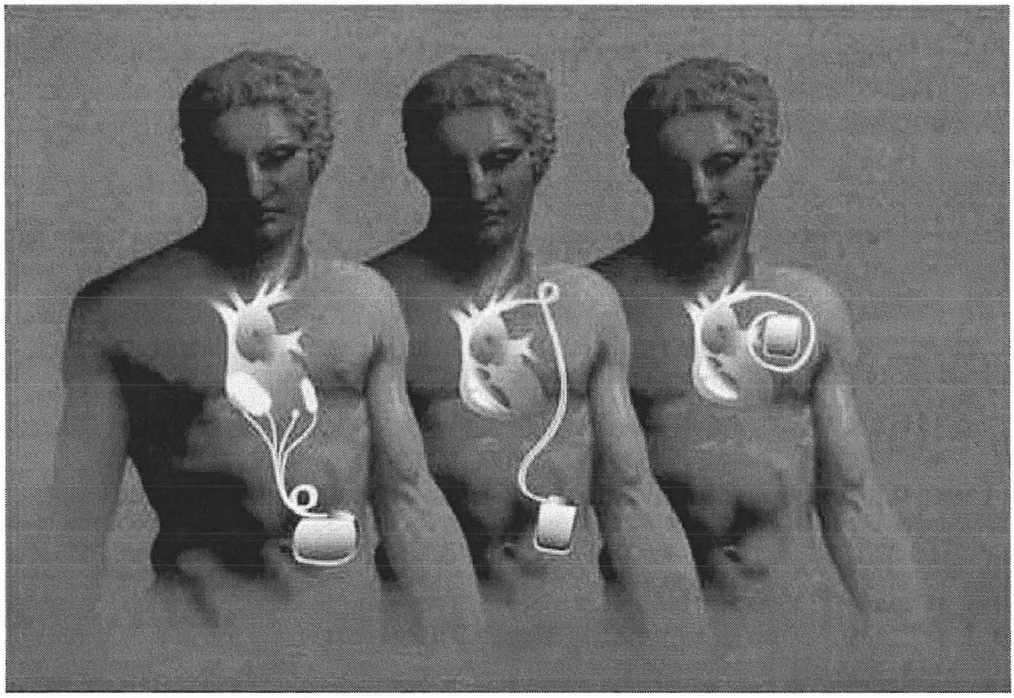
The Primary Prevention of Sudden Cardiac Death



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James D. Daniels, MD
Assistant Professor of Medicine
Division of Cardiology, EP Section
Director, Pacemaker and ICD Clinic, University Hospital

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Glossary of Abbreviations

AF – Atrial fibrillation
AVID – Antiarrythmics Versus Implantable Defibrillator Trial
BiV – Biventricular
CABG-Patch – Coronary Artery Bypass Graft Patch Trial
CASH – Cardiac Arrest Study Hamburg
CHB – Complete heart block
CIDS – Canadian Implantable Defibrillator Study
DEFINITE – Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation Trial
DINAMIT – Defibrillator in Acute Myocardial Infarction Trial
ECG – Electrocardiogram
EF – Ejection Fraction
EGM – Electrogram
ESRD – End-stage renal disease
FVT – Fast ventricular tachycardia
ICD – Implantable Cardioverter-Defibrillator
LBBB – Left bundle branch block
MADIT(-2) – Multicenter Automatic Defibrillator Trial (– 2)
MMVT – Monomorphic ventricular tachycardia
MUSTT – Multicenter Unsustained Tachycardia Trial
PMVT – Polymorphic ventricular tachycardia
RBBB – Right bundle branch block
SB – Sinus bradycardia
SCD – Sudden cardiac death
SCD-HeFT – Sudden Cardiac Death in Heart Failure Trial
ST – Sinus tachycardia
VT – Ventricular tachycardia
VF – Ventricular fibrillation

Introduction

Sudden cardiac death (SCD) is a significant cause of mortality in the United States. In 1999 there were approximately 760,000 cardiac deaths, of which 450,000 were sudden deaths.[1] Of those sudden deaths, 47% occurred out of hospital, and another 16.5% were occurred in an ED or were dead on arrival. Left ventricular systolic dysfunction resulting in heart failure is known to be a strong risk factor for sudden death. In recent years, several large, multicenter, randomized trials have demonstrated the efficacy of the implantable cardioverter-defibrillator (ICD) for the primary and secondary prevention of SCD in susceptible individuals.[2-9] Since the publication of these trials, ICD use has increased exponentially. However, certain subgroups of patients who meet guidelines for ICD implantation for primary prevention have not been well-studied, and the efficacy of the ICD in these patients is unclear. Furthermore, some trials of ICD therapy did not show a reduction in all-cause mortality in patients who are nonetheless at high risk for sudden death.[10,11] Other alternative devices in addition to the transvenous ICD system are available to treat sudden death[12], and future versions of the implantable defibrillator will be smaller and possibly completely intravascular, potentially reducing infection risk.[13]

Randomized Controlled Trials of ICD Therapy

Secondary Prevention (Table 1)

The first randomized trials of ICD therapy were initiated in the late 1980s, and the results were published in the early 1990s. The highest risk subgroub was known to be those patients who had survived sudden death, so the first randomized trials were undertaken in that patient population. The first of these so-called secondary prevention trials was the Antiarrhythmics Versus Implantable Defibrillators trial which compared treatment with antiarrhythmic medications (primarily amiodarone) to implantation of an ICD in patients who had been resuscitated from a ventricular fibrillation (VF) arrest or who underwent cardioversion from sustained ventricular tachycardia. (ref) After a mean follow up of 18 months, the mortality rates were 15.8% in the ICD group and 24% in the antiarrhythmic drug (AAD) arm. The survival rates in the ICD arm versus the AAD arm were were 89.3% vs. 82.3%, 81.6 vs. 74.7%, and 76.4% vs. 64.1% at 1, 2, and 3 years of follow up, respectively. Of note, the defibrillator group had a higher percentage of patients taking beta-blockers compared to the AAD group (42.3% vs. 16.5%).

Two other large randomized trials of secondary prevention, the Canadian Implantable Defibrillator Study (CIDS) and the Cardiac Arrest Study Hamburg (CASH), also randomized patients who survived cardiac arrest to ICD versus antiarrhythmic

medications. The CASH study initially randomized survivors of cardiac arrest (86% VF) to ICD or one of three AADs- amiodarone, propafenone or metoprolol. Enrollment in the propafenone group was discontinued after an interim analysis revealed a 61% increase in mortality in patients randomized to that group. There was a 23% nonsignificant reduction in all-cause mortality in the ICD group compared to the metoprolol/amiodarone group. The survival was very similar among patients randomized to amiodarone when compared with those randomized to amiodarone. Interestingly, this trial only enrolled a total of 298 patients (after excluding those patients who were randomized to propafenone) over an eleven-year period from 1987 to 1998. The CIDS trial enrolled 659 patients with documented VF, cardiac arrest requiring defibrillation, symptomatic sustained VT, or other syncope with inducible ventricular arrhythmias. Patients were randomized to receive amiodarone or an ICD. The primary endpoint was all-cause mortality. There was a nonsignificant reduction in mortality from 10.2% per year in the amiodarone group to 8.3% per year in the ICD group (P=0.142).

Shortly after the publication of the CIDS trial, the primary investigators for the AVID, CASH, and CIDS trials published a meta-analysis of the data accumulated in the 1866 patients enrolled in those three trials. After pooling the primary data from the three trials, the hazard ratio for all-cause mortality was 0.72 (P= 0.0006) for the ICD group compared to the amiodarone group.[17] The mortality benefit was most prominent in patients with an EF<35%, and was not apparent in patients with an EF >35% when these subgroups were analyzed using the pooled data. The secondary prevention trials are summarized in Table 1.

Trial	Patients	Trial design	All-cause mortality
AVID	1016	EF<40% ICD or optimal drug therapy (amiodarone/sotalol)	Overall survival: 75.4% vs. 64.1%, *p*=<0.02 31% reduction in death at 3 yrs with ICD
CIDS	659	EF<40% ICD or amiodarone	20% reduction in all cause mortality (3 yrs) with ICD (*p*=ns vs. amiodarone)
CASH	288	ICD, amiodarone, metoprolol or propafenone	23% reduction all-cause mortality (9 yrs) with ICD (*p*=ns vs. drug treatment)

Table 1. Summary of secondary prevention ICD trials

Primary Prevention (Table 2)

Another group of patients that were known to have a higher risk of sudden death were those patients with nonsustained ventricular tachycardia who had a myocardial infarction (MI) and left ventricular dysfunction. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) was designed to assess the efficacy of ICD therapy in this group of patients.[5] Patients in this trial were required to have had a MI at least 3 weeks prior to enrollment, NYHA class 1-3 congestive heart failure, and left ventricular ejection fraction (LVEF) $\leq$ 35%. Patients then underwent electrophysiology study (EPS), and if sustained VF or VT could be reproducibly induced and not suppressed by procainamide, they were then randomized to ICD or usual care. A total of 196 patients were enrolled – 95 patients underwent ICD implant, and 101 were randomized to the medical therapy group. At the start of the trial, only transthoracic (ie, requiring a thoracotomy) ICD systems were FDA approved, but during the trial, transvenous systems were approved. Fifty of the ICD patients underwent ICD implant with a transvenous system and 45 with a transthoracic system. The primary endpoint was all-cause mortality. After an average follow up of 27 months, there were 15 deaths in the ICD group and 39 in the conventional therapy group resulting in a hazard ratio of 0.46 (0.26 to 0.82) in the ICD group for the primary endpoint.

Three years after the publication of the MADIT trial, the Multicenter Unsustained Tachycardia Trial (MUSTT) was published.[8] The enrollment criteria for this trial were similar to the MADIT trial in that patients with ischemic cardiomyopathy with nonsustained VT were enrolled. Unlike MADIT, the MUSTT trial required the LVEF to be $\leq$40%. All patients underwent an electrophysiology study, and if sustained ventricular arrhythmias were induced, the patients were then randomized to electrophysiologically-guided therapy versus usual medical therapy. Those patients who were randomized to EP-guided therapy, the electrophysiology testing was repeated in the presence of 1-3 antiarrhythmic medications. If one or more AADs were unsuccessful in suppressing the ventricular arrhythmias, then an ICD could be implanted. A total of 704 patients were randomized, 351 of which were assigned to receive EP-guided therapy. The Kaplan-Meier estimates at five years showed a 7% absolute risk reduction in the primary endpoint of cardiac arrest or death from arrhythmia for the group who received EP-guided therapy (relative risk 0.73, 95 percent CI 0.53 to 0.99).

Because of the fairly stringent enrollment criteria and requirement for EP study in the MUSTT and MADIT trials, the MADIT investigators sought to assess ICD therapy using a simpler, more clinically relevant criteria, namely LVEF. The MADIT-2 trial enrolled 1232 patients with a prior MI at least 1 month prior to enrollment, NYHA class 1-3 congestive heart failure and LVEF $\leq$ 30%.[6] Patients were randomized in a 3:2 manner to ICD therapy or conventional medical therapy. The primary endpoint was again all-

cause mortality. Interestingly, the mean time from most recent MI to enrollment in this study was 81 ± 78 months.[14] During an average follow up of 20 months, there was an absolute risk reduction of 5.6% in the primary endpoint for ICD therapy versus usual care (14.2% vs 19.8%, HR 0.69, 95% CI 0.51 to 0.93, P=0.016). The survival curves began to separate at about 9 months and continued to separate thereafter.[6] Furthermore, the risk of death increased as time from the most recent MI increase, whereas this was not the case in the ICD group.[14] Recently, these same investigators published the 8-year follow up data for the MADIT-2 trial (Figure 1). The risk of all-cause mortality after 8 years was 49% for those treated with an ICD and 62% among those not treated with an ICD (per protocol analysis). When the treatment groups were analyzed on an intention-to-treat basis, the hazard ratio for the risk of death was 0.77 for treatment with an ICD.[15]

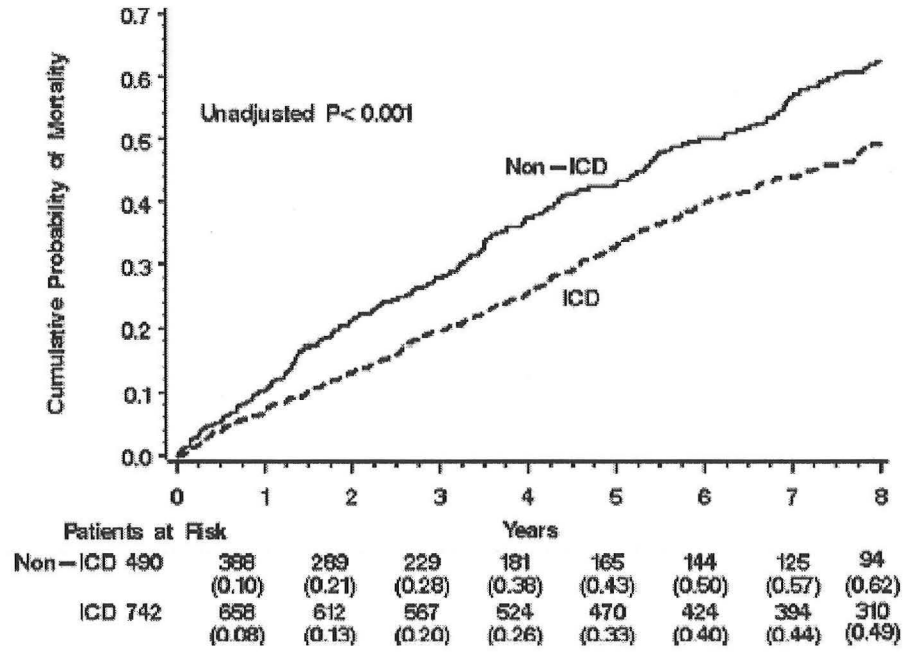


Figure 1. MADIT-II trial 8-year follow up.
Kaplan-Meier estimates of the cumulative probability of all-cause mortality in ICD and non-ICD patients. All enrolled patients are included at time 0 by treatment allocation, and follow-up is censored on change in treatment arm after enrollment.[15]

While MUSTT and the MADIT trials showed the benefit of ICD therapy for the primary prevention of SCD in patients with ischemic cardiomyopathy, whether or not ICDs are useful in patients with nonischemic cardiomyopathy was as yet not known. The first trial to attempt to answer this question was the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial.[9] This trial randomized a total of 458 patients with nonischemic cardiomyopathy with LVEF ≤ 35% and NYHA Class 1-3 heart failure symptoms to usual medical therapy or ICD plus usual medical therapy. After a mean of 29 months of follow up, there was a trend towards a reduction in all-

cause mortality for ICD therapy (hazard ratio 0.65, 95 percent confidence interval 0.40 to 1.06, P=0.08) compared to the medical therapy arm.

In 2005, the Sudden Cardiac Death in Heart Failure Trial was published, and proved that amiodarone was not as effective as an ICD in preventing sudden death.[7] This trial enrolled 2521 patients with LVEF≤ 35%, and NYHA class 2 or 3 heart failure to conventional medical therapy plus placebo, conventional medical therapy plus amiodarone or conventional medical therapy plus ICD implantation. The primary endpoint, like the other primary prevention trials, was all-cause mortality. After a median follow up of 45 months, the hazard ratio for ICD therapy was 0.77 (P=0.006) compared to the placebo group and the hazard ratio for the amiodarone group was 1.06 (P=0.53). At 5 years, the absolute risk reduction in all cause mortality in the ICD group was 7.2% (Figure 2). An interesting finding in the SCD-HeFT trial was that 32% of patients in the amiodarone group discontinued the drug while 22% of patients discontinued the

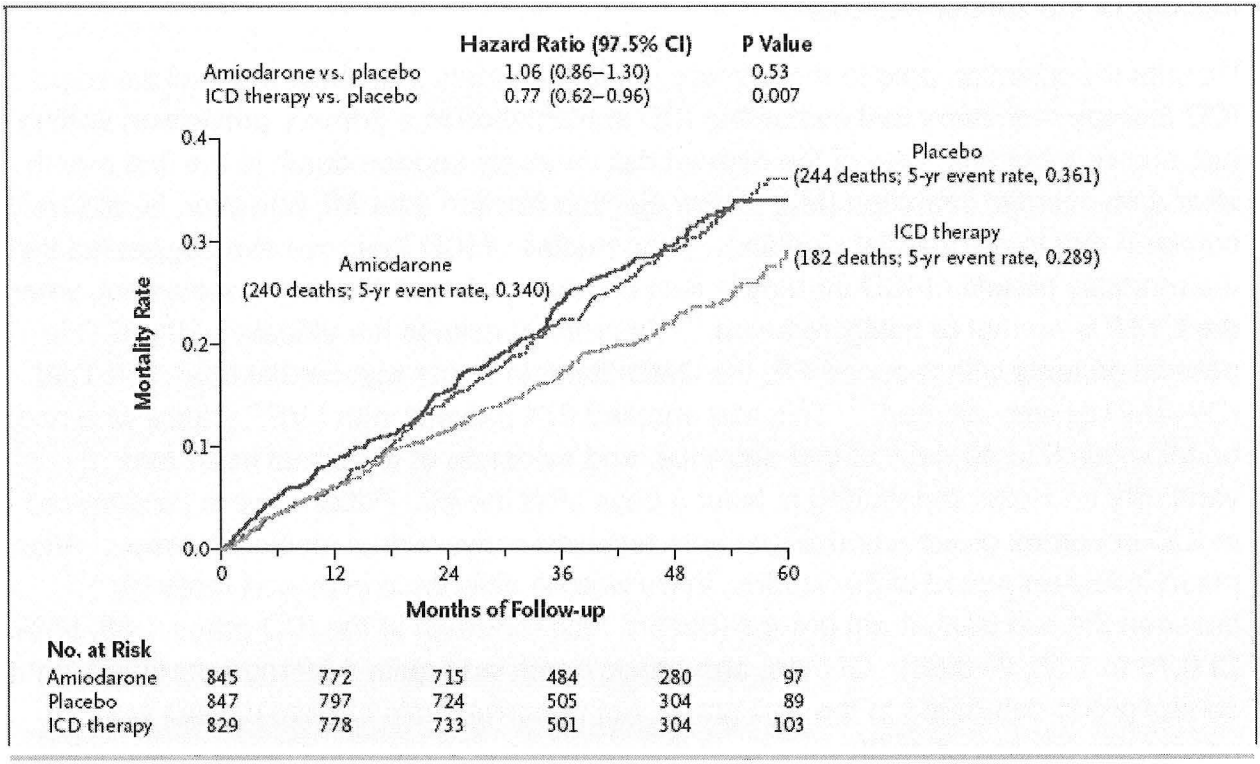


Figure 2. Kaplan-Meier survival curves from the SCD-HeFT trial. ICD therapy was associated with a hazard ratio of 0.77 for all cause mortality compared to placebo

placebo. Despite the known multitude of potential side effects of amiodarone therapy, the only significant complications of amiodarone therapy compared to the placebo arm were increased tremor in 4% of patients, and increased hypothyroidism in 6% of patients.[7]

The SCD-HeFT trial is the only primary prevention trial to enroll patients with either ischemic or nonischemic cardiomyopathy. Prespecified subgroubs in this trial included both the cause of the cardiomyopathy and the severity of CHF. Those patients with NYHA class II CHF appeared to derive a benefit from ICD therapy whereas the patients with class III CHF had a similar risk of death compared to placebo. Class II patients in the amiodarone group had similar survival curves to the placebo group while Class III patient had a higher risk of death over the follow up period than the placebo group suggesting that treatment with amiodarone may be harmful in this group of patients. For patients with ischemic cardiomyopathy, ICD therapy was associated with a hazard ratio of 0.79 (97.5% CI 0.60 to 1.04, P=0.05) compared to placebo while the amiodarone group derived no benefit compared to placebo (HR 1.05, 97.5% CI 0.81-1.36, P=0.66). For patients with nonischemic cardiomyopathy, ICD therapy resulted in a hazard ratio of 0.73 (97.5% CI 0.50 to 1.07, P= 0.06). Therefore, patients with worse CHF symptoms appeared to derive less benefit from ICD therapy and possibly harm from amiodarone, whereas ICD therapy appeared to be beneficial regardless of the etiology of the cardiomyopathy.

Despite the attention paid to the primary prevention trials that show a beneficial effect of ICD therapy, not every trial evaluating ICD implantation in a primary prevention setting has shown a benefit. One of the highest risk times for sudden death is the first month after a myocardial infarction (MI). A low ejection fraction after MI, however, is relatively common due to myocardial stunning. Prior studies of ICD therapy have suggested that the mortality benefit of ICD therapy is less pronounced, and possibly nonexistent, when the LVEF is normal or mildly reduced.[2-4] In order to assess the efficacy of the ICD in post-MI patients with reduced EF, the Defibrillator in Acute Myocardial Infarction Trial (DINAMITE) was initiated.[11] This trial enrolled 674 patients with LVEF $\leq$ 35% who had an MI within 6 to 40 days of trial entrance, and evidence of abnormal heart rate variability on Holter monitoring at least 3 days after the MI. Patients were randomized to ICD or control groups, and all patients received conventional medical therapy. After a mean follow-up period of 30 months, there was no difference in overall mortality between the two treatement groups (hazard ratio for death in the ICD group 1.08, 95% CI 0.76 to 1.55, P=0.66). Of note, arrhythmic death was quite a bit more frequent in the control group compared to the ICD group, but nonarrhythmic cardiac causes and noncardiac causes of death were more frequent in the ICD group (Table). According to the authors, this increase in death was not related to the procedure or the device, and could not be readily explained. It is possible that the ICD prevented an arrhythmic death and simply converted the mode of death to a nonarrhythmic one.[11] Based on the results of this trial, ICD implantation in the first 40 days after acute myocardial infarction is contraindicated.[16]

The Coronary Artery Bypass Graft (CABG) Patch trial enrolled patients undergoing coronary artery bypass grafting with a positive signal-averaged ECG (SAECG) and with an EF $\leq$ 35%.[10] An epicardial ICD system was implanted at the time of CABG in those patients randomized to ICD therapy. After an average follow up of 32 months, the hazard ratio for all-cause mortality, the study's primary endpoint, was 1.07 (P=0.64). The authors attempted to explain the discrepant results of their study compared to the MADIT and AVID studies (the only two ICD studies published at that time). The obvious difference was the inducibility of ventricular arrhythmias required by those studies for inclusion versus the CABG-Patch trial which required a positive SAECG. However, subsequent primary prevention trials did not have this requirement, as noted above, and the benefit of ICD therapy was still present. The authors also suggested that there was significantly higher beta-blocker use in the ICD arm of the MADIT trial (27% vs 8%) and this difference contributed to the mortality benefit seen in the MADIT trial. The overall beta-blocker use was quite low in MADIT, and, once again, this difference in beta-blocker use between trial arms was not present in subsequent trials that showed a benefit for ICD therapy.[5-9] The most plausible explanation put forth by the CABG-Patch authors is that the complete revascularization achieved in both groups resulted in a substantial mortality benefit that that rendered ICD therapy unhelpful, and possibly deleterious as there were more postoperative complications in the group that received an ICD.[10]

Trial	Year	Patients (n)	LVEF	Additional Study Features	Hazard Ratio*	95% CI	p
MADIT I	1996	196	$\leq$ 35%	NSVT and EP+	0.46	(0.26-0.82)	p=0.009
MADIT II	2002	1232	$\leq$ 30%	Prior MI	0.69	(0.51-0.93)	p=0.016
CABG-Patch	1997	900	$\leq$ 36%	+SAECG and CABG	1.07	(0.81-1.42)	p=0.64
DEFINITE	2004	485	$\leq$ 35%	NICM, PVCs or NSVT	0.65	(0.40-1.06)	p=0.08
DINAMIT	2004	674	$\leq$ 35%	6-40 days post-MI and Impaired HRV	1.08	(0.76-1.55)	p=0.66
SCD-HeFT	2006	1676	$\leq$ 35%	Prior MI of NICM	0.77	(0.62-0.96)	p=0.007

Table 2. Summary of primary prevention ICD trials

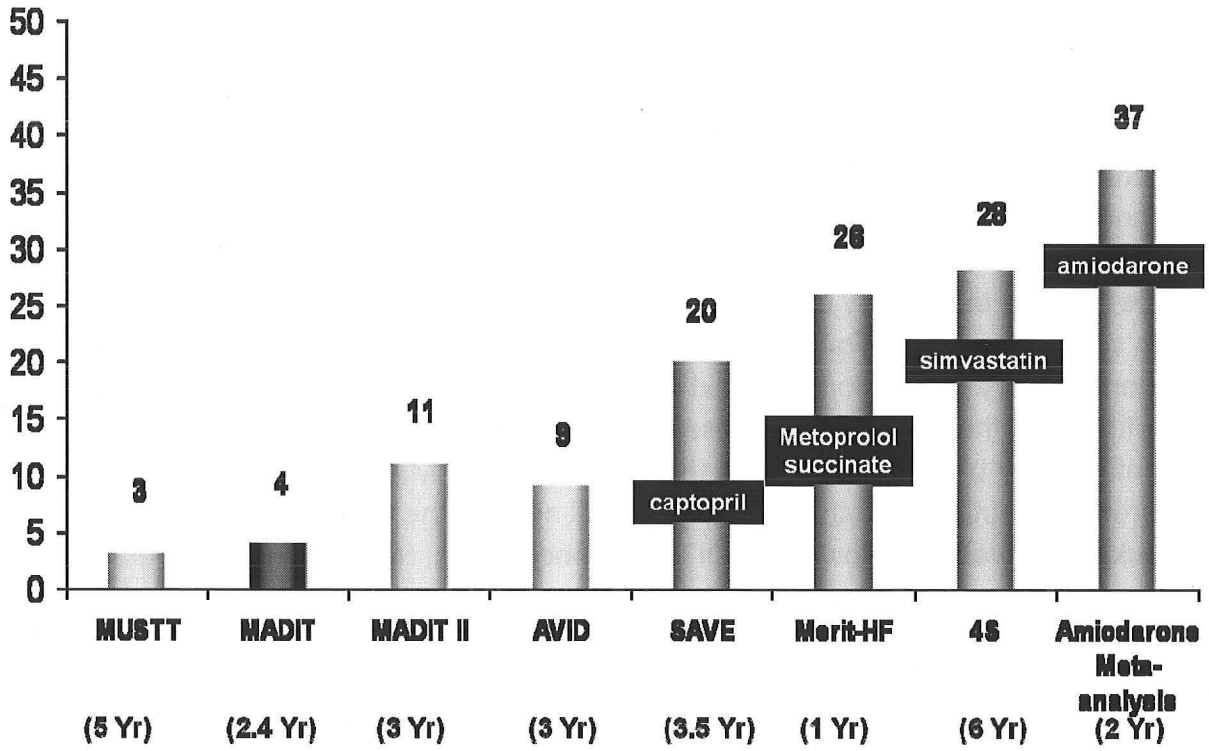


Figure 4. Number needed to treat from various trials of ICDs and medical therapy.

Medical Therapy (Antiarrhythmics)

For completeness, medical therapy with antiarrhythmic medications should be mentioned. As noted above, the CASH trial initially randomized some patients to a propafenone arm, but this arm was removed from the trial due to excess mortality.[4] The Cardiac Arrhythmia Suppression Trial (CAST) enrolled 3549 patients with myocardial infarction and left ventricular systolic dysfunction and randomized them to treatment with encainide, flecainide, moricizine or placebo. At 1 year of follow up, the placebo group had a 95% survival rate and the drug-treated patients had a 90% survival rate (P=0.0006), so the trial was stopped. Based on these data, Class 1 antiarrhythmics do not improve survival and may increase mortality in these patients and should not be used.[25]As noted above, several of the primary and secondary prevention trials contained separate trial arms comparing amiodarone to ICD therapy. Specifically, the SCD-HeFT trial randomized patients to amiodarone versus ICD therapy, and the ICD group had a reduced mortality rate compared to the amiodarone group. In patients with more advanced heart failure, there was a suggestion of harm in the group randomized to amiodarone compared the placebo group.[7] In addition, nearly 95% of patients in the antiarrhythmic drug arm were treated with amiodarone, and the ICD arm had a higher survival rate compared to the AAD arm, as noted above.[2] One smaller randomized trial[26] published prior to SCD-HeFT showed no difference in patients with nonischemic

cardiomyopathy randomized to amiodarone treatment versus ICD. This trial was limited by the smaller numbers of patients (103 total patients), and the fact that 15% of patients were classified as NYHA class 1, a group that has not been directly studied with regard to ICD therapy in nonischemic cardiomyopathy.

Complications of ICD implantation

When considering the efficacy of any particular therapy, it is important to consider the adverse effects of that therapy. With an invasive procedure such as ICD implantation, the adverse effects are largely related to procedural complications, but also include long-term complications. Procedural complications of ICD implantation include hematoma, pocket infection, pneumothorax, lead dislodgement, cardiac perforation/tamponade, and death. Late complications include lead fracture, insulation breach, device-related endocarditis, and an increase in heart failure admissions due to RV pacing.

The complications recorded in all of the primary and secondary prevention trials discussed above were compiled in a systematic review published in 2010.[18] In addition, the authors also analyzed complications that occurred in several trials of cardiac resynchronization therapy. The authors found that in nonthoracotomy implantations, which is by far the most common method of ICD implantation today, the procedural mortality rate was 0.2% in-hospital and 0.6% at 30 days. The rate of pneumothorax was 0.9%, and the rate of hematoma was 2.2%. The rate of lead dislodgement was not reported in several trials, but was found to be 1.8% in the three trials that reported these events (total of 870 patients). A registry study found a lead dislodgement rate of 0.56% for single chamber ICDs and 0.97% for dual chamber ICDs.[19]

Long term complication rates are not well-defined in most cases. Device malfunction is dependent on the make and model of the device and can vary widely. Each company makes pulse generator and lead performance statistics available on their respective websites.

Importantly, the complication rates in the systematic review likely underestimate the real-world complication rate due to the high level of expertise on the part of the implanting physician, as well as the enrichment of the patient population with healthier patients as is commonly seen in randomized trials. A large registry study[20] and a study of Medicare beneficiaries[21] showed hospital mortality rates of 1.0% and 0.9% respectively. Despite these potential complications, ICD implantation via the transvenous approach is overall a very safe procedure with approximately 5% risk of any complication.

Special Patient Populations

Elderly patients

The efficacy of ICD therapy in reducing SCD and overall mortality in elderly patients is unknown, and studies to date have revealed conflicting results. The incidence of SCD increases with advancing age; concurrently, the elderly population in the United States is growing. The US Census Bureau estimates that by 2030, 20% of the US population will be over 65 years old, and by 2050, 5% will be over 85 years old.

A recent study which reviewed insurance claims originating between 1997-1998 showed that 28% of patients who qualified for ICD implantation were aged >79 years.[26] Despite the fact that many elderly patients qualify for ICD therapy, patients aged 80 and over (octogenarians) comprise a group who are particularly underrepresented in the aforementioned clinical trials of ICD therapy. Several retrospective studies in patients aged between 65 and 80 years have suggested that ICD therapy is safe and efficacious in this age group,[27-34] however very scant data exists for octogenarians in whom the efficacy and use of ICDs is poorly-defined. Although many elderly patients otherwise fulfill criteria for ICD implantation, competing co-morbidities assume prominence in old age and may negate the beneficial effects conferred by ICD therapy. Since many patients who meet standard criteria for an ICD are older than those included in the clinical trials of ICD therapy, its use in these patients requires further definition.

Several retrospective, single-center studies have compared older patients (over 65 or 70 years old depending on the study) to younger patients.[31-34] In general, there was no difference in arrhythmic death in the older compared to the younger patient groups. Two of these studies showed a higher total mortality rate in the older group,[33,34] while two other studies did not.[31,32] ICDs in these retrospective studies were implanted almost exclusively for secondary prevention of SCD, and many of the ICDs involved epicardial systems. A more recent retrospective study in which 30% of ICDs were implanted for primary prevention included 40 patients aged 75 years or older.[28] This study showed a significantly higher total mortality at 5 years for the older patients compared to younger patients, but there was no difference in sudden death, ICD therapies or complications between the groups. Conversely, a propensity-score-matched case-control study involving over 7000 Medicare beneficiaries with an average age of 76 years showed a significant reduction in mortality for the patients who underwent ICD implantation compared to those who did not.[29]

Although octogenarians were not represented in the large randomized trials of ICD efficacy, two of the trials carried out subgroup analysis according to age.[6,7] In MADIT-2, patients aged< 60 and >70 years had a statistically significant reduction in all-cause mortality, however there was no such reduction in those aged 60-70 years.[6] In contrast,

in the SCD-HeFT study, patients aged ≥65 years did not receive a statistically significant benefit from ICD therapy.[7] Furthermore, a meta-analysis of the secondary prevention trials was recently published and showed higher rates of both arrhythmic and nonarrhythmic death in patients older than 75 years of age (252 patients) compared to younger patients. However, this study also showed a significant reduction in overall mortality among patients older than 75 years old who were randomized to ICD therapy.[35]

Only studies have assessed survival benefit from ICD implantation specifically in octogenarian patients.[36,37] The first study showed that the median survival was 4 years after implant for octogenarians compared with 7 years for those aged 60 to 70 years ($p<0.01$). Furthermore, a depressed EF and lower estimated glomerular filtration rate were predictors of mortality in octogenarians.[36] In our study, conducted using data from the Dallas VA ICD clinic, after two years of follow-up, the three age groups (70-74, 75-79, and ≥ 80 years old) had similar rates of death and development of co-morbid illness following ICD implantation.[37]

When faced with the option of implanting an ICD, many physicians may be concerned about the potential development of co-morbid illnesses negating benefit in older patient groups. The results of our study suggest that octogenarians who do not have other severe co-morbid illnesses at the time of ICD implant are unlikely to develop them at a significantly higher rate than patients in the 70-80 year age group.[37] Nonetheless, a detailed and frank discussion with the patient and, ideally, his or her family, regarding expectations, quality of life desires, and risks and benefits of ICD implantation must be conducted prior to proceeding with implantation of an ICD. Many elderly patients will decline ICD therapy once they fully understand the implications of device implantation, and others should not be considered candidates because of other life-limiting comorbidities. Because primary care providers often know the patient the best, they must play a vital role in helping the patient through this sometimes difficult decision.

Patients with renal disease

The efficacy of ICD therapy is patients with renal disease, especially those requiring dialysis, is unclear. In addition to chronic renal disease patients who have congestive heart failure and meet primary prevention guidelines for sudden cardiac death, renal patients, specifically dialysis patients, have an increased risk of sudden death even without evident heart disease.[39] According to the USRDS Report 2011[40], arrhythmias/cardiac arrest accounted for 26.1% of the deaths seen in this patient population between 2007 and 2009, nearly identical to data collected between 1997 and 1999, and 60% of all CVD deaths in these patients (Figure). In addition, patients initiating hemodialysis are at high risk for sudden death, and the risk of death in patients on dialysis has been estimated to be 7% per year. Not only do renal patients have

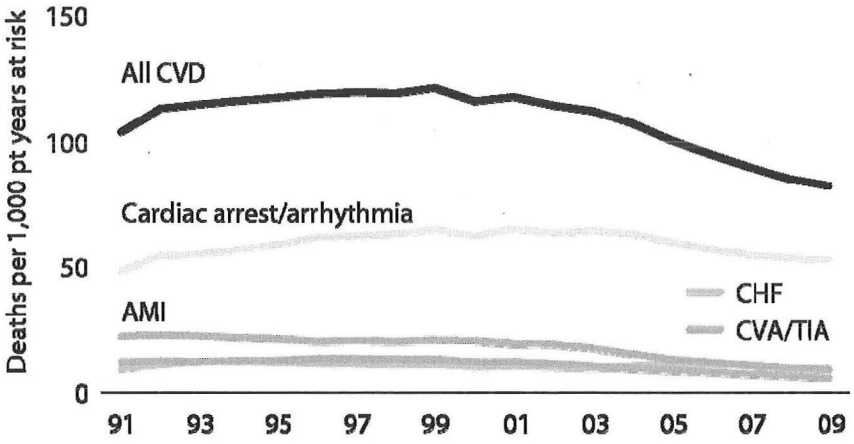
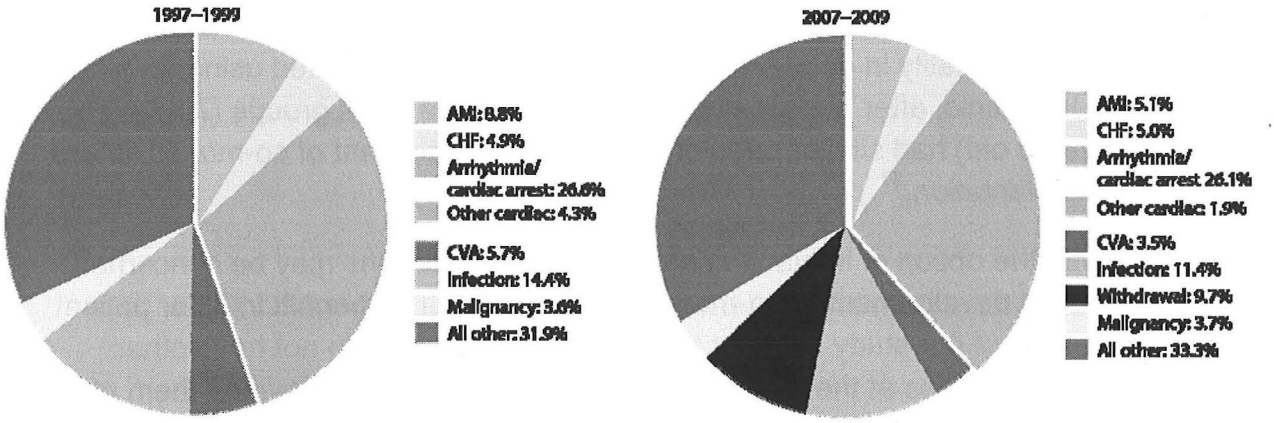


Figure 5. Cardiac arrest in ESRD patients. (USRDS annual report 2011)

Top: Death rates per 1000 patient years among incident dialysis patients from 1991-2009.

Bottom: Mode of death among incident dialysis patients in 1997-1999 and 2007-2009



cardiovascular disease, but many patients with CHF have renal disease. Data from a large registry of heart failure admissions showed that approximately ¼ of patients admitted with decompensated CHF had chronic renal insufficiency.[41] This proportion was identical among those with decompensated systolic heart failure and diastolic heart failure. Several observational studies in patients with ICDs have identified an abnormal estimated glomerular filtration rate (eGFR) as a risk factor for all-cause mortality and appropriate ICD therapy.[42-51] Despite these observations, many of these studies as well as subgroup analyses from major ICD trials have not shown a reduction in mortality in patients with severe renal dysfunction[42-52]. A relatively recent meta-analysis of the observational studies concluded that CKD is associated with increased mortality in patients who receive ICD therapy.[53] It is not clear if this lack of benefit is related to competing comorbidities common in patients with kidney disease that may nullify the ability of the ICD to reduce arrhythmic death, or is simply because these trials are largely retrospective and enroll relatively small numbers of patients.

Furthermore, patients with ESRD appear to be at higher risk for device-related complications. A retrospective, single-center study[54] evaluating 4,856 device (pacemaker and ICD) procedures found that elevated creatinine (≥ 1.5 mg/dL) was

much more common in patients with device infection than in patients without device infection. Other risk factors for infection included congestive heart failure, diabetes, generator changeout, and warfarin therapy. Moderate or severe renal disease defined as an estimated glomerular filtration rate ≤ 60 cc/min/1.73m^2 was the most potent risk factor for infection. Another study[55] using data from the National Cardiovascular Data Registry/ICD registry found that unadjusted mortality was five times higher among patients on dialysis (1.9% vs 0.4%, P<.0001). Multivariable analysis also showed an odds ratio of 1.38 for total in-hospital complications and total complications at 2 days.

Alternative/Future Devices

Subcutaneous ICD

Recently, a subcutaneous ICD (S-ICD) system has been evaluated in humans as an alternative to the transvenous system (Figure 5).[22] The advantage to this type of system lies in the lack of intravascular hardware, thereby negating the risk of pneumothorax at implant and the risk of device-associated endocarditis in the long term. Furthermore, since the leads are not moving with each heartbeat, there is likely less mechanical stress on the lead thereby enhancing lead longevity. Investigators actually performed several small observational studies to confirm device function in humans, and to determine the ideal lead and generator placement that would result in the lowest defibrillation thresholds. In the study that compared a transvenous ICD to the S-ICD showed mean defibrillation threshold of 11.1 ±8.5J for the transvenous ICD versus 36.6 ±19.8J for the S-ICD. A clinical trial recently finished enrolling patients in the US, and the results of this trial are likely still at least a year away. This device has not yet been approved by the FDA for prevention of sudden death, but is currently under review.

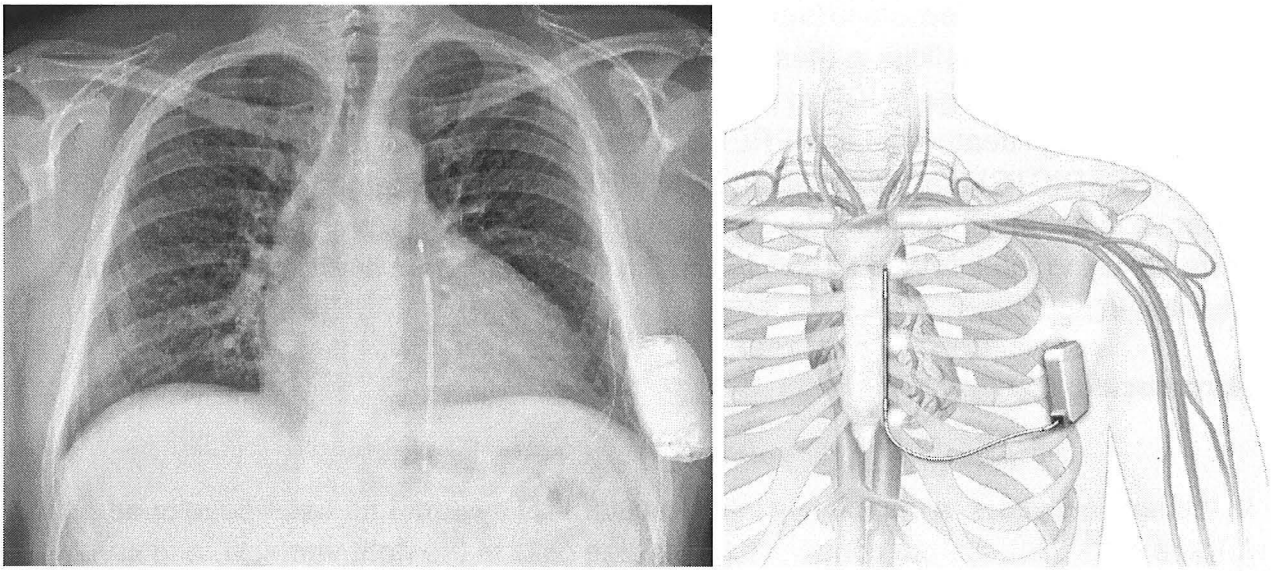
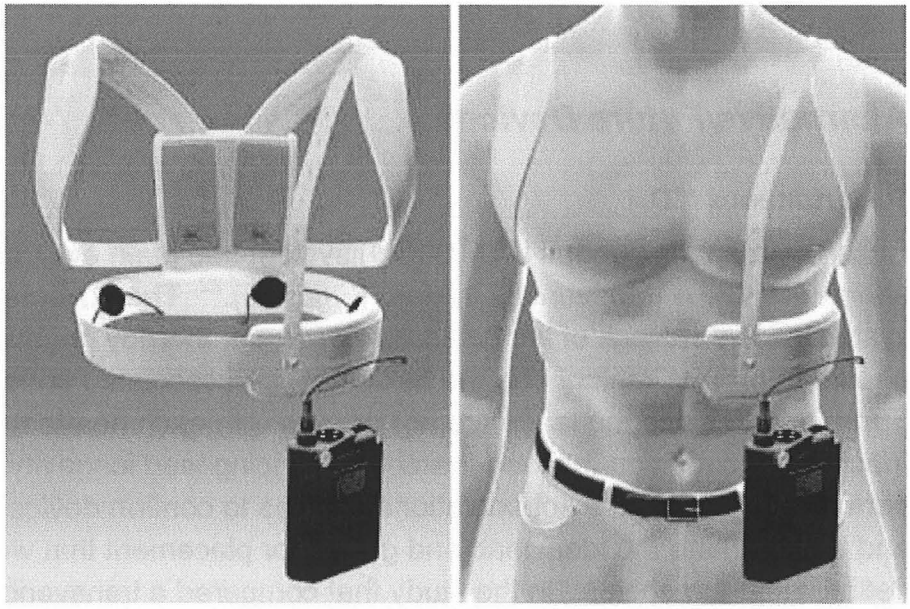


Figure 6. The Subcutaneous ICD (S-ICD).

Wearable defibrillator vest

In 2002, a wearable defibrillator vest (LifeVest, Zoll, Inc.) was approved for use in the United States. Only two clinical trials assessing this technology have thus far been reported. Both trials were published in the same manuscript in 2004.[23] In these trials, a total of 289 patients were prescribed the device. Only 8 appropriate therapies were delivered, 6 of which were successful. There were 6 inappropriate shocks during the 901 patient-months of follow-up (0.67% per month). Six sudden deaths occurred with 5 patients not wearing the device and 1 wearing it incorrectly. Sixty-eight patients stopped wearing the device.

Figure 7. Wearable Defibrillator Vest.



One group of patients where this device may have a role are in those patients with a recent MI and LVEF $\leq$ 35%, ie, those who would have been enrolled in the DINAMIT trial. That group of patients is known to be at risk for sudden death, yet ICD therapy has not been proven beneficial in these patients. In order to determine whether the LifeVest might serve as a bridge to ICD in these patients, the NHLBI-sponsored Vest prevention of Early Sudden death Trial and PREDiction of ICD Therapies Study (VEST/PREDICTS) trial was initiated in July 2008.[24] With a target enrollment of 4500 patients, the study should definitively answer this question. Many physicians are currently using the LifeVest for this indication despite the fact that it's efficacy in this situation in not known.

Intravascular ICD

In the last few years, a completely intravascular ICD system has been developed (Figure 8).[38] This system contains high voltage coils in the right ventricle, and superior

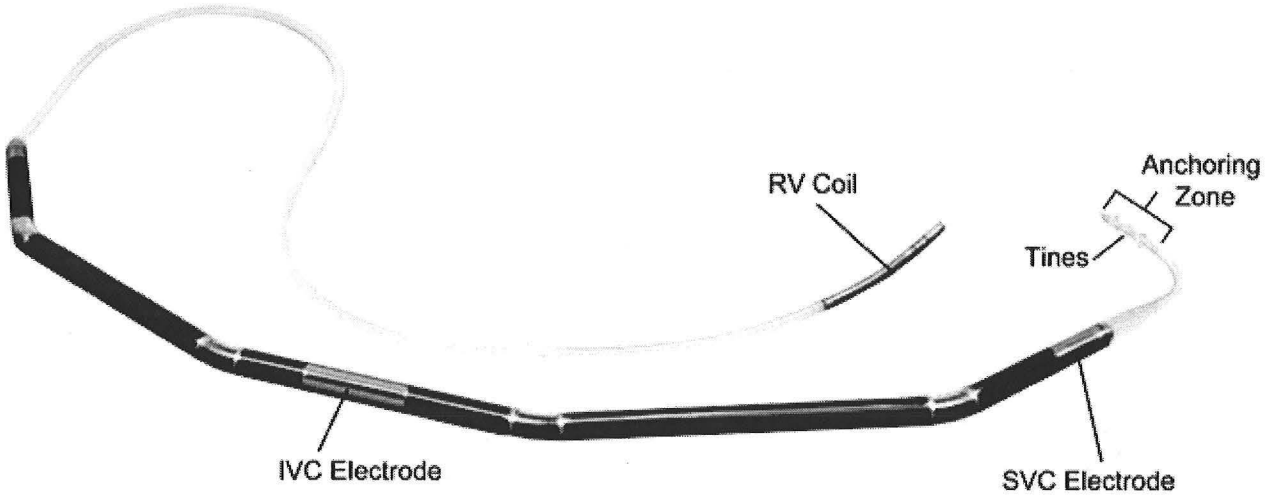
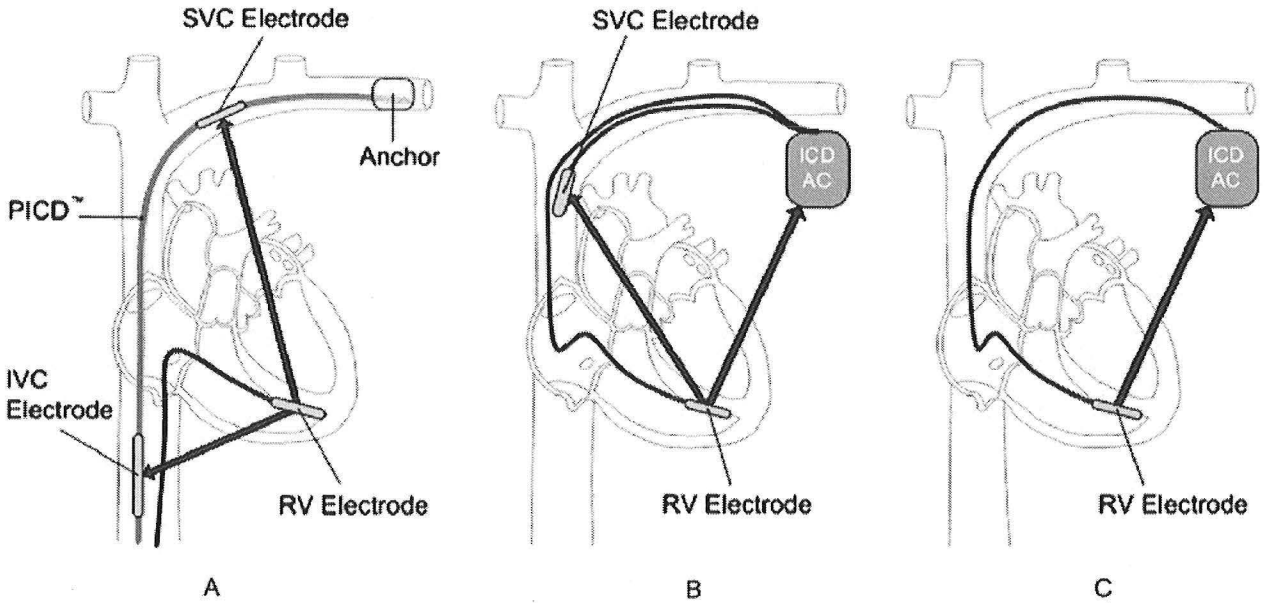


Figure 8. A completely intravascular ICD system.[38]

vena cava, similar to a conventional ICD. However, there is no subcutaneous pulse generator, so the intravascular ICD also has a coil in the inferior vena cava to achieve adequate defibrillation thresholds, which were actually lower than the traditional ICD in one canine study. The advantage to this device is the completely percutaneous insertion procedure and elimination of local infection at the pulse generator site. However, the stability, durability and extractability of this device and well as its function in humans remain to be proven. A human clinical trial is underway.[38]

Figure 9. Defibrillation vectors with intravascular ICD versus conventional ICD.[38]



Conclusions

ICDs have been shown to reduce all-cause mortality and arrhythmic death in patients who survive cardiac arrest (secondary prevention); those with moderate to severe LV dysfunction (EF ≤ 35%) due to coronary artery disease and NYHA class 1 to 3 congestive heart failure symptoms; and those with moderate to severe LV dysfunction (EF ≤ 35%) due to nonischemic cardiomyopathy and NYHA class 2 or 3 congestive heart failure symptoms.

In addition, alternatives to an implantable device exist in the form of AEDs, and wearable defibrillator vests, but these devices rely on patient compliance and/or the presence of a bystander. ICD technology continues to advance with the advent of less invasive and smaller devices which may increase the number of patients who could be candidates for device implantation. However, the efficacy and utility of ICDs in older patients, especially those over the age of 80, and in patients with kidney disease, especially dialysis patients, remains unclear as these patients tend to have competing comorbidities. While it remains imperative to treat appropriate patients with ICD therapy, careful discussion should occur with each patient to clearly elucidate the patient's expectations for quantity and quality of life when considering appropriateness of ICD implantation.

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