Chapter 31
Contemporary Management of Sudden Cardiac Death

SN Narasingan

ABSTRACT
Sudden cardiac death (SCD) is a major public health problem. It is estimated that approximately 50% of all cardiac deaths are sudden and unexpected. Sudden cardiac death is a direct consequence of cardiac arrest, which may be reversible if addressed promptly. Solid evidence has been obtained from Randomized Clinical Trials (RCTs), which had changed the approach in the recent guidelines. There are limitations in determining the true estimate of SCD, as there is a lack of uniform criteria for definition and classification of mode of death. Most studies define SCD as death occurring within 1 hour of symptom onset. This chapter focuses on risk stratification, prevention of ventricular arrhythmias and sudden cardiac arrest with pharmacotherapy, and implantable cardioverter-defibrillator (ICD).

DEFINITION OF SUDDEN CARDIAC DEATH
Sudden cardiac death is defined as "natural death due to cardiac causes in a person who may or may not have previously recognized heart disease but in whom the time and mode of death are unexpected. In the context of time, sudden is defined for most clinical and epidemiologic purposes as 1 hour or less between a change in clinical status heralding the onset of the terminal clinical event and the cardiac arrest itself." An exception is witnessed deaths, in which pathologists may expand the definition of time to 24 hours after the victim was last seen to be alive and stable.

ETIOLOGY OF SUDDEN CARDIAC DEATH
The incidence of SCD increases markedly with age regardless of sex or race. The most common electrical event with SCD is progression of ventricular tachycardia (VT) to ventricular fibrillation (VF). The most important common causes are:
- Coronary artery disease (CAD)
- Anomalous origin of coronary arteries
- Cardiomyopathies
- Left ventricular (LV) hypertrophy due to hypertension
- Infiltrative myocardial diseases: Amyloidosis
- Congenital cardiac anomalies
- Primary electrophysiologic abnormalities like long QT syndrome (LQTS).

Sudden Cardiac Death: Indian Epidemiological Data
In 2011, a study by Madhavan SR et al. reported that CVD was the underlying cause in majority of SCD events during a study period of 22 months involving total deaths of 1,916. Prevalence of CV risk factors among sudden cardiac and non-sudden deaths was evaluated in this study. The majority of SCD events are due to CV causes even in the absence of a history of cardiac disease. The majority of Indian population lives in rural India. This study in rural India showed that subjects experiencing SCD were significantly more likely to have hypertension, diabetes and a history of myocardial infarction (MI)/CAD (P < 0.0001 for all) (Figure 1).

Sudden Cardiac Death Following ST-Segment Elevation Myocardial Infarction
Study by Rao BH et al. in India, reported that SCDs occurred after acute ST-segment elevation myocardial infarction (STEMI) (Figure 2). Interestingly, the study revealed that sudden deaths constituted about 10% of total mortality in a population from Southern India and 33.5% of cases had past history of MI. It involved...
younger population and most of SCDs occurred within 1 month after MI. Out of 159 total deaths reported, 78 were due to SCD and 81 were due to nonsudden death. This study has shown that SCDs following STEMI accounts for about 50% of total deaths.

**Sudden Cardiac Death in Patients with Myocardial Infarction and Left Ventricular Dysfunction, Heart Failure or Both**

The results of an analysis of a study published in the New England Journal of Medicine (NEJM) confirm that patients with LV dysfunction, heart failure (HF) or both after MI are at high risk for SCD or cardiac arrest with resuscitation. The risk of SCD from cardiac causes is increased among survivors of acute MI with reduced LV systolic function. The risk of sudden death is highest in the first 30 days after MI among patients with LV dysfunction, HF or both. Thus, earlier implementation of strategies for preventing sudden death may be warranted in selected high-risk patients.

**First Cardiac Rhythm Documented at the Time of Sudden Cardiac Death**

The most common cardiac rhythm abnormality seen at the time of SCD is VT, which accounts for nearly 63% in a study recently published. Thirteen percent were due to torsade de pointes, 16% were bradycardia and 8% were due to primary VF.
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BETA-BLOCKERS AND PREVENTION OF SUDDEN CARDIAC DEATH

Beta-blockers are the agents most frequently studied in post-MI patients for the prevention of SCD. More than 12 large RCTs were reported. A meta-analysis of the beta-blocker trials showed a significant reduction in mortality. Highly significant 30% reduction in SCD was seen. The risk of non-sudden death was also decreased by 12%. Recent beta-blocker trials in congestive heart failure (CHF) patients also show a reduction in both overall deaths and SCD. Beta-blockers are effective against arrhythmic death (20–30% reduction) and nonarrhythmic deaths, and reduce overall mortality significantly. Beta-blocker therapy is indicated in all patients at high risk for SCD.

PREVENTION OF VENTRICULAR ARRHYMIA S AND SUDDEN CARDIAC DEATH

Ventricular ectopy is considered an electrical trigger of sustained ventricular arrhythmias and potentially SCD. Suppression of ventricular arrhythmia and prevention of SCD are effectively controlled by antiarrhythmic drugs in various trials.

Class I Antiarrhythmic Agents

Mexiletine, encainide, flecainide or moricizine have been abandoned for the reduction of the risk of SCD in patients with ischemic cardiomyopathy and nonsustained ventricular arrhythmia. Class I antiarrhythmic drugs are harmful, and are prescribed in patients with ischemic heart disease and reduced LV ejection fraction (LVEF) rarely.

Class III Antiarrhythmic Agents

Amiodarone

Class III antiarrhythmic agents were tested in a series of randomized trials. The two largest trials using amiodarone are: (1) the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) and (2) the European Myocardial Infarction Amiodarone Trial (EMIAT). Both showed a reduction in arrhythmic death but no significant reduction in overall death. Meta-analysis of data from all 13 randomized controlled trials (RCTs) of amiodarone in which 89% of patients were after MI, showed a significant reduction in total mortality and a significant reduction in arrhythmic death. Amiodarone has a moderate effect against SCD and a neutral effect on other deaths. The overall effect on total mortality is modest. In Valsartan in Acute Myocardial Infarction Trial (VALIANT) Study, a randomized comparison of valsartan, captopril, or both in patients with acute MI with HF and/or LV systolic dysfunction were analyzed. Amiodarone use was associated with excess early and late all-cause mortality and CV mortality. Positive relationship between beta-blocker use and amiodarone effect, such that patients on beta-blockers received a significantly greater benefit from amiodarone than those not on beta-blockers. More recently, the association of amiodarone and beta-blockers has been demonstrated to markedly reduce the incidence of appropriate ICD therapy. In the Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) Trial, amiodarone plus beta-blocker significantly reduced the risk of appropriate ICD shocks compared with beta-blocker alone.

D-Sotalol

D-sotalol, a pure Class III agent, was evaluated in a multicenter double-blind randomized study. The mortality was 18% lower in the sotalol than in the placebo group, but this difference was not statistically significant. D-sotalol is actually a harmful drug.

ROLE OF UPSTREAM THERAPY IN THE PREVENTION OF SUDDEN CARDIAC DEATH

Angiotensin-Converting-Enzyme Inhibitors

The effect of angiotensin-converting-enzyme inhibitors (ACEs) on the risk of SCD following MI has been demonstrated in randomized trials. A recent meta-analysis of 15 trials that included 15,104 patients having 900 SCD, ACEI therapy resulted in a significant reduction in total mortality, CV death and SCD. The exact mechanism by which ACEIs reduce SCD is not known. Proposed mechanism...
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is attenuation of remodeling, thereby reducing the substrate for ventricular tachyarrhythmia. They also provide significant neurohumoral modulation and protection from future ischemic events.

Angiotensin II Receptor Blockers

The Angiotensin II receptor blockers (ARBs) are potentially antiarrhythmic. They inhibit the proarrhythmic effects of Angiotensin II. Various trials of different ARB have demonstrated equivalent effects to those of ACEIs on cardiac and overall mortality. Except for the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) Trial results, the addition of an ARB to ACEI has not yielded any additional benefits. The Angiotensin II receptor blockers should be used as an alternative therapy in patients who are intolerant to ACEIs.

Aldosterone Antagonists

In the Randomized Aldactone Evaluation Study (RALES), aldactone was evaluated in patients, having New York Heart Association (NYHA) III-IV. After a mean follow-up for 24 months, the incidence of SCD was significantly decreased. The magnitude of this effect was similar to the effect on total mortality. In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) Trial, patients with an acute MI complicated by symptomatic LV dysfunction were randomized to standard therapy plus eplerenone. Eplerenone significantly reduced all-cause mortality, CV death and the risk of CV death and hospitalization. Interestingly, SCD was also significantly reduced. Either spironolactone or eplerenone is recommended as adjunctive therapy in patients with HF with LV dysfunction and NYHA Class III-IV.

N-3 Polyunsaturated Fatty Acids

Alpha-linolenic acid is an essential n-3 polyunsaturated fatty acid (PUFA) derived from plant sources. Long-chain n-3 PUFA include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), predominantly derived from seafood consumption. In animal-experimental and in vitro studies, n-3 PUFA directly affects myocyte electrophysiology (e.g. altering the function of membrane sodium channel, L-type calcium channel, and sodium-calcium exchanger). Such effects might contribute to reduced myocyte excitability and cytosolic calcium fluctuations, particularly in ischemic or damaged cells susceptible to partial depolarization and triggered arrhythmia. In a larger study, the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico (GISSI)-Prevenzione Trial, patients who are vulnerable to malignant ventricular arrhythmias and are recommended for patients with recurrent shocks. The effects of fish oils on SCD and CV morbidity and mortality remain debated. The protective effect of fish oils may be limited to patients with a previous MI. Current guidelines recommend that patients with documented CAD consume approximately 1 g of EPA + DHA per day, preferably from oily fish; although supplements can also be considered.

Implantable Cardioverter-Defibrillator Therapy for Prevention of Sudden Cardiac Death

Number of clinical trials have shown efficacy of ICD therapy for SCD prevention in various clinical settings. Highly selected and high-risk individuals have shown benefits of ICD therapy. The primary indication is LVEF, which is less than or equal to 35%. The American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) 2008 Guidelines for current indication for ICD therapy is the presence of a persistently depressed LVEF of 35% or less in patients with ischemic cardiomyopathy who are on appropriate medical therapy at least 30 days beyond MI. In some instances, the presence of nonsustained VT or the induction of VT during programmed electrical stimulation have been used as inclusion criteria. However, the limitations of ICD therapy have to be taken into account. Implantable cardioverter-defibrillator shocks may be associated with increased mortality and sometimes ICD shocks may change the mode of death from arrhythmic to nonarrhythmic or HF death. Implantable cardioverter-defibrillator malfunction may interfere with success of therapy. It is not uncommon to witness patients having ICD to develop states of anxiety and depression. Cost may be prohibitive apart from the longevity of the device.

Immediate Risk-Stratification Improves Survival (IRIS) Trial had shown the benefit of the ICD in reducing SCD and this was negated by the higher rate of mortality due to nonarrhythmic death. Defibrillator in Acute Myocardial Infarction Trial—ICD therapy did not reduce mortality in high-risk patients early after MI. The ICD significantly reduced arrhythmic death by more than 50%. However, this was offset by a significant increase in nonarrhythmic death. It may be that the use of an ICD in patients early after MI changes the mode of death from arrhythmic to nonarrhythmic. Interpretation of Multicenter Automatic Defibrillator Implantation Trial (MADIT I and II) is that patients who are vulnerable to malignant ventricular arrhythmias early post-MI are also likely to have more HF and increased risk for other cardiac nonarrhythmic mortality. Although SCD may be aborted with ICD therapy, recent studies have demonstrated that ICD shocks may be associated with increased mortality.

Adjunctive therapy for the prevention of recurrent shocks has clinical relevance primarily by improving quality of life by preventing both appropriate and inappropriate shocks. Amiodarone and beta-blocker have both shown significant reductions in device therapy, and are recommended for patients with recurrent shocks.

Long QT Syndrome

The long QT syndrome (LQTS) is frequently associated with SCD. Long-term therapy with beta-blockers, permanent pacing or left cervicothoracic ganglionic sympathectomy, have been reported to reduce cardiac events. A number of clinical markers have been suggested as risk-stratifiers for SCD. History of syncope, family history of SCD, cardiac arrest, torsade de pointes and type of LQTS have been suggested by some investigators as markers of SCD. ICD is recommended for patients who have a recurrence of syncope or VF while receiving beta-blockers. Genetic analysis may in the future aid in identifying patients at higher risk of SCD, and may justify implanting an ICD for primary prevention.
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Cardiac Resynchronization Therapy and Implantable Cardioverter-Defibrillator for Sudden Cardiac Death Prevention

Whether ICD therapy alone or combined with cardiac resynchronization therapy (CRT) in appropriate HF candidates has an impact on SCD remains a matter of debate. The Cardiac Resynchronization Heart Failure (CARE-HF) Study randomized 813 patients with advanced HF, QRS prolongation (>120 msec) and LVEF less than 35% who were followed for a mean of 29.4 months. The primary endpoint was significantly reduced in the CRT compared to medical therapy group. Death was also significantly reduced in the CRT compared to medical therapy group. The extension of the study observed a significant reduction in SCD. Hence, it is reasonable to recommend CRT + ICD, when there is an overlapping indication (advanced HF, EF < 35%, QRS duration > 120 msec).

CONCLUSION

Sudden cardiac death is a major public health problem. There is increased incidence of SCD in developing countries including India. Indian data revealed that SCD was commonly seen following STEMI. It is estimated that about 40–50% of all CV deaths are SCDs and about 80% of these are caused by ventricular tachyarrhythmias. The survival rate from sudden cardiac arrest is less than 1% worldwide. There is a need to develop complementary strategies for management of SCD. Implantable defibrillators improve mortality in patients who have experienced an episode or are at high risk of developing ventricular tachyarrhythmias. Patients with EF less than 35% derive benefit from ICD. Beta-blocker therapy is indicated in all patients at high risk for SCD. Suppression of ventricular arrhythmia and prevention of SCD are effectively controlled by antiarrhythmic drugs. More recently, the association of amiodarone and beta-blockers has been demonstrated to markedly reduce the incidence of appropriate ICD therapy. Accumulated evidence supports the use of ACEI, ARBs, aldosterone antagonists and n-3 PUFA as upstream interventions in appropriate patients to prevent SCD.

REFERENCES