Introduction

In 1970, Mirowski et al. published their first experience with the standby automatic defibrillator in animals. Ten years later, the first implantable cardioverter-defibrillator (ICD) was used in 3 patients. In the past 10 years, there has been an exponential growth in our knowledge, and technological evolution of the device has been striking.

In the United States, the incidence of sudden cardiac death is between 300,000 and 400,000 a year. Only 2%–15% of the patients suffering from sudden cardiac death reach the hospital, and half of these early survivors die before discharge. The understanding that sudden cardiac death (SCD) from fatal ventricular arrhythmias is one of the most common causes of death in Indian population, which is facing the epidemic of coronary artery disease (CAD), has increased the awareness as to the use of ICD in our country. Clinicians need to carefully consider and analyze the various studies done in the last decade proving the efficacy of ICD over and above the drug therapy in the management of patients with CAD and severe LV dysfunction.

This poses a major therapeutic challenge. It is however difficult to predict with certainty which particular patients will have fatal arrhythmias and which others will remain clinically stable and free of serious ventricular arrhythmias. If such patients could be identified, then therapy could be targeted to only that selective population which would constitute about 40-60% of all patients with moderate to severe LV dysfunction.

“High Risk Predictors” of SCD are
1. Documentation of nonsustained ventricular tachycardia (NSVT) on holter
2. The presence of ECG abnormalities of depolarization and repolarization using the signal-averaged ECG
3. The presence of microvolt T-wave alternans
4. The presence of abnormal autonomic modulation of cardiac function i.e. abnormally low heart rate variability (HRV)
5. Depressed baroreceptor sensitivity
6. Left ventricular ejection fraction (LVEF)
7. The inducibility of VT or VF on invasive electrophysiological study (EPS)

Although each of these tests is of some prognostic value, they are individually insufficiently accurate for practical clinical purposes, to direct therapy. Hence patients with poor ejection fraction, past history of myocardial infarction & presence of ventricular scar are actually believed to be at high risk of SCD.

However there is no available diagnostic modality by which one can identify the exact population of patient liable to have SCD amongst thousands with these characteristics. This is a serious limitation in our capability to identify patients requiring protection from SCD, as the incidence of sudden death amongst all patients with prior myocardial infarction is relatively low.

Another practical problem is the inability to identify the timing of sudden death from VT/VF. Such events occur suddenly with no clearly identifiable factors which precede SCD in most individuals. However, in known cases of CAD the most important etiologic factors leading to life threatening ventricular arrhythmias are angina, sudden worsening of heart failure and behavioral factors such as stress or exercise are observed to immediately precede sudden death. Improved acute and long term therapies have increased survival for patients with myocardial infarction, hence leading to a relative increase in the number of the patients with chronic coronary disease and LV dysfunction.

Beyond the universal requirement for beta blockers unless absolutely contraindicated, there is however not much room for optimism that antiarrhythmic therapy (AAT’s), at least for the time being, will be even a partial solution to the problem of SCD in susceptible coronary populations like ours. ICD’s are being increasingly used in such patients with previous MI, depressed ventricular function and nonsustained VT inducible by EPS. In addition, ICD has been commonly used as primary prevention in conditions that predispose to SCD, such as long QT syndrome, Brugada syndrome, idiopathic VF, arrhythmogenic right ventricular dysplasia and hypertrophic cardiomyopathy.

ICD

The implanted defibrillator represents an effective, intellectual therapy to prevent death from ventricular arrhythmias. The device does not prevent such arrhythmias but only treats them after they occur. The device is expensive and the follow-up of patients is technically challenging.

The ICD has two components, the pulse generator and the leads. Most of the newer generation of pulse generators weigh less than 100 g and are the size of <60 cc. They are implanted pectorally by electrophysiologists in the electrophysiology laboratory under local anesthesia. The leads are inserted via the subclavian vein into the right ventricle (single-chamber ICD). Additional lead is required in right atrium for dual chamber ICD. Most patients are hospitalized for only 1–2 days.

The device detects ventricular arrhythmia by analyzing the heart rate and duration of the arrhythmia. The rate criterion differentiates a tachycardia from normal rhythm and the duration criterion prevents the detection and treatment of nonsustained tachycardias. All these criterias are programmable. An ICD terminates VT or VF in three ways:

1. Anti tachycardia pacing (overdrive) (Fig. 1)
2. Synchronized shock (cardioversion) (Fig. 2)

All these treatments are programmable. While VF is treated by defibrillation, VT is often treated by anti tachycardia pacing or low-energy cardioversion when anti tachycardia pacing fails. ICD’s can deliver 4–8 successive shocks with maximum shock energies ranging from 25 to 42 J.

Up to 30% of ICD recipients may experience sinus bradycardia or high-degree atroventricular block which requires physiologic pacing. The presence of atrial fibrillation or flutter may also trigger inappropriate ICD intervention because the device may read this supraventricular tachycardia as VT. Hence, dual-chamber ICD has been developed for physiologic pacing and also for better differentiation.
of supraventricular and ventricular tachycardias to avoid spurious shocks. Another recent advance has been the incorporation of ICD and biventricular pacing into a single device to prevent SCD and to improve LV function by resynchronizing left and right ventricular contraction.

Appropriately tested devices have a 99% or greater probability of successfully restoring a normal sinus rhythm in patients with VT or VF. Current devices can be implanted with a less than 1% major morbidity or mortality. Studies in patients with a prior history of cardiac arrest, or sustained ventricular tachycardia i.e. the “secondary prevention” have demonstrated convincingly that the implanted defibrillator is both effective and superior to antiarrhythmic drug therapy in preventing all cause mortality in such patients. Since the majority of SCD occur in patients without a prior history of documented sustained VT or VF, studies have assessed the usefulness of defibrillators as “primary prophylaxis” of SCD.

Analysis of Various Clinical Trials
The Antiarrhythmics Versus Implantable Defibrillators (AVID) trial, which was a secondary prevention trial, enrolled 1016 patients. It compared ICD implantation and drug therapy with amiodarone in the prevention of SCD. All the patients presented with resuscitated VF or symptomatic VT (chest pain, pre syncope or hypotension) and had LV dysfunction (EF<40%). At 3-year follow-up, mortality was reduced by 29% in patients treated with ICD implantation. AVID data also indicate that patients with a relatively good ejection fraction (>0.35) do not have better survival when treated with an ICD as compared with amiodarone therapy. However, ICD implantation was associated with improved survival in patients with lower ejection fraction (0.20–0.34) when compared with AAT’s.

The Canadian Implantable Defibrillator Study (CIDS) was another large, randomized, multicenter secondary prevention trial, comparing ICD therapy with amiodarone. In this trial, 659 patients with unmonitored syncope were randomized into ICD therapy (328 patients) and amiodarone and followed up for a mean period of 3 years. The risk of death in the ICD arm was reduced from 10.2% per year to 8.3% per year, a 19.7% relative risk reduction. However, this relative risk reduction was statistically nonsignificant.
A nonsignificant reduction in the risk of arrhythmic death was also observed, from 4.5% to 3.0%, which is equivalent to a 32.8% relative risk reduction. However, in a presentation at the American Heart Association annual scientific meeting in 2002, long-term follow-up of a subgroup of CIDS patients 11 years after the ICD implantation found that the ICD was associated with a significant decrease in cardiac death compared with amiodarone-treated patients.

Patients with the highest risk of SCD benefit most from ICD therapy. CIDS investigators retrospectively stratified the 659 patients into 4 risk quartiles on the basis of reduced ejection fraction, advanced age, and poor NYHA functional class. In the highest risk quartile, a 50% relative risk reduction in death occurred with ICD therapy when compared with amiodarone, with no benefit from ICD treatment over amiodarone in the 3 lower risk quartiles. The patients who are most likely to benefit from an ICD are those who are 70 years of age and above, those with a left ventricular ejection fraction <0.35, and those in NYHA class III or IV.

In the Cardiac Arrest Study Hamburg (CASH) trial, 228 cardiac arrest survivors were randomized to ICD, amiodarone, metoprolol or propafenone groups. ICD therapy was associated with a 23% reduction (p<0.08) in all-cause mortality as compared with drug therapy, after a mean follow-up period of 57 months.

The above data show that ICD therapy is more effective than AAT’s in cardiac arrest survivors and in patients with hemodynamically unstable ventricular arrhythmias. The meta-analysis of AVID, CIDS, and CASH studies have shown an approximately 20-30% reduction in all cause mortality.

The CABG PATCH study randomized patients undergoing coronary bypass surgery to either an implanted defibrillator or control therapy without the ICD. The inclusion criteria were ejection fraction <35% and a positive signal-averaged ECG. This study failed to show any benefit whatsoever from the implanted defibrillator, but both defibrillator and no defibrillator patients had a low cardiac mortality (5.9% per year), suggesting that surgical revascularization has a very important protective effect against sudden death.

The MADIT I study assessed patients with CAD, poor LV function and asymptomatic nonsustained ventricular tachycardia (NSVT), with inducible VT or VF at electrophysiological study (EPS), not suppressible by AAT’s. This study showed a 54% reduction in mortality in patients implanted with a defibrillator as opposed to those receiving “conventional medical therapy” and hence was the first to document a potential benefit from prophylactic ICD. In the MADIT study, the reduction in sudden cardiac death following ICD therapy occurred mainly in patients with an ejection fraction <0.26. However, the clinically impractical sequence of EP study and need for VT induction, followed by attempted VT/VF suppression with procainamide, that was required for risk stratification, a relatively small total patient number, inadequate therapy with beta blockers and ACE inhibitors were a few drawbacks of this trial. Nevertheless, the results from this study led to FDA approval of implanted defibrillators for the particular subset of patients meeting the inclusion criteria for this study.

The MUSTT study, like the MADIT study, selected patients with coronary artery disease and ejection fraction <40% having either asymptomatic nonsustained VT on holter or inducible VT in EP study. They were randomized to either EPS guided therapy or no AAT’s. The EPS guided arm included either AAT’s to suppress the inducibility of VT or implantation of ICD. The choice between defibrillator versus drug therapy was not randomized. SCD at the end of 5 years was significantly lower in the EPS guided arm (25 vs. 32%, p=0.04) but all cause mortality was not (48 vs. 42%, p=0.06). However, a secondary analysis showed some striking trends. The relative risk of death from all causes in the ICD group compared to the no AAT’s group was 0.45 (95%, CI 0.32-0.63) and compared to EPS guided AAT’s was 0.40 (0.27-0.59). Although this was not strictly a randomized therapy outcome, the study was widely and reasonably interpreted as showing superiority of the ICD to no AAT’s or AAT’s. As a consequence of the MUSTT study most expert bodies stipulating guidelines for the treatment of
ventricular arrhythmias concluded that patients with CAD, ejection fraction <40%, and nonsustained VT if they had inducible ventricular tachycardia at EP study, should preferably be treated with an implanted defibrillator.\textsuperscript{14}

Fig. 3 shows the meta-analysis of various primary and secondary prevention trials resulting in significant reduction in mortality.

The MADIT II study, published in March 2002\textsuperscript{15}, took a simplified approach to the testing of the hypothesis that implanted defibrillators would reduce all cause mortality in high risk populations. The only criteria to identify patients at risk from SCD were the presence of CAD, a prior MI and an ejection fraction of <30%. This study randomized a total of 1232 patients to either the ICD (742 patients) or conventional medical therapy (490 patients). Neither nonsustained VT nor an EPS was required for entry into this study. The patient population in this study was reasonably representative of a potentially very large group of patients with chronic CAD and prior MI. Patients were followed to a common primary endpoint of death from any cause. The defibrillator therapy resulted in an increasing mortality benefit over conventional therapy with a 31% reduction in the risk of death. In absolute terms, this meant a 1%, 6%, and 9% reduction in mortality at 1, 2, and 3 years.

**Conclusion**

The latest data from the MADIT II trial will have a major impact on future ICD therapy. First, it has further clarified the indications for ICD therapy and provided more insight in guiding routine therapy for patients with impaired LV function as defined by a reduced left ventricular ejection fraction. Currently, approximately 300 000 patients each year in the United States are estimated to be eligible for receiving an ICD. Results from MADIT II have indicated that ICD implantation is an effective primary prevention for SCD in post MI patients with poor LV function. These findings will substantially increase the population of patients eligible for implanted devices in the USA and worldwide.

The main barrier to more widespread use of prophylactic implanted defibrillators, at least in the Indian context seems to be the cost of device and resource limitations i.e. the non availability of medical personnel to perform the procedures and follow the patients. For the time being, in all patients with a history of prior MI and ejection fraction of <30%, optimal pharmacological therapy including beta-blockers, ACE inhibitors, aspirin, statins should be given. If revascularization is indicated and feasible, it should be performed. The presence of nonsustained VT on Holter monitoring probably adds to
prognostic significance, although the amount of information contained in this finding is not clear. Performing an EPS for risk stratification is probably required for most such patients. If VT is inducible on EPS then these patients should be given the benefit of implantation of ICD.

The first ICD implantation in India was implanted on April 1995 at Escorts Heart Institute and Research Centre (Fig. 4) and All India Institute of Medical Sciences, New Delhi. The annual ICD implantations in India are increasing every year (Fig 5). Single-chamber ICD is still the most popular choice for cardiologists and patients. Dual-chamber ICDs have been increasingly used in patients with a standard indication for permanent pacing and ICD implantation. The cost of one ICD device, depending upon the model or complexity of function, ranges from Rs 4.5 to 9 lakh in our country. Incorporation of an ICD with biventricular pacing may provide a better clinical outcome than the ICD alone in patients with interventricular conduction delay and congestive heart failure.
References