30%) and is not a candidate for myocardial revascularisation.*
- *non-inducibility of sustained ventricular arrhythmia at baseline EPS in a patient with spontaneous episodes of poorly tolerated sustained VT or VF and well preserved left ventricular function (>30%)*
- *inducibility of poorly tolerated sustained VT or VF at baseline EPS in a patient with recurrent syncope of unknown origin in whom no effective or tolerated drug is found during serial testing*
- *very frequently recurring episodes of haemodynamically well tolerated sustained VT despite the best drug treatment and despite surgical or catheter ablation in a patient in whom the tachycardia is easily reproduced by means of the ICD anti-tachycardia pacing program without recourse to shock.*

(After: ACC/AHA 1995, Breithardt et al. 1992, Akhtar et al. 1993)

## 10.1 EXCLUSIONS

Some patients are probably inappropriate to receive a device irrespective of indications (Based on Raviele,1996; ACC/AHA,1995; Kaiser et al,1995; Breithardt et al,1992)

- *patients with a poor prognosis due to irremediable and progressive heart damage, unless they are candidates for heart transplantation (Sweeney et al 1995.*
- *sustained VT or VF mediated by factors amenable to correction or reversibility, such as acute ischaemia, electrolyte imbalances or drug toxicity*
- *sporadic episodes of haemodynamically well tolerated sustained VT*
- *incessant VT or VF (very frequent triggering of the ICD disturbs the patients quality of life and quickly exhausts the ICD battery)*
- *recurrent syncope of undetermined cause in a patient without an inducible tacharrhythmia*
- *syncope of another cause unrelated to a ventricular arrhythmia*
- *patients with a life expectancy of less than one year*
- *patients who are contraindicated because of their psychological/psychiatric state or in whom there are other significant medical or surgical contraindications*

## 10.2 COST IMPLICATIONS OF RESEARCH EXAMINING THE INDICATIONS FOR ICD IMPLANTATION

A mathematical model developed by Anderson and Camm (1993) calculate the likely total cost if the ICD was made available to all patients estimated to benefit as a result of various trials. This model has been adapted to include the number of patients that would be eligible in each group based on a population comparison with the United Kingdom. Cost estimates are also provided.

**Table 28: Approximate number of patients eligible for ICD implantation in New Zealand and the associated cost**

Patient group or trial	APPROXIMATE NUMBER OF PATIENTS IN NEW ZEALAND PER ANNUM	Approximate cost if the device was available to all eligible patients (\$million).
All Survivors of cardiac arrest	300 (1)	15
Survivors of cardiac arrest with arrest low EF	106 (2)	5.3
Survive cardiac arrest inducible non suppressible low EF	37 (2)	1.8
Non sus VT (MADIT)	183	9.2
Non sustained VT MUSTT or SDSP	85	4.3
SAECG and low EF ie CABG patch	61	3
DEFIBRLAT	9 (3)	0.45
AHTAC (1995). All patients with sustained VT	95-190	4.75-9.5
ICD as post MI treatment	405 (4)	20

- (1) Extrapolated from Iowa study finding that there was 8.3 survivors of cardiac arrest per 100000 people (Anderson and Camm 1993)
- (2) Based upon UK figures and adapted to New Zealand population size
- (3) Assuming each device costs NZ \$50,000 for implantation, and that all eligible patients receive a device.
- (4) Current clinical data suggests that 30-60% of post MI deaths are due to arrhythmia however from this number must be subtracted competing causes of death such as ischaemia or heart failure after device insertion; a reasonable expectation of device benefit may be a reduction of 20-50% of post MI deaths.
- (5) Adapted form Anderson and Camm 1993

Although the figures presented in the table are gross estimates and subject to a number of assumptions, it is possible to conclude that the results of some recently completed and other ongoing large trials will have a significant impact on the utilisation of ICDs and ultimately upon national health care expenditure.

Table 29: Indications for insertion ICD presented in assessed literature							
Descriptive Studies							
	Saskena	Neuzner	PCD	Bardy	Palatiano		
Cardiac arrest 2o to VT/VF	x	x	x	x	x		
Cardiac arrest victims excluded							
Old MI							
No acute MI			x	x			
Exclude if no recent ischaemia							
No reversible cause for arrhythmia	x	x	x	x			
Age criteria							
Life expectancy > 1 year	<6months		<6months				
Inducible tachyarrhythmia by SEP test		x					
No inducible ventric. tachycardia							
Unsustained VT							
Sustained VT/VF refractory to drugs	x	x	x	x			
Sustained VT (with syncope or symptoms)					x >2meds		
Exclude if sustained ventr. Tachycardia							
Exclude if VT haemodynamically tolerated				x			
VT/VF frequency < detection threshold	x						
Frequent tachyarrhythmias	x		x				
Able to tolerate drugs							
Replacement ICD device needed	x	x					
Syncope + inducible ventr arrhythmia							
Syncope other cause found							
NYHA Groups I, II, III							
Ejection fraction specified							
Exclude if need surgical Rx							
Exclude if has pacemaker		x					
Exclude if had recent revascularisation							
Exclude if not had recent revascularisation							
Exclude if SVT with freq. ventric response	x		x				
Exclude if surgical Rx indicated							
Exclude if not eligible for coronary bypass							
Exclude if not eligible for transplant							
Exclude if renal insufficiency							
Exclude if IDDM and vasc problems							
Exclude if receive cerebrovasc. surgery							
Exclude if thrombolysed							
Exclude if has valvular disease				x			
Exclude if non compliant/can't follow up	x		x	x			
Exclude if contraindication to ICD							
For all trials assume that informed consent is also a pre-requisite.							
Palatianos: ICD inserted in VT + syncope patients after >2 medications and/or surgery							





Table 32: Indications for insertion ICD presented in assessed literature						
Descriptive Studies						
			Link	Brooks	Kim 95	Bocker 95 Trappe97
Cardiac arrest 2o to VT/VF				N/C	x	
Cardiac arrest victims excluded			x			x
Old MI						
No acute MI						
Exclude if no recent ischaemia						
No reversible cause for arrhythmia						
Age criteria						
Life expectancy > 1 year						
Inducible Tachyarrhythmia by SEP test					x	
No inducible ventric. tachycardia						
Unsustained VT					x	
Sustained VT/VF refractory to drugs						x
Sustained VT (with syncope or symptoms)					x	tolerated
Exclude if sustained ventr. tachycardia			x			
Exclude if VT haemodynamically tolerated						
VT/VF frequency < detection threshold						
Frequent tachyarrhythmias						
Able to tolerate drugs						
Replacement ICD device needed						
Syncope + inducible ventr arrhythmia			x		x	
Syncope other cause found			x			
NYHA Groups I, II, III						
Ejection fraction specified						
Exclude if need surgical Rx						
Exclude if has pacemaker						
Exclude if had recent revascularisation						
Exclude if not had recent revascularisation						
Exclude if SVT with feq. ventric response						
Exclude if surgical Rx indicated						
Exclude if not eligible for coronary bypass						
Exclude if not eligible for transplant						
Exclude if renal insufficiency						
Exclude if IDDM and vasc problems						
Exclude if receive cerebrovasc. surgery						
Exclude if thrombolysed						
Exclude if has valvular disease						
Exclude if non compliant/can't follow up						
Exclude if not contraind. to ICD						

Table 33: Indications for insertion ICD presented in assessed literature												
Comparative non-randomised studies												
	Newman	Powell	Choue	Sweeney	Bocker96	Ector	Crandall	Shaihian	Jafar	Zipes		
Cardiac arrest 2o to VT/VF	x	x	x	x		x	x	N/C	x	x		
Cardiac arrest victims excluded												
Cardiac arrest and absence of induc. arrhyt				x								
Old MI												
No acute MI		x					x		x	x		
No reversible cause for arrhythmia			x				x		x	x		
Age criteria												
Life expectancy > 1 year									<6months			
Inducible Tachyarhythmia by SEP test		x		x					x	x		
Induc. tachy by SEP unresponsive to drugs												
Non-inductible arrhythmia on SEP			x				x					
Unsustained VT				x								
Sustained VT/VF refractory to drugs	x			x	x				x	x		
Sustained VT (with syncope or symptoms)	x		x									
Exclude if VT haemodynamically tolerated												
Syncope and inductible ventric arrhythmias				x								
Exclude if frequent tachyarrhythmias			x									
Unable to tolerate drugs	x											
Patient request	x											
Poor prognosis red. EF, holter	x											
NYHA Groups I, II, III			x									
Ejection fraction specified												
Exclude if surgical rx indicated												
Exclude if has pacemaker									x			
Exclude if had recent revascularisation												
Exclude if has valvular disease												
Exclude responders to sotalol on EPS					x							
Exclude if non-compliant or cant follow up												
Defib threshold low and no contraind to ICD												
Choue: indications changed during study.												



Table 35: Indications for ICD insertion presented in the reviewed literature.								
Randomised controlled trials								
	Wever	Siebel	Moss	AVID	CIDS	CABG		
Cardiac arrest 2o to VT/VF	x	x		x	x			
Cardiac arrest victims excluded						x		
Old MI	x		x					
No acute MI	x							
No reversible cause for arrhythmia				x				
Age criteria	<75 yrs							<80yrs
Life expectancy > 1 year	x							<2yrs
Inducible Tachyarrhythmia by SEP test	x		x (Proc)					
Unsustained VT			x					
Sustained VT (with syncope or symptoms)	x			x	x			
Frequent tachyarrhythmias	x							
Able to tolerate drugs	x			x				
NYHA Groups I, II, III	x		x					
Ejection fraction specified	<35%		<35%					>35%
Exclude if surgical Rx indicated	x			x				ablative
Exclude if has pacemaker	x							x
Exclude if had recent revascularisation			x					
Exclude if SVT with freq. ventric response				x				
Exclude if other severe disease needs hosp	x							
Exclude if not eligible for coronary bypass								x
Exclude if not eligible for transplant								
Exclude if renal insufficiency								x
Exclude if IDDM and vasc problems								x
Exclude if receiving cerebrovasc. surgery								x
Exclude if thrombolysed								x
Exclude if has valvular disease								x
			Not clear	Unsuppressed by procainamide				

**APPENDIX**

## Glossary

### Cardiac conditions

Arrhythmia	An abnormality in the rate or rhythm of the heart beat, caused by a defect in the generation or conduction of electrical impulses.
Atrio-ventricular block	Block of the electrical impulses between the atria and the ventricles in the heart.
Bradycardia	A slow heart rate.
Cardiomyopathy	A defect of the heart muscle.
Conduction defect	A defect in the transmission of electrical impulses in the heart
Congestive heart failure	Failure of the heart to pump blood around the body
Coronary artery disease	Usually due to atherosclerosis this manifests itself as an obstruction of the blood supply to the heart muscle.
Fibrillation	Rapid, chaotic activity of the heart muscle.
Ischaemic heart disease	same as coronary heart disease
Myocardial infarction	Death of a part of the heart muscle due to an interruption in it's blood supply.
Supraventricular tachycardia	An abnormally fast heart rate caused by fast impulses, originating in the upper chambers of the heart (instead of the sinus node)
Tachycardia	A rapid heart rate
Tachyarrhythmia	A rapid and abnormal heart rate.

### Cardiology interventions

Anti-tachycardia device	An implantable device for the automatic reversion of arrhythmias.
Angioplasty	Treating a blocked blood vessel by dilating a balloon inserted in the vessel.
Cardioversion	A carefully timed direct current shock applied to the heart to treat an arrhythmia.
CABG grafting	Grafting of coronary arteries to bypass an obstruction
Defibrillator	An apparatus used to terminate fibrillation usually by cardioversion (or pacing)
Electrophysiology	Study of electrical activity of the heart

Myocardial revascularisation	Re-establishment of blood supply to the heart
Radiofrequency catheter	A catheter-used to treat cardiac arrhythmias with some energy

## **Epidemiological terms**

Relative risk reduction (RRR)	The proportional reduction in rates of bad events between experimental and control participants in a trial. If there was an increase in the rate of bad events the term would then be relative risk increase.
Absolute risk increase (ARR)	The subtracted difference in event rates.
Number needed to treat (NNT)	The number of patients who need to be treated to achieve one additional favourable outcome. Calculated as $1/ARR$ . If the intervention harmed people the term would be the number needed to harm.
Odds ratio (OR)	The odds of a patient in an experimental group having an outcome event relative to a patient in a control group.
Confidence intervals (CI)	The CI quantifies uncertainty. The 95% CI is the range of values in which it is 95% certain that the true value lies for the whole population.
Relative risk (RR)	The ratio of the risk in the intervention group relative to the risk in a control.

**(After :AHTAC, Superspecialty service guidelines for acute cardiac interventions, 1995 and Evidence-Based Medicine 1997 July/August;2:128)**

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