

Implantable Cardioverter-Defibrillators

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Introduction

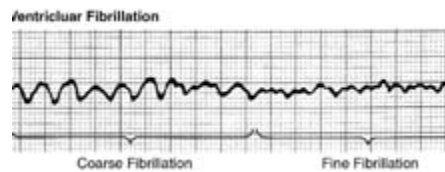
Sudden cardiac arrest (SCA) is the sudden, abrupt loss of heart function generally caused by a rapid, irregular rhythm of the ventricles (ventricular tachycardia [VT] or ventricular fibrillation [VF]). These arrhythmias result in quivering ventricles that cannot pump blood to the body. Loss of consciousness and pulse follow within seconds. In approximately 94-95% of cases, SCA is fatal leading to sudden cardiac death or SCD¹. SCA, an electrical conduction problem, is not the same as a heart attack (myocardial infarction [MI]), which is caused by a blocked vessel leading to loss of blood supply to a portion of the heart muscle.

The implantable cardioverter-defibrillator (ICD) has revolutionized the treatment of patients at risk for sudden cardiac death due to ventricular tachyarrhythmias. Initially introduced in humans in 1980 and approved by the FDA in 1985, the ICD has evolved from a treatment of last resort to a first-line treatment and prophylactic therapy for patients at risk for ventricular tachycardia (VT) or ventricular fibrillation (VF).

Sudden cardiac death (SCD) resulting from fatal ventricular arrhythmias is one of the most common causes of death in the developed world. Patients suffering from a potentially fatal arrhythmia are at risk of death before they even reach medical intervention and out-of-hospital survival rates are as low as 2-15% (¹). Immediate defibrillation treatment is the only remedy for arrhythmic sudden death caused by hemodynamically compromising ventricular tachycardia (VT) and ventricular fibrillation (VF) (²). The implantable cardioverter-defibrillator (ICD) has seen dramatic changes in design to accommodate its role in preventing sudden cardiac death, particularly given the fact that anti-arrhythmic drug therapy has proven to be of limited use and in some instances increased the risk of death (³). This said, it is still universally accepted that treatment with beta-blockers and ACE-inhibitors reduce the risk of sudden cardiac death and should therefore be administered to those patients that are not contraindicated (⁴, ⁵).

Of those patients who do survive a potentially fatal arrhythmia, the implantation of an ICD has proved invaluable to their continued survival as these patients are at an especially high-risk of ventricular arrhythmia recurrence. A number of randomised trials, the Antiarrhythmics Versus Implantable Defibrillators (AVID),

Cardiac Arrest Study Hamburg (CASH), and the Canadian Implantable Defibrillator Study (CIDS) have been conducted to assess the role of ICDs in the secondary prevention of SCD and have proven to be effective with a reduction in all-cause mortality of 20-30% ([6](#), [7](#), [8](#)). Given the large battery of trials supporting the use of the ICD in the secondary prevention of SCD, further trials have been envisioned to assess the use of an ICD in the primary prevention of SCD to address the large number of patients who have not experienced fatal arrhythmias before ICD therapy. Addressing the question of who should be prophylactically implanted with an ICD in order to prevent SCD is one that can not be answered easily, and ethical considerations should not be overlooked when contemplating the use of such a device for treatment.



History of ICDs

Michel Mirowski conceived of and developed the implantable cardioverter-defibrillator (ICD) almost single-handedly. Prompted by the sudden death of a colleague, Mirowski conceived of an automatic, fully implantable defibrillator. After building a prototype device, Mirowski tested and refined it in animals. Despite considerable skepticism and criticism from many of his colleagues, Mirowski implanted the first device in a human in 1980. In 1985, the FDA initially approved the ICD, specifying that patients had to have survived 2 cardiac arrests to qualify for ICD implantation. Initially, lead systems were epicardial, requiring a thoracotomy for implantation. Pulse generators initially were large and bulky, requiring abdominal implantation.

Remarkable technological advances have made ICDs easier and safer to implant and better accepted by patients and physicians. The development of transvenous lead systems, more effective biphasic defibrillation waveforms, and "active can" technology allows implantation in nearly all patients without the need for thoracotomy. Significant miniaturization of the capacitors and other components has reduced the size of the pulse generator tremendously, permitting subcutaneous pectoral implantation in most patients.

Current devices are considerably smaller than early generations of ICDs, and therapeutic and diagnostic functions have progressed markedly. Early devices were simple shock boxes, offering only high-energy shocks when the patient's heart rate exceeded a cut-off point. Diagnostic information was limited to the number of shocks delivered. Current devices offer tiered therapy with programmable antitachycardia pacing schemes, as well as low-energy and high-energy shocks in multiple tachycardia zones. Dual-chamber, rate-responsive

bradycardia pacing is now available in all ICDs, and sophisticated discrimination algorithms minimize shocks for atrial fibrillation, sinus tachycardia, and other non-life-threatening supraventricular tachyarrhythmias. Diagnostic functions, including stored electrograms, allow for verification of shock appropriateness. Device battery longevity has also increased; early devices lasted 2 years or less, while current devices are expected to last 6 years or longer.

Pathophysiology of Sudden Cardiac Arrest

The most common electrophysiologic mechanisms leading to SCD are tachyarrhythmias such as VF or VT. Interruption of tachyarrhythmias, using either an automatic external defibrillator (AED) or an implantable cardioverter defibrillator (ICD), has been shown to reduce mortality and morbidity from SCD. Patients with tachyarrhythmias, especially VT, carry the best overall prognosis of SCD patients because of the success of defibrillation. In patients with ischemic heart disease, the most common form of VT is monomorphic, which arises from a reentrant circuit.

Approximately 20-30% of patients from all documented sudden death events have bradyarrhythmia or asystole at the time of initial contact. Oftentimes, it is difficult to determine with certainty the initiating event in a patient presenting with a bradyarrhythmia because asystole and pulseless electrical activity (PEA) may result from a sustained VT. An initial bradyarrhythmia producing myocardial ischemia may then provoke VT or VF.

Most cases of SCD occur in patients with structural abnormalities of the heart, related to either a prior myocardial infarction (MI) or a congenital abnormality. Acute thrombosis in an atherosclerotic coronary artery may present as unstable angina, acute myocardial infarction (MI), or SCD. Although more than 80% of SCD events occur in individuals with coronary artery disease (CAD), evidence of acute MI is far less common. Hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) both are associated with increased risk of SCD. Heart failure and various valvular diseases such as aortic stenosis are associated with increased risk of SCD. The strongest predictor of SCD is left ventricular dysfunction of any cause. Acute illnesses, such as myocarditis, may provide both an initial and sustained risk of SCD due to inflammation and fibrosis of the myocardium.

Less commonly, SCD happens in patients who may not have apparent structural heart disease. These conditions usually are inherited arrhythmia syndromes.

At the molecular level, VT and VF can be caused by altered Ca hemodynamics, neurohormonal changes, altered K hemodynamics especially in ischemia, or mutations resulting in dysfunction of a sodium channel (Na channelopathy)

resulting in enhanced automaticity or reentry with unidirectional block. In patients who survive a myocardial infarction (MI), it has been demonstrated that the presence of premature ventricular contractions (PVCs), particularly complex forms, such as multiform PVCs, short coupling intervals (R-on-T phenomenon), or VT (salvos of 3 or more ectopic beats), reflect an increased risk of sudden death.

Even though many patients have anatomic and functional cardiac substrates that predispose them to develop ventricular arrhythmias, only a small percentage develop SCD. The interplay between the regional ischemia, LV dysfunction, and transient inciting events (eg, worsened ischemia, acidosis, hypoxemia, wall tension, drugs, metabolic disturbances) has been proposed as being the precipitator of sudden death

Diverse etiologies of sudden cardiac death

Coronary artery disease

Myocarditis

Drug abuse

Hypertrophic cardiomyopathy

Idiopathic dilated cardiomyopathy

Arrhythmogenic right ventricular dysplasia/cardiomyopathy

Congenital cardiac syndromes (coronary anomalies, cyanotic/non-cyanotic syndromes)

Myocardial infiltrative diseases (e.g. sarcoidosis, amyloidosis)

Long QT syndrome

Brugada syndrome

Unexplained sudden cardiac death (idiopathic polymorphic tachycardia/ventricular fibrillation)

Risk Factors

Heart rhythm disorders can affect anyone, regardless of age, gender, physical fitness, etc. Post myocardial patients with low ejection fraction are at a particularly high risk for lethal arrhythmias — even if they are being optimally managed with ace-inhibitors and beta blocker therapy.² Patients with premature ventricular complexes (PVCs) and ventricular tachycardia are also at increased risk. While there is no standard list of SCA symptoms and SCA typically occurs without warning, SCA risk factors include:

- Survival of a previous SCA episode
- Previous MI
- Poor heart pumping (ejection fraction) indicator of 40% or less
- History of heart disease or heart rhythm disorders
- Family history of SCA or other heart disease

Magnitude of Sudden Cardiac Arrest

- SCA and subsequent death (sudden cardiac death, SCD) is a major health problem, claiming over 450,000 lives every year in the U.S.³
- Most SCA victims are on average 60 years of age, and many victims are relatively healthy and lead active lives right up to the moment when SCA strikes.⁴
- People who have had a previous myocardial infarction have a 4-6 times higher risk of SCA than the general population. In people diagnosed with chronic heart failure (CHF), SCA occurs at 6-9 times the rate of the general population.⁴
- SCA is responsible for approximately 60% of deaths in New York Heart Association (NYHA) Class II or III CHF patients.⁵
- Only 5-6% of patients survive a SCA event.¹

Indications for Prophylactic ICD Therapy

2006 ACC/AHA/ESC Guidelines for the Management of Ventricular Arrhythmias: Primary Prevention of SCD

ICD Class I Recommendations:

- Patients with ischemic cardiomyopathy who are at least **40 days post-MI** with an **LVEF \leq 30 - 40%** and **NYHA functional class II or III**
- Patients with **NYHA Class II-III, LVEF \leq 30 - 35%, non-ischemic cardiomyopathy**
- Patients who are at high risk of SCA due to genetic disorders such as **long QT syndrome, Brugada syndrome, hypertrophic cardiomyopathy and arrhythmogenic right ventricular dysplasia (ARVD).**

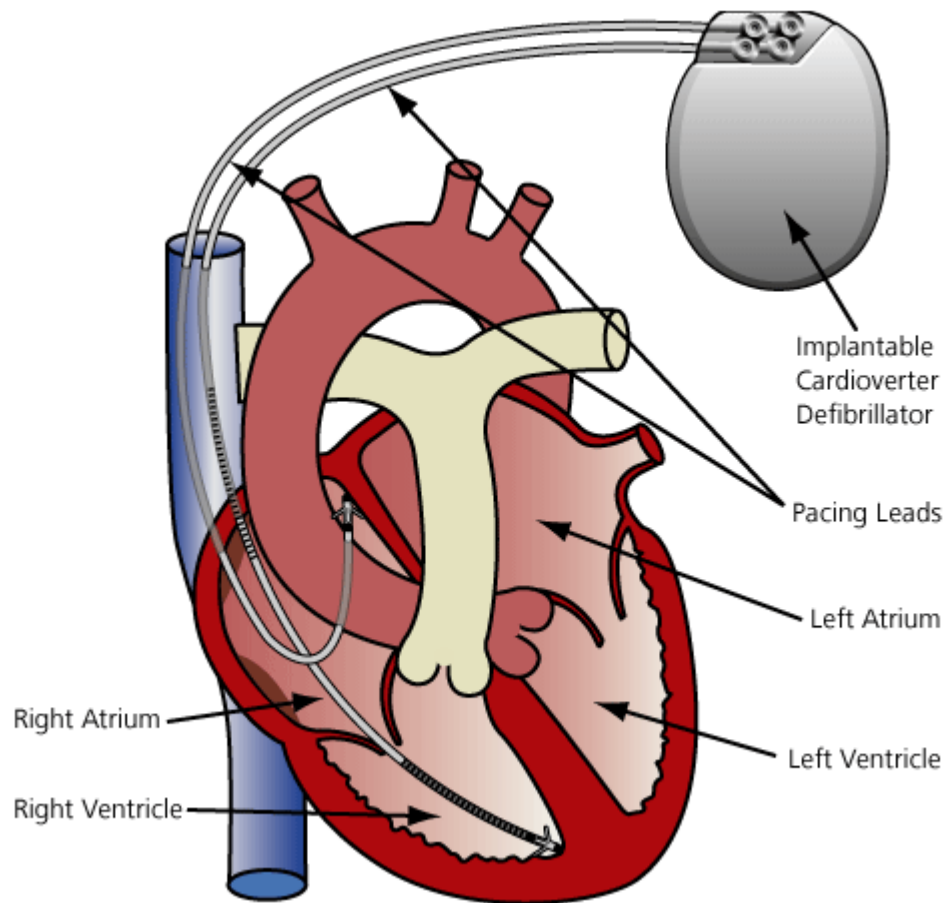
ICD Class II Recommendation:

- Ischemic and non-ischemic patients with **NYHA functional class I, LVEF \leq 30-35%**

Zipes, DP, et al. 2006 ACC/AHA/ESC Practice Guidelines 5. *Circulation*. 2006;114:385-484

Physician guidelines recommend ICD therapy as the standard of care for patients at risk for SCA

The ICD System

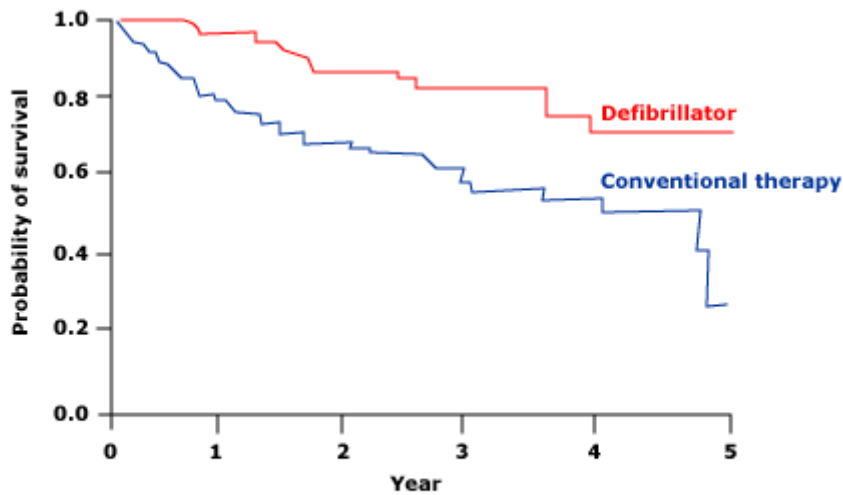


Clinical Trials: Primary Prevention of Sudden Cardiac Death

The ICD has become the primary therapeutic modality for the secondary prevention of SCD. It is well accepted as the standard of care for patients with previously life-threatening arrhythmias. The recommendations for the use of an ICD for primary prevention in patients with prior myocardial infarction or nonischemic cardiomyopathy have just recently been proven and widely accepted. The results of recent ICD trials have been used to shape new guidelines regarding ICD therapy for primary prevention. Randomized controlled trials demonstrating benefit have been performed in patients with ischemic and nonischemic cardiomyopathy.

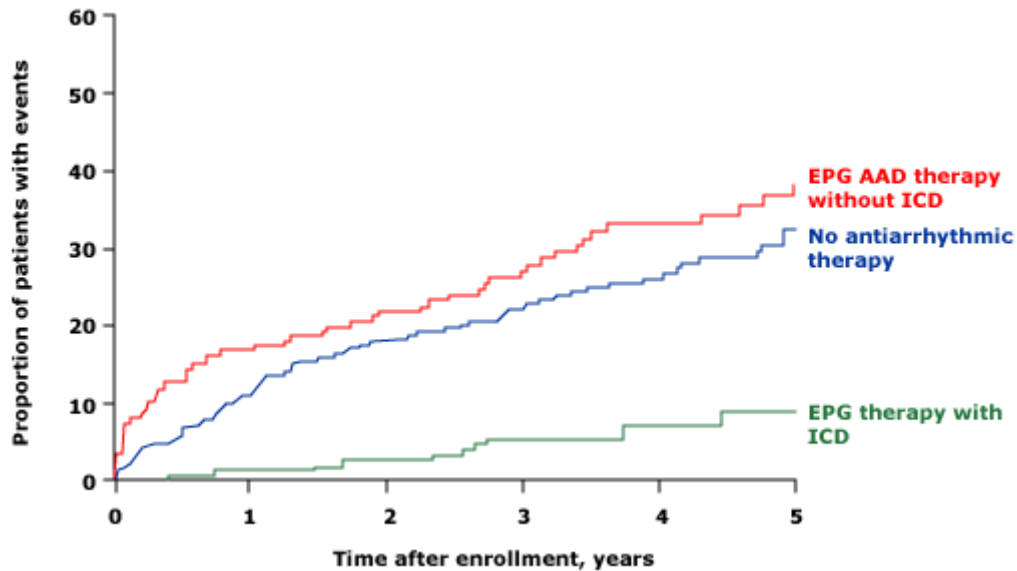
In the last decade also, a large amount of information has been available in the investigation of the uses of an ICD, particularly in regards to the prevention of sudden death from cardiac causes. Initial trials of this nature focused on patients at an increased risk of sudden cardiac death, based on a combination of low ejection fraction, and additional risk markers (⁵). While initial trials pertain exclusively to small numbers of patients due to restricted patient selection criteria, later trials used more simplified entry criteria and hence broadened the horizons for ICD indications.

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) was the first completed randomised primary prevention trial which investigated whether prophylactic therapy with an ICD would improve survival rates in high-risk patients with coronary artery disease when compared with conventional medical therapy (¹⁰). A total of 196 patients were included in the two-sided sequential designed trial with death from any cause as the primary end point (¹⁰). MADIT reported that patients that were randomly assigned to ICD therapy with a previous myocardial infarction, a left ventricular ejection fraction < 0.35, a documented episode of asymptomatic unsustained ventricular tachycardia and inducible, non-suppressible ventricular tachyarrhythmia on electrophysiology study, were shown to have improved survival rates (54% reduction in mortality) when compared with medical therapy (¹⁰). The weakness of this study is that the study involved a small number of patients and there was a lack of treatment with beta-blockers and ACE inhibitors (⁵).



Defibrillator	95	80	53	31	17	3
Conventional therapy	101	67	48	29	17	0

Investigators of the Multicenter Unsustained Tachycardia Trial (MUSTT) tested the hypothesis that antiarrhythmic therapy guided by electrophysiological testing reduces the risk of sudden cardiac death in a total of 704 patients with coronary artery disease and ejection fraction of < 0.4 , with inducible, sustained ventricular tachycardia at electrophysiology study ([11](#)). In this randomised trial, patients were assigned to receive either antiarrhythmic therapy, consisting of the administration of antiarrhythmic drugs or an ICD, or no antiarrhythmic therapy ([11](#)). The primary end point in this trial was cardiac arrest or death from arrhythmia. MUSTT verified the hypothesis that electrophysiological guided antiarrhythmic therapy reduces the risk of SCD in high-risk patients with coronary artery disease and concluded that therapy with an ICD was useful and superior to treatment with antiarrhythmic drugs in the primary prevention of SCD ([11](#)).



The effect of prophylactic implantation of an ICD on survival rates in patients with coronary heart disease, a depressed left ventricular ejection fraction and an abnormal signal-averaged electrocardiogram was assessed in the Coronary Artery Bypass Graft (CABG) Patch Trial, in which an ICD was randomised for implantation in 446 patients at the time of elective bypass surgery ([12](#)). The remainder of the 900 patients randomised for the trial (454 patients) was assigned to CABG surgery alone (CABG Patch 1997). The CABG Patch trial found no evidence of improved survival among the patients implanted with an ICD ([12](#)). While this study showed no added benefit of ICDs to surgical revascularisation, this may be due to the positive antiarrhythmic effect that CABG surgery has on patients at high-risk of ventricular arrhythmias ([2](#), [3](#), [5](#), [11](#)).

In the second Multicenter Automatic Defibrillator Implantation Trial (MADIT II), 1,232 patients with a prior myocardial infarction and a left ventricular ejection fraction of < 0.3 were randomised to either implantation of an ICD (n =742) or conventional medical therapy (n =490) (3:2 ratio) to assess if the prophylactic implantation of a defibrillator would reduce all-cause mortality ([12](#)). Compared to previous primary prevention trials, MADIT II did not require invasive electrophysiological testing for risk stratification ([3](#)). Death from any cause was selected as the end point for the trial. The findings of MADIT II proved that the implantation of a defibrillator in patients with a previous MI and a reduced ejection fraction improves survival rates (12%, 28%, 28% relative reduction in mortality at 1, 2, and 3-years, respectively) and as a result recommends the use of an ICD in the primary prevention of SCD in this population subgroup ([14](#)).

A relatively recent trial, the defibrillator in acute myocardial infarction trial (DINAMIT), investigated the prophylactic use of an ICD after acute myocardial infarction to assess any mortality benefit that may exist ([15](#)). A total of 674 patients was randomised to both the ICD or control group with 332 and 342

patients in each group; respectively. Of note was that 20 patients randomized to ICD therapy refused implantation, and exclusion of these patients from the study is suspected, however confirmation of this is not certain at this juncture ([14](#)). The patients enrolled in the study had a myocardial infarction documented as no less than 6 and no greater than 40 days with an average time from myocardial infarction to randomisation in the two groups of 18 days. A left ventricular ejection fraction ≤ 0.35 was also required for entry with a reported mean left ventricular ejection fraction of 0.28 ([14](#)).

The primary outcome in DINAMIT was death from any cause. Death due to cardiac arrhythmia was reported as being the secondary outcome. The results of this trial insinuates that while a statistically significant reduction in arrhythmia mortality occurred with implantation of an ICD when compared to control group (annual death rate, 1.5% and 3.5%, respectively), this is offset by the significantly increased rate in the ICD group from death from cardiac, nonarrhythmic causes when compared to the control. This led to the conclusion that prophylactic implantation does not reduce overall mortality in high-risk patients who have recently had a myocardial infarction ([15](#)). The reason given to the similar differences in magnitude in opposite directions for the two groups is concisely explained by Hohnloser et al ([15](#)) when they suggest that 'that the patients "saved" from an arrhythmia related death by ICD therapy are also at risk for death from other cardiac causes'. The authors, however, noted their uncertainty when explaining the unprecedented increase in mortality from nonarrhythmic causes of death ([15](#)).

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) remains one of the latest and largest randomised trials on the clinical effects of ICD therapy in the prevention of SCD. This largely awaited trial enrolled patients during the period from September 1997 to July 2001 and randomly assigned the 2,521 participants in relatively equal proportions to receive placebo (n = 847), amiodarone (n = 845), or a single-chamber ICD (n = 829) ([22](#)). In this trial, patients were followed every three months until October 2003 and death from any cause was the primary end point. Entry into the trial required the subject to be classified as having New York Heart Association (NYHA) class II or III heart failure and a left ventricular ejection fraction of ≤ 0.35 . The trial reported that placebo and amiodarone was associated with a similar risk of death (hazard ratio, 1.06; 97.5 % confident interval, 0.86 to 1.30; P =0.53) and further concluded that single-lead, shock-only ICD therapy resulted in a decreased risk of overall mortality of 23 % (hazard ratio, 0.77; 97.5 % CI, 0.62 to 0.96; P =0.007) ([22](#)).

The Cost of ICD Therapy

Research shows that ICDs provide an invaluable form of life insurance for people most at risk. Evidence-based medicine has demonstrated that ICDs significantly reduce death among Americans at highest risk:

- 31% reduction in death among SCA survivors from a second event.⁹
- 31% reduction in death among post-heart attack sufferers.¹⁰

Despite these statistics, ICDs are underutilized.

- Fewer than 20% of currently indicated patients receive the benefits of an ICD despite being at high risk for sudden death.¹¹

The value of ICDs outweighs their cost to the system.

- The cost per day of ICD protection has decreased by nearly 90% over the last 10 years from more than \$90 in 1990 to approximately \$13 today (equivalent to the cost of optimal medical therapy for these same patients).¹¹
- ICD Medicare expenditures are significantly less than for other cardiovascular procedures. In 2002, Medicare reimbursed \$1.2 billion for ICD procedures vs. \$6.4 billion for stent implants and \$7.8 billion for bypass surgery.¹²
- The cost of ICD therapy per year is less than 0.2% of projected Medicare spending over the next 10 years.¹³

Conclusions and future perspectives

SCA can be reversed, but only if treated within minutes with an electrical shock via an automated external defibrillator (AED) or with an implantable cardioverter defibrillator (ICD). The American Heart Association recommends defibrillation within 3-5 minutes of arrest, or sooner, for cardiac arrests occurring outside the hospital. In the U.S., on average, it takes emergency medical services teams 6-12 minutes to arrive. SCA survival rates drop 7-10 percent for every minute without defibrillation.

ICDs reduce mortality and improve prognosis of patients susceptible to SCD. The use of an ICD has become a mainstay treatment option for the management of patients at an increased risk of sudden cardiac death. ICD implantation indications have broadened to include high-risk patients with coronary artery disease and reduced left ventricular ejection fraction in the primary prevention of

SCD. The growing trend of broadening indications for ICD implantation in the primary prophylaxis of SCD is necessary to move forward in the task of reducing mortality from a condition that is accepted as one of the leading causes of death in the world today.

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