The Implantable Cardioverter-Defibrillator: From Historical Evolution to Current Controversies

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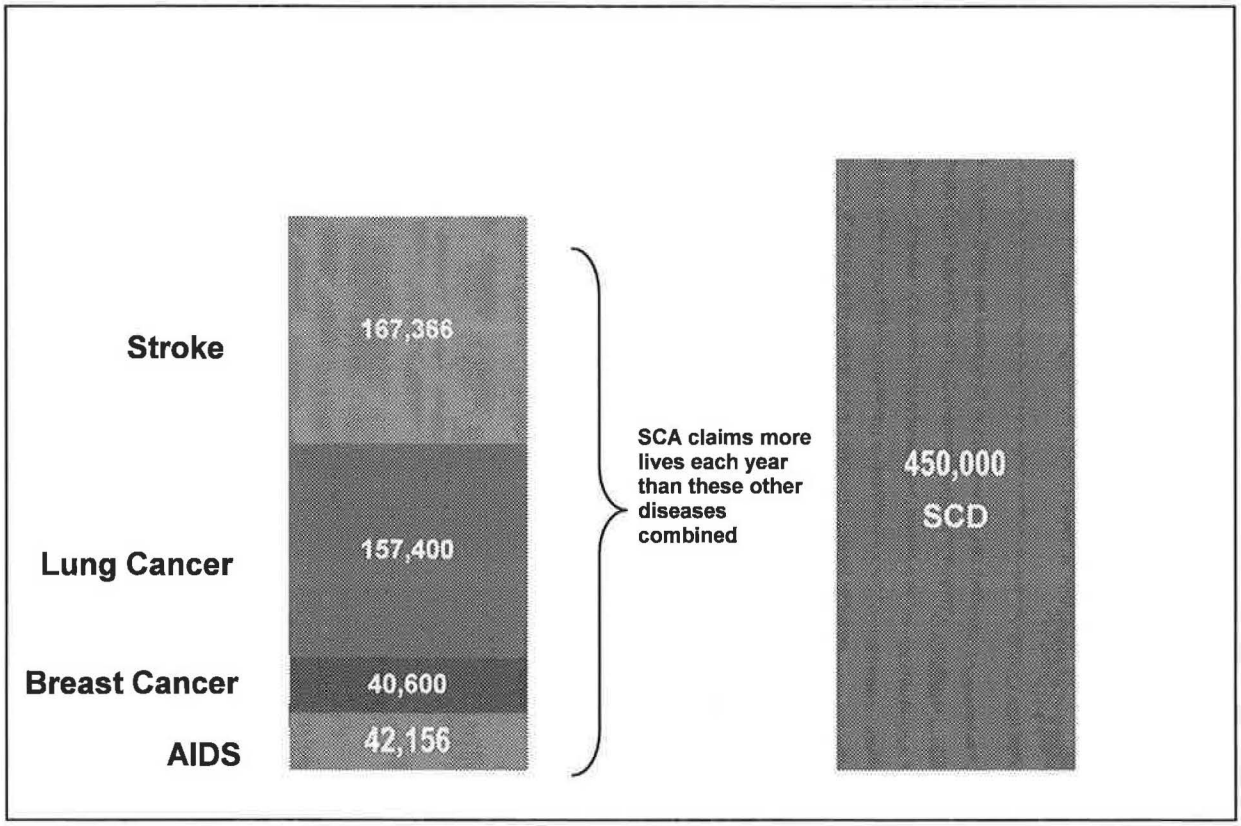
SUDDEN CARDIAC DEATH STATISTICS

Sudden cardiac death (SCD) remains a leading cause of death in many countries around the world. In the United States, a recent survey reported 728,743 cardiac related deaths in 1999, with 63% being sudden (462,340) and 47% occurring out of the hospital.(1) If these statistics were true, SCD would account for more deaths than the combined deaths from stroke, lung cancer, breast cancer and AIDS.



The Most Commonly Cited SCD Statistics are Most Likely Overestimated

Fortunately, these numbers are probably not accurate, as the incidence of SCD over the years has most likely been overestimated. The main reason for this overestimation is that previous studies have obtained data from first responder agencies, or from death certificates, which are not very accurate methods. To obtain a more accurate estimate on the incidence of SCD in the general population, Chugh and colleagues performed a prospective assessment among all residents of Multnomah County, Oregon, using multiple sources of surveillance.(2) The sources included first responders, medical examiner, area hospitals, and physician's records. As demonstrated in the figure below, compared to their prospective assessment, death certificate-based estimates were found to over estimate the incidence of SCD by a factor of 3.(2)

	Presumed Cardiac Arrest	Prospectively Defined SCD	Death Certificate-Based SCD
Annual incidence/100,000	67*	53*	153*
Total number	439*	353*	1,007*
Female	178 (41%)	151 (43%)†	495 (49%)†
Median age (yrs)	67	69‡	81†
Witnessed	208 (47%)	184 (52%)	N/A
Attempted resuscitation	286 (65%)	237 (67%)	N/A
Return of spontaneous circulation	43 (10%)	39 (11%)	N/A
Survival to hospital discharge	29 (7%)	28 (8%)	N/A

*p < 0.05 for differences between the three groups (chi-square test); †p = 0.05 for prospective versus death certificate SCD (chi-square test for nominal variables, Wilcoxon-Mann-Whitney for medians).
N/A = not applicable; SCD = sudden cardiac death.

Death certificate-based analysis exaggerates SCD statistics.

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If we were to extrapolate the aforementioned data to national statistics, the true number of SCD would be about 150,000. Still, even the this lower incidence represents 5.6% of overall deaths, an important number that needs to be treated seriously, especially since in about a third of patients with cardiovascular disease the first manifestation is SCD.

Although a reduction of total cardiac mortality has been seen over the past decade, the percentage of SCD has increased from 38% to 47%,(3) mainly due to an increase in out-of – hospital SCD. Of the etiologies, coronary disease with or without infarction is by far the most common cause of SCD in the USA, being present in about 75% of SCD victims over the age of 35. The table below shows the most common etiologies of sudden cardiac death. It is important to reiterate that patients do not have to have a large transmural myocardial infarction to die suddenly; in fact only 20% of patients have evidence of such a large infarct.

Causes of SCD	**Example**
Coronary artery disease / spasm / anomaly (75-80%)	Myocardial ischemia/infarction Previous infarct with VT
Structural nonischemic heart disease (10-20%)	Idiopathic dilated cardiomyopathy Hypertrophic cardiomyopathy Acute Myocarditis Arrhythmogenic RV dysplasia Inflammatory/infiltrative diseases Aortic stenosis
No structural heart disease (< 5%)	Long QT syndrome Brugada syndrome Primary VF WPW
Acute mechanical (< 5%)	Aortic rupture Commotio cordis

In the study by Chugh et al, the gender distribution was 43% female and 57% male, in contrast with prior reports of a 3:1 male predominance.(2) Again, this probably reflects the way cases were defined previously. The majority of SCD occurred at home (82%), which was associated with a worse survival. In patients under the age of 35, the highest incidence was seen in the 0-5 year-age group, whereas in those over 35 y/o the highest incidence was seen in the 75 to 84 year-age group.

The rhythm observed at the time of SCD depends on the time elapsed since collapse. When the time is unknown, 40% is ventricular fibrillation (VF), 40% is asystole, 20% is pulseless electrical activity (PEA) and 1% ventricular tachycardia (VT).(4) By contrast, when the time from collapse is under 4 minutes, 95% of the time VF is documented. This suggests that most cases of PEA and asystole are manifestations of the progression of the death process and not the primary rhythm abnormality. It is also important to understand that in patients with heart failure (CHF) the cause of SCD changes with the degree of CHF severity. As the class increases from I to IV, there is an increase in annual risk of total mortality, whereas there is a decreased risk of SCD. Thus, in class I patients, about 60% will die suddenly, whereas in class IV only 10-40% die suddenly; another half die of pump failure.(4) Therefore, in many patients with advanced CHF, an implantable cardioverter defibrillator (ICD) would not be helpful.

Risk Factors for SCD and Early Drug Studies on Prevention

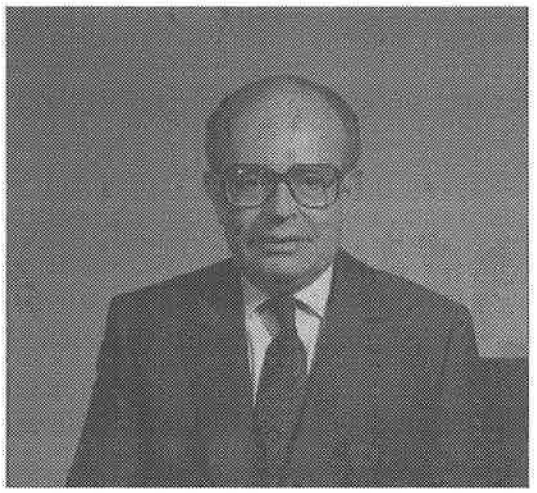
The most important risk factors for SCD are a prior cardiac arrest, depressed left ventricular function (LVEF) and clinical CHF.(4) These are followed by ambient ventricular arrhythmias (nonsustained VT, PVCs), ischemia, and left ventricular hypertrophy. Although inherited lethal disorders have been recognized, such as the long QT syndrome, they represent only a small portion of all SCD.

The pathophysiology of SCD involves an interaction between triggering events and the presence of abnormal substrates. As such, frequent PVCs in the presence of a normal heart is benign. In contrast, frequent PVCs in patients with impaired LVEF confers a worse prognosis.(5) For example, both Bigger et al. and the GISSI 2 trial demonstrated that the combination of PVCS and low LVEF were independent negative prognostic indicators of survival.(5, 6)

With this knowledge in mind, early attempts at preventing SCD were aimed at suppressing ventricular ectopy. Unfortunately, it became obvious that when some conventional antiarrhythmics were used for this purpose, the drugs were not only ineffective but were harmful as demonstrated by the CAST study, where suppression of ventricular ectopy with flecainide and encainide resulted in a worse survival.(7) In fact, of all antiarrhythmic drugs, only beta-blockers(8) and perhaps amiodarone (especially if combined with beta-blockers)(9), demonstrated an ability to reduce SCD. Therefore, due to the minimal (or negative) effect of drugs as targeted therapy for SCD survivors, the idea of the implantable cardioverter defibrillator (ICD) was conceived. More recently aspirin, ACE inhibitors, angiotensin receptor blockers, aldosterone blockers, statins, and fish oils have shown to reduce SCD.(10)

HISTORICAL EVOLUTION OF THE ICD

By the 1960s, thanks to the research conducted by Dr. Paul Zoll, external electrical cardioversion was already considered effective therapy for termination of cardiac arrhythmias including VF.(11) The idea of the ICD was conceived by Dr. Michele Mirowski in 1966, after his colleague, mentor and friend, Dr. Harry Heller died suddenly.(12) At that time, physicians had virtually no treatment choices for patients at risk of SCD. Some were initially skeptical; in an editorial in Circulation in 1972, Bernard Lown called the ICD idea "an imperfect solution in search of a plausible and practical application".(13)



Dr. Michel Mirowski, the inventor of the ICD.

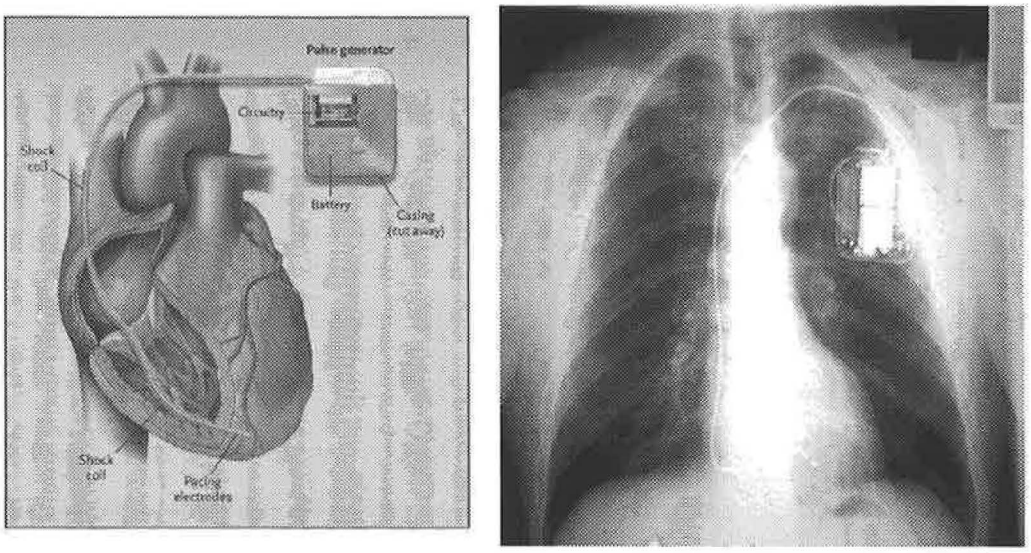
The first working models were built with over the counter electronics. Over the years, working in a dog model and later in patients undergoing coronary artery bypass surgery, the concept slowly evolved. For example, initially sensing of VF was achieved by a pressure transducer and a drop in blood pressure triggered the device. The device had evolved sufficiently such that the FDA approved it for clinical investigation in humans. The first human implant occurred at Johns Hopkins on February 4, 1980.(12) To meet criteria, the patient had to have survived two episodes of cardiac arrest not associated with an infarction and VF had to be documented at least once.

Initial devices had many limitations including: short-lived, non-programmable (could not change detection rate), were shock only devices, had no telemetry, were large, and required surgical implantation via thoracotomy. Since then, a steady evolution in device technology has resulted in miniaturization of the devices, as well as the development of enhanced features that allow for greater patient treatment options, safety and comfort. Part of this progress can be attributed to the development of biphasic energy waveform for defibrillation, which reduces energy requirement by about 30%.(14)

ICD SYSTEM DESCRIPTION

An ICD system includes a pulse generator, and one or more leads for pacing/sensing and defibrillation. The pulse generator has a number of components, including a sealed titanium case, a lithium-silver vanadium oxide battery, voltage converters and resistors, capacitors to store

energy, microprocessors, integrated circuits to control the analysis of the rhythm and the delivery of the therapy, memory chips to store electrocardiographic and other data, and a telemetry module. The top is an epoxy header for lead connection. Dual chamber or biventricular ICDS have additional ports for the atrial of left ventricular leads.(15)



DiMarco JP. NEJM:349;1836

Modern ICDs are small devices that can be implanted subcutaneously over the pectoralis muscle with a single incision using local anesthesia and transvenous leads. Only a short hospital stay is required and complications are few. In addition, today's devices have full pacing capabilities; they are like a "pacemaker on steroids". Other enhanced features compared to earliest models include:

- Programmable therapy options
- Energy selection
- Multiple zones with lower rate boundaries
- Antitachycardia pacing
- Data storage
- Discrimination of SVT and VT/VF
- Single- or dual-chamber pacing therapy
- Therapy for atrial arrhythmias
- Patient alerts
- Battery longevity up to 8 years

In ICDs, two basic methods are used to terminate arrhythmias; either a direct-current shock or antitachycardia pacing. A defibrillation shock can be used to terminate either VT or VF, and the amount of energy can be selected. In most patients, VF can terminate with as little of 6 Joules, but it can be more and a safety margin is required to allow for 99% effectiveness. Therefore, most ICD are capable of delivering between 27 to 36 Joules. Antitachycardia pacing is most effective for VT, and works by overwhelming the arrhythmia circuit by pacing at a slightly faster rate than the arrhythmia rate.

The main method for sensing is by determination of the rate of the R wave. Several therapy "zones" can be programmed, and therapy in different zones can be individualized. For example, a faster zone (VF zone) can be programmed to deliver only shocks, where as a slower VT zone can be programmed to start with painless antitachycardia pacing, followed by shocks. Up to six shocks can be programmed, and many different combinations of antitachycardia pacing. Because the amplitude of the signal can vary considerably, all ICDs allow for sensitivity gain adjustments. Filters prevent sensing of potential artifactual signals such as skeletal muscle activity. Since some of the zones can overlap with sinus or supraventricular tachycardias, ICDs offer algorithms to help discriminate between ventricular and non-ventricular arrhythmias.

Other features include data storage. When an arrhythmia requires treatment, the entire episode can be printed so the physician can analyze it and decide on best therapy. Audible patient alerts allow for prompt intervention when dangerous situations develop, such as low battery status. All ICDs have full pacing capabilities in single, dual or biventricular mode.

CLINICAL TRIALS

Early on, the ICDs demonstrated to be effective at terminating ventricular arrhythmias. Uncontrolled studies showed better survival in high-risk patients as compared to historical controls. Nevertheless, randomized clinical trials were conducted with the rational that the benefits of the ICD could have be exaggerated since not all shocks are necessary life saving, not all ventricular arrhythmias are necessarily fatal, and mortality could result from other causes related or unrelated to the ICD.

The first clinical trials were secondary prevention studies, were patients who either survived a cardiac arrest not due to a reversible causes, or who had hemodynamically important VT were randomized to ICD or drug therapy. Subsequently, primary prevention trials followed, in which patients with no prior documented arrhythmias but considered at high risk, were randomized to ICD, drug therapy, no treatment or both.

Secondary Prevention Trials

The Antiarrhythmic versus Implantable Defibrillator (AVID) trial(16) enrolled 1016 survivors of cardiac arrest due to VF or hemodynamically important VT with impaired LVEF. The subjects were randomized to ICD, or drug therapy (mainly amiodarone). The trial was terminated early by the safety monitoring committee after a 29% relative risk reduction in mortality was observed in the ICD group (see figure below).

A second study was the Canadian Implantable Defibrillator Study (CIDS)(17). The study, which enrolled 659 patients, was similar to AVID but also enrolled patients with syncope, impaired LVEF and inducible sustained VT. There was a 20% relative reduction in total mortality in the ICD group, which did not reach statistical significance.

The smaller study was the Cardiac Arrest Study Hamburg (CASH), with 288 patients.(18) The main difference to AVID and CIDS was that in the drug arm, in addition to amiodarone patients were also assigned to either metoprolol (a beta-blocker) or propafenone (a class IC antiarrhythmic). The propafenone arm was stopped early due to excess mortality. The ICD group experienced a 23% reduction in mortality compared to amiodarone and metoprolol, but this was not statistically significant.

ICD Trails for Secondary Prevention of Sudden Cardiac Death

		Mortality			
	STUDY GROUP	**Control**	**ICDs**	**Rel RR**	**P Value**
AVID	**VF, sustained VT; EF ≤ 40% ICD vs amiodarone Mean EF 35% F/U: 18 mo**	**24%**	**15.8%**	**-30%**	**0.02**
CIDS	**VF, symptomatic VT; EF ≤ 35%, CL < 400ms Mean EF 34% F/U: 36 mo**	**29.6%**	**25.3%**	**-20%**	**0.14**
CASH	**Survivors of SCD (VF/VT) propafenone/metoprolol/ amiodarone/ICD Mean EF 45% F/U: 57 mo**	**44.4%**	**36.4%**	**-23%**	**0.08**

The AVID trial was the only study to reach statistical significance, probably due to the fact that was the largest study, therefore was adequately powered. CIDS and CASH did not achieve statistical difference for total mortality, but they were significant for prevention of arrhythmic death. Subsequently, a meta-analysis of the three trials demonstrated a 28% reduction in total mortality ($p = 0.006$).(19) Since then, ICD therapy has been considered standard of care for survivors of cardiac arrest due to VT or VF.

Several other lessons were obtained from these trials. First, the greater benefit was derived in patients with the most advanced heart disease. Second, in AVID patients with arrhythmias thought to be due to a reversible cause were excluded from the trials but included in a registry.(20) These patients remained at a high risk for death, similar to the drug therapy group. Finally, in CASH total mortality with amiodarone and metoprolol was identical.

Primary Prevention Trials

The success of ICDs in preventing SCD in patients with prior malignant arrhythmias led to the design of primary prevention trials in patients at high risk. The evolution of the primary prevention trials over the years has been such that as the trial results turn positive, new trials are designed in patients with fewer risk criteria for SCD. As it is shown in the table below, the primary prevention trials progressed from the first one, the Multicenter Automatic Defibrillation Implantation Trail (MADIT) published in 1996 (21), where patients had to have the combination of CAD, a prior infarct, nonsustained VT, and inducible VT that was not suppressible on electrophysiologic study, to SCD-Heft (not published yet), which included patients with ischemic and nonischemic heart disease, with the only requirement being an ejection fraction of under 35% and class II-III CHF.

Primary Prevention Trials Criteria Comparison

Inclusion Criteria	MADIT 1996 (n = 196)	MUSTT 1999 (n =704)	MADIT II 2002 (n =1232)	SCD-HeFT (n =2521)
CAD/Post-MI	✓	✓	✓	
LV Dysfunction	✓ (≤35%)	✓ (≤40%)	✓ (≤30%)	✓ (≤35%)
NSVT	✓	✓		
Inducible VT on EPS	✓	✓		
Inducible, non-suppressible VT on EPS	✓			

The first two trials MADIT and MUSTT (Mutlicenter Unsustained Tachycardia Trial(21, 22) were similar in that both required nonsustained VT, a prior myocardial infarction, a low LVEF ($\leq$ 35% and $\leq$ 40% respectively), and inducibility of VT on electrophysiologic study (see table below). MADIT, which enrolled 196 patients, was a direct comparison between ICD and the best drug, which in most cases was amiodarone. In MUSTT, the comparison was between ICD therapy, no therapy, and electrophysiologic guided drug therapy. Both studies had flaws, for example in MADIT there was no registry for patients who were not inducible. Nevertheless, the results of both trials were similar, demonstrating a remarkable 55% reduction in total mortality and a 75 % reduction in SCD.

The second Multicenter Automatic Defibrillation Trail (MADIT II) (23)enrolled 1232 patients with coronary disease, a prior myocardial infarction and an ejection fraction of 30% or less (see table below). Patients were randomized to ICD or conventional therapy. Documentation of ventricular arrhythmias was not required, and less than 20% of patients received antiarrhythmic drug therapy. The study was stopped prematurely after an average follow-up period of 20 months; the mortality was 19.8% in the control group, and 14.2% in the ICD group (31% relative risk reduction). The results of this study led to significant controversy, which will be discussed in the cost section of this protocol.

All the clinical trials cited above included only patients with coronary artery disease. More recently, the Sudden Cardiac Death in Heart Failure (SCD-Heft) trial results were presented in a national meeting.(24) The trial included patients with ischemic and nonischemic heart disease. The only entry criteria was LVEF $\leq$ 35%, and class II or III CHF. Patients were randomly assigned to receive an ICD, amiodarone or placebo. There was no difference between the placebo and amiodarone arms, but after 5 years mortality was lower in the ICD group compared to placebo (28.9% versus 35.8%).

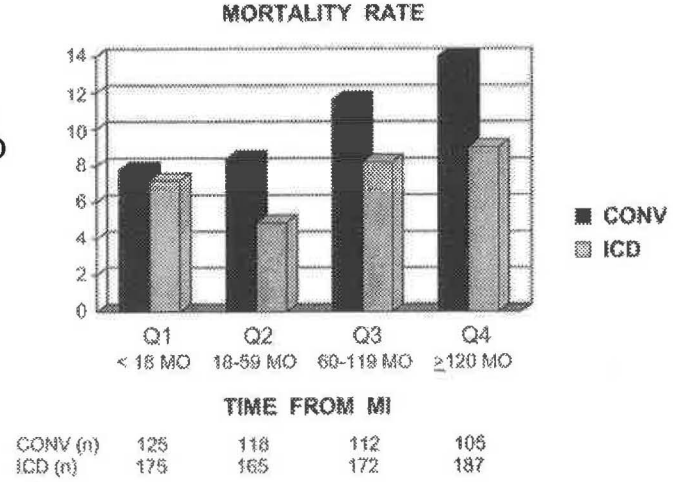
Primary Prevention Trials with Negative Results

Not all ICD trials have shown positive results. The Coronary Artery Bypass Graft Patch (CABG Patch) trial(25) enrolled patients with LVEF $\leq$ 35% and an abnormal signal-averaging ECG, to either receive an epicardial ICD system at the time of coronary artery bypass surgery, or no therapy. With 900 patients enrolled, after a mean follow-up period of 32 ± 16 months, the study was terminated due to lack of efficacy in the ICD group. The lack of mortality benefit by ICDs might be attributed to the beneficial effects of revascularization surgery.

Most 1ry prevention enrolled patients with ischemic cardiomyopathy. The Cardiomyopathy Trial (CAT)(26) enrolled 104 individuals with non ischemic cardiomyopathy and an LVEF of 35 % or less to ICD or no therapy. The study was negative, with difference in mortality between the groups. One limitation is that the study was stopped early for futility, since mortality was too low in the control group. The results were in concordance with a very similar study, the Amiodarone versus Implantable Cardioverter-Defibrillator trial (AMIOVIRT)(27), which also involved patients with nonischemic cardiomyopathy randomized to either ICD therapy or amiodarone. The trial was different to CAT in that patients had to have documented nonsustained VT, but was also stopped early for futility, and the results were also negative. The results of these two trials highlight the benefit of other therapies in preventing SCD, such as ACE-I, beta-blockers and aldactone. Also serve as a reminder that not all mortality is prevented with ICDs, and that in some instances ventricular arrhythmias are just a marker of cardiac function deterioration.

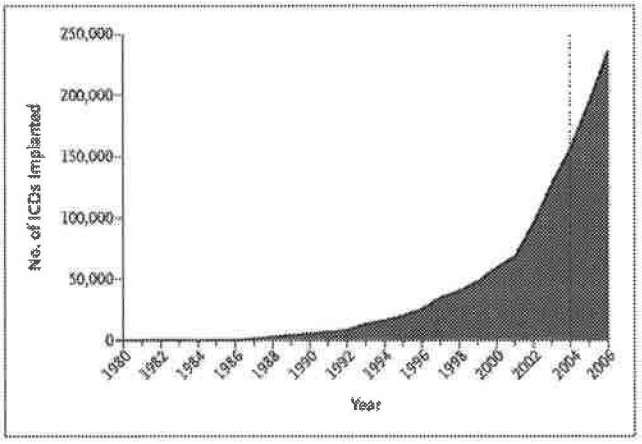
Last, more recently the results of the Defibrillator in Acute Myocardial Infarction (DINAMIT) trial were published(28) This trial sought to evaluate whether ICD therapy was beneficial when implanted shortly after an acute myocardial infarction. There were 674 patients with an LVEF of 35% or less 6 to 40 days after a myocardial infarction. The patients also had to have impaired autonomic function, which is a risk factor for subsequent death. Multivessel revascularization was an exclusion criterion. Despite the fact that patients were considered high risk, the trial did not show benefit in total mortality ($p = 0.66$). There was a big benefit in arrhythmic death prevention (relative risk reduction of 58%) with ICD, but this benefit was offset by a similar increase in nonarrhythmic death. These results make some question of whether in this study ICDs merely transformed death from SCD to pump failure. Lack of benefit early after myocardial infarction was also reported in MADIT II.(29) It is important to remember that in MADIT II, despite an enrollment requirement of an infarction only over 30 days old, the meant time from infarction to enrollment was 6.5 years. The subgroup of patients with a recent infarction (< 18 months) did not benefit as demonstrated in the figure below.(29)

In patients with ischemic heart disease, more benefit from ICD is seen as the time from prior infarction increases.
Circulation 2004;109:1084



The results of the main trials have allowed for an exponential growth in the number of ICDs implanted in the USA and worldwide. As positive trials in patients with fewer risk factors for SCD are published, the number of candidates increases, while the absolute benefit decreases. Therefore, as the picture below demonstrates, the number of ICD implants over the next few years is expected to grow rapidly.

Exponential Growth in ICD Implants in the USA



Jauhar, S. et al. N Engl J Med 2004;351:2542-2544

COST AND CONTROVERSIES

With the exponential increase in the number of ICDs in the USA, discussions about cost are inevitable. After the results of SCD-Heft are published, the number of ICD implants is expected to double in the USA from 150,000 last year. Currently the penetration of ICDs is only 25%; if that number would increase, the number of implanted devices will increase even further. The cost is not trivial at $52,000 per DRG.

Interestingly, the number of devices in planted per capita in the USA is 5 times as high as the rate in Western Europe.(30) The differences in ICD use may be explained by different factors, such as differences in the manner in which sudden cardiac death is perceived by politicians and physicians (sudden cardiac death is perceived as a "nice way of dying"); differences in indications; physicians' information and availability; prevalence of coronary artery disease; sudden cardiac death survival rates; perceived reliability of alternative treatment (namely, antiarrhythmics including amiodarone); economic backgrounds; and health care politics. Although the cost of this treatment strategy must be considered, the low acceptance in Western Europe may not be entirely related to budget constraint but also to the perceived efficacy of ICDs by physicians and health authorities.

Estimates of cost depend on the design used for analysis. Defibrillators have large upfront cost plus additional cost throughout the life of the device. For secondary prevention, estimates of cost have varied, but AVID reported a cost of $66,677 per year of life saved over the 3 years duration of the study.(31) This is considered moderately expensive as it exceeds the accepted threshold of $50,000 for "economically attractive" therapies. For the primary prevention study MADIT, not surprisingly, since the survival difference was 3.6 times greater

than in AVID, the cost came lower at $30,337 per year of life saved, which is considered economically attractive.(32)

Things got a bit more complicated after MADIT II was published(23), despite the fact that the results received the endorsement of the FDA and received a class IIa indication in the AHA/ACC/NASPE consensus guidelines.(33) Because the absolute reduction in mortality observed, 5.6%, was smaller than in prior ICD studies on primary prevention (MADIT and MUSTT), controversy erupted regarding cost and applicability.(34) Some of the criticism includes the following: 1. the possibility of selection bias since patients were recruited from high risk settings as demonstrated by the high mortality in the control group; 2. patients who fitted MADIT I criteria, already known to be high risk, were not excluded and could have affected the results towards ICD. In fact, 78% of patients randomized to ICD had EP studies in conjunction with their implants, of which 36% were inducible; 3. the number of patients needed to save one life was much more higher than in the first two primary prevention trials.

With those arguments at hand, the Centers for Medicare and Medicaid Services (CMS) decided to extend coverage only to those patients meeting MADIT II criteria who also had a QRS duration > 120 msec. This decision was based on subgroup analysis, which demonstrated the greatest benefit to those with a wide QRS. The decision was made to reduce cost, since less than half of patients in MADIT II had a wide QRS. Physicians called this an intrusion by the government aimed at containing cost based on poor science.

Subsequently, the results of SCD-Heft were presented at national meetings. The results were somewhat similar to MADIT II, although a bit more modest.(24) Furthermore, subgroup analysis did not find differences based on QRS width. The government now had pressure from physician organizations and industry lobbyist. Therefore, it was decided to release payment for patients with ischemic or nonischemic cardiomyopathy and LVEF $\leq 30\%$, but with two conditions. First, that patients are entered in a registry subsidized by the device industry. Second, that only a single chamber device is implanted unless clear indications for atrial-based pacing exist. This last condition emanates from the fact that in the USA, 85% of all ICDs implanted are dual chamber, despite the fact that no more than 40% of these patients have indications of bradycardia. In comparison, in Europe, only 35% of ICDs are single chamber. This is probably reflection on the way devices are marketed in the USA; by a motivated sales force that stresses innovative features and technological advancements. The release of payment by Medicare is just waiting for the results of SCD-Heft to be published in a peer-reviewed journal.

INDICATIONS AND CONTRAINDICATIONS (33)

Indications	Contraindications
•Spontaneous or inducible VT/VF	•Incessant VT or VF
•Sustained VT with structural heart disease	•VT or VF due to a "completely" reversible cause
•Unexplained syncope with inducible VT/VF or in very high-risk patients	•Psychiatric illness potentially aggravated by ICD therapy
•LVEF < 30%	•Terminal illness
•High risk inherited conditions	•Class IV CHF without option of cardiac transplantation
	•Implantation at time of CABG for 1ry prevention

COMPLICATIONS

Potential complications of ICD therapy may include:

- Acutely: Bleeding, pneumothorax, lead dislodgement, hematoma
- Infection may occur in 1-2% of cases and requires system removal
- Malfunction of device; lead is the weakest link and can fracture or fail
- Inappropriate shocks, such as for atrial fibrillation
- Ventricular pacing is detrimental in patients with LV dysfunction:

  For example, the DAVID trial demonstrated increased mortality in patients who received dual chamber ICDs with DDD pacing as compared to ICDs with only backup VVI pacing.(35) The mortality was 6.5% for VVI, versus 10.1% for DDD pacing. Patients were paced in the ventricle 56% in the DDD group, versus only 2.9% in the VVI group. Further evidence comes from MADDIT II, which demonstrated an increased incidence of CHF in patients who received ICDs.

ICD SHOCKS AND ELECTRICAL STORM

ICD Shocks

Of the patients who receive ICDs for primary prevention, approximately 50% will receive treatment for ventricular arrhythmias within three years of implantation, compared to 74% of patients with a prior myocardial infarction who received the ICD for secondary prevention of SCD.(36) Clinical data suggest, that in primary prevention patients a larger percentage of shocks are inappropriate, compared to those with prior ventricular arrhythmias.(37) The majority of inappropriate shocks are for atrial fibrillation.

In patients who receive single isolated shocks, no specific therapy is necessary although this should not be dismissed completely. A recently published long-term follow up study of MADIT II demonstrated that receiving appropriate therapy for ventricular arrhythmias was a strong risk factor for sudden death.(38) As demonstrated below, ICD therapy was a stronger mortality predictor than a high BUN or lack of beta-blocker therapy.

All-cause Mortality Risk after Appropriate ICD Therapy for Ventricular Tachyarrhythmias

Variable	HR (95% CI)*	P value
A first therapy for VT	3.4 (1.9-5.9)	<0.001
A first therapy for VF	3.3 (1.3-8.1)	0.01
Blood urea nitrogen >25 mg/dL	2.3 (1.4-3.7)	<0.001
No beta-blocker therapy	2.2 (1.4-3.4)	0.001

***Compared with patients who never experienced appropriate ICD therapy.**

Moss AJ et al. *Circulation* 2004;110:3760

These findings suggest that the extent and severity of the underlying myocardial disease process that provides the substrate for electrical instability also influences subsequent outcome. In this study, 80% of patients were alive 1 year after receiving appropriate therapy,(38) although it can not be concluded that all therapies were lifesaving as many VT episodes would have terminated spontaneously.

Electrical Storm and ICD Emergencies

Electrical storm is most commonly defined in the literature as 2 or more episodes of VT/VF within a 24-h period, usually requiring electrical cardioversion or defibrillation. An ICD emergency occurs when the patient receives multiple shocks, either appropriately or inappropriately. Electrical storm is an ICD emergency, but not all ICD emergencies are due to electrical storm. A list of ICD emergencies is illustrated below.

ICD Emergencies

Appropriate shocks

- Frequent or recurrent VF or VT (**Electrical Storm**)
- Failure to terminate VF or VT reliably

Inappropriate shocks

- Nonsustained VT
- Proarrhytmia from the device
- Supraventricular arrhythmias: atrial fibrillation is most common
- Artifactual:
    - T wave oversensing
    - Lead failure
    - Electromagnetic Interference

Approximately 10% of ICD patients will suffer electrical storm.(39) The majority of storm cases occur late after implant (6-12 months), therefore is not related to surgical factors. In two series, the mean number of events was 5 and 17.(39, 40) Patients who suffer from storm are at increased risk of subsequent nonarrhythmic death, which is not surprising since ICD therapies have shown to adversely predict prognosis as discussed above.

Electrical storm can be the first episode of appropriate ICD therapy, suggesting a period of electrical instability. Precipitating factor can only be identified in only 26% of patients; may include myocardial ischemia, electrolyte disturbances, CHF exacerbation, drug proarrhythmia, and atrial fibrillation. Impaired baroreflex sensitivity has also been demonstrated.(39)

Management of ICD emergencies requires that the device be interrogated, so the etiology of the shocks can be determined. In the emergency setting, it is important to remember that a

magnet placed over the ICD will disable therapies. This would be especially helpful in someone getting shocks for artifactual reasons, such as T wave oversensing. After the interrogation, the management is directed towards treating the specific reason for the shocks. For example, patients with inappropriate shocks for atrial fibrillation can be treated with antiarrhythmic drug therapy.

For electrical storm, one study demonstrated oral amiodarone combined with sympathetic blockade (mainly with beta-blockers) to be superior than ACLS guided therapy.(41) One limitation is that this study preceded the incorporation of intravenous amiodarone into the ACLS guidelines. Since then, intravenous amiodarone have been shown to be superior to placebo and lidocaine for shock resistant VF in out-of-hospital cardiac arrest.(42, 43) The data for electrical storm in ICD patients is unfortunately scant, but most authors extrapolate from the aforementioned studies and consider the combination of beta-blockers with intravenous amiodarone as the best option. Specific conditions causing electrical storm should be considered and treated. Examples of some of these conditions include:

- •Ischemia: emergent revascularization
- •Post CABG: r/o surgical problems
- •Torsade de pointes: exclude drug-induced, intravenous magnesium and overdrive pacing
- •Brugada syndrome: quinidine
- •Digoxin toxicity: digibind

Deep sedation and ventilatory support can stabilize refractory patients. Ablative therapy is an option in selected cases of electrical storm after myocardial infarction triggered by premature ventricular beats, or for sustained monomorphic VT.(44) Destination therapy, such as cardiac transplantation, should be considered if available and the patient is a candidate. Finally, turning off ICD is an option to consider if believed to be prolonging patient suffering, but keeping in mind that this would be considered withdrawal of care.

Prevention of Shocks

ICD have shown to be effective therapy for SCD, nevertheless shocks can be painful and create great anxiety. Furthermore, they may result in hospitalizations and early battery depletion. In fact, a large proportion of patients with ICDs receive concomitant antiarrhythmic drug therapy. Therefore, strategies to prevent shocks have been studied. Smart ICD programming, as well as drug therapy, have shown to prevent painful shocks.

Of the drugs, beta-blockers make a logical choice since this drug has shown to prolong survival in patients with impaired LVEF, as is the case with most patients with ICDs. One study showed that sotalol, a drug that combines class III antiarrhythmic properties with a beta-blocker, reduced appropriate shocks by 44%.(45) The main weakness of this study was that sotalol was compared to placebo and not to a conventional beta-blocker. A subsequent study did not find difference between sotalol and metoprolol, suggesting that beta-blockers are just as efficacious as sotalol preventing therapies for ventricular arrhythmias.(46)

Recently, the results of the Shock Inhibition Evaluation with Azimilide (SHIELD) trial were published. They demonstrated that therapy with Azimilide, a new class III antiarrhythmic drug, at doses of 75mg and 125 mg reduced the need for appropriate therapies in patients with ICDs by 57% and 47% respectively. Reduction in all-cause shocks was 28% and 17% respectively, but this difference was not statistically significant. The SHIELD study is the only randomized trial that evaluated prophylactic antiarrhythmic drug therapy in patients with ICDs, and at present no drug is FDA-approved for this purpose. The role of prophylactic amiodarone therapy is currently under investigation.

Programming the device with antitachycardia pacing has shown to prevent shocks, as it has shown to terminate over 80% of slow ventricular tachycardias. Recently, in the PainFree Rx II trial it was demonstrated that a simple empirical algorithm can terminate 73% of fast VT episodes (over 200 bpm), and 27% of all ventricular arrhythmias which would have otherwise required shocks.(47) This algorithm was safe, and did not result in proarrhythmia.

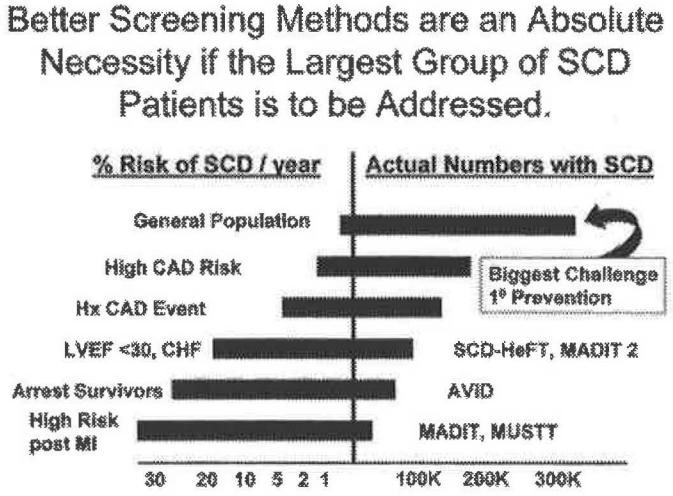
Psychological Response to ICD

Psychological states and cardiac arrhythmias are closely related. For example, after the terrorist attacks to the World Trade Center, patients with ICDs experienced a 2.8 fold increase in ventricular arrhythmias, even if they lived remotely from New York City.(48) Perhaps, therapies to block exaggerated response to stressors might prevent arrhythmias in ICD patients. This concept must be investigated further.

Psychological response is variable, but in general patients who receive multiple shocks report reductions in their physical function and mental well-being.(49) Anxiety disorders, including panic disorder and agoraphobia, are reported in 16% of patients, with a higher incidence in those who receive shocks.(50) Physicians must have understanding of these possibilities to pursue psychological interventions early.

FINAL THOUGHTS

Although it is clear that ICDs can prevent SCD in populations at high risk, a bigger challenge is to develop strategies to prevent SCD in the population in general, where most of the sudden death occurs (see figure below).(3) Furthermore, national survival from SCD remains low (about 5%), therefore strategies to improve resuscitation outcomes must be developed.(51)



From Josephson, et al. Circulation 2004;109:2685-91.

Even in high-risk populations, it might be necessary in the future to develop strategies for identifying patient in whom the benefit is cost-effective. The rate of health care inflation is not

sustainable, perhaps in the future analysis on cost will be considered during the approval process of medical therapies.

It is expected that the number of ICD implants will continue to grow. This will also create problems such as lack of manpower, increased number of emergencies, need for follow up, and increased number of complications. On the other hand, newer technologies might help resolve some of these issues. For example, as ICDs become more reliable follow-up can done less often and even remotely via the Internet.

There is presently great interest in stem cell transplantation in patients with structural heart disease. A possible problem is the potential arrhythmogenicity of these cells because of their inability or reduced ability to transmit current to the surrounding native cells.(52) This may facilitate the development of arrhythmias based on reentry or abnormal automaticity. The arrhythmogenicity may vary according to the type of cell used for transplantation. Whether these patients will need ICDs for arrhythmia protection after stem cell transplantation remains to be determined.

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