Primary Prophylaxis of Sudden Death in Hypertrophic Cardiomyopathy, Arrhythmogenic Right Ventricular Cardiomyopathy, and Dilated Cardiomyopathy


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Primary Prophylaxis of Sudden Death. We present an evidence-based overview of primary prevention of sudden cardiac death. Several recent studies have provided important data regarding pharmacologic and device-based therapy for patients with conditions that confer high risk for sudden death. A rational approach to these therapies, with emphasis on implanted cardiovertor defibrillators, is discussed. (J Cardiovasc Electrophysiol, Vol. 16, pp. S28-S34, Suppl. 1, September 2005)

implanted cardiovertor defibrillator, primary prevention, sudden death, cardiomyopathy

Introduction

The implantable cardiovertor defibrillator (ICD) is arguably one of the most significant developments in cardiology of the last century. Its efficacy in secondary prevention after resuscitation from cardiac arrest is well established.1-3 Primary prophylaxis is more difficult, requiring accurate risk stratification with good sensitivity, specificity, and predictive accuracy, a goal that has proved elusive. Considerable data are available for patients after myocardial infarction (MI)4,5 and consensus exists about the general efficacy of ICD in patients with prior MI and poor left ventricular function. Several randomized trials have also established the basis for the management of patients with idiopathic dilated cardiomyopathy (DCM) and symptomatic left ventricular dysfunction.6-8 Unfortunately, cardiac arrest can occur with virtually any cardiac disorder. Large randomized trials may not be feasible if the disease in question is relatively uncommon, or if reasonably useful risk stratifiers for arrhythmic death are not available. A definitive trial may also be unrealistic in a disease that is detected at an early age, where the meaningful clinical endpoint is lifetime prevention of sudden death. The risk of sudden death can be estimated, albeit imperfectly, from cohort data in disorders such as myotonic dystrophy, amyloid heart, valvular disease, and most patients do well for many years or a lifetime. The decisions are even more problematic in other disorders such as hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and the repolarization syndromes, but considerable judgment is required with the acceptance of uncertainty in ICD decisions since the annual risk of sudden death is generally low and most patients do well for many years or a lifetime. The decisions are even more problematic in other disorders such as myotonic dystrophy, amyloid heart, valvular disease, and others where rigorous data are lacking and often difficult to obtain.

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follow-up showed fewer deaths in the ICD group versus control (13 vs 17, respectively). The AMIOVERT study, enrolled 103 patients with dilated cardiomyopathy, ejection fraction (EF) <35, and non-sustained ventricular tachycardia, and was started early with no difference between amiodarone and ICD groups. The Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) enrolled 458 patients with non-ischemic cardiomyopathy, EF <35%, and frequent premature ventricular complexes (PVCs) or non-sustained ventricular tachycardia. After 2 years, mortality was 13.8% with usual therapy versus 8.1% (PVCs) or nonsustained ventricular tachycardia. After 2 years, mortality was 13.8% with usual therapy versus 8.1% in the ICD group, amounting to a 5.7% absolute reduction and a 34% relative risk reduction with ICD implantation (P = 0.06). The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) compared amiodarone, ICD, and usual therapy in 2,521 patients with coronary artery disease or non-ischemic cardiomyopathy who were in New York Heart Association (NYHA) class II or III heart failure with ejection fraction <35%. The median follow-up was 45.5 months. The total mortality in the medical group was 7.2% per year over 5 years with a risk reduction of 22% in the ICD group versus placebo, confidence intervals, 0.62–0.96, P = 0.007. There was no mortality difference between the amiodarone and placebo groups. Forty-eight percent of patients had non-ischemic cardiomyopathy with a 27% reduction in mortality versus 23% for ischemic patients. The trials for primary prophylaxis of sudden death in DCM did not generally include functional class 1 individuals. It is probable that dilated cardiomyopathy with EF less than 30 in NYHA class 2 and 3 patients will become a class 1 or at least class 2A indication for prophylactic ICD with emerging guidelines both in the United States and elsewhere.

Hypertrophic Cardiomyopathy

Most individuals with HCM are asymptomatic and the first manifestation may be sudden cardiac death. Sudden death is usually related to ventricular arrhythmia with triggers such as ischemia, outflow obstruction, or atrial fibrillation. Sudden death is less frequent due to bradycardia. The annual mortality from HCM has been estimated to be as high as 6%, but community-based studies suggest a range of 1% or less. This relatively low incidence creates a challenge for risk stratification. Features suggesting higher risk of sudden death have been derived from observational studies. In one study, 23 of 480 patients died suddenly over a mean follow-up of 6.5 years. The risk of sudden death was directly related to septal wall thickness, with essentially no mortality over 20 years with wall thickness less than 20 mm and almost 40% for wall thickness of 30 mm or greater. Patients with such extreme wall thickness were relatively young and frequently asymptomatic. The degree of outflow obstruction has been shown to predict cardiovascular but not sudden death. MRI and CT have been suggested to be helpful in assessing the extent of disease and predicting sudden death. Sudden death in one or more family members has been suggested to signify higher risk. Specific genetic abnormalities have been associated with increased risk and the role of genetic testing is likely to increase. Syncope, has been correlated with increased risk of sudden death. A flat or hypotensive response to upright or supine exercise testing has been shown to predict sudden death albeit with low predictive value. A normal blood pressure response identifies a low-risk group. Spontaneous ventricular tachycardia has been associated with higher risk while VT induced in the electrophysiology laboratory has been associated with a higher risk in one but not other studies. A consensus document of the American College of Cardiology and European Society of Cardiology has categorized the known risk factors for sudden death as “major” and “possible” in individual patients.

Major risk factors for sudden death in HCM

1. Cardiac arrest (ventricular fibrillation)
2. Spontaneous sustained ventricular tachycardia
3. Family history of premature sudden death
4. Unexplained syncope
5. LV thickness greater than or equal to 30 mm
6. Abnormal exercise blood pressure
7. Nonsustained spontaneous ventricular tachycardia

Possible risk factors in individual patients

1. Atrial fibrillation
2. Myocardial ischemia
3. LV outflow obstruction
4. High-risk mutation
5. Intense competitive physical exertion

The major independent risk factors may prove to be a measure of the extent of disease and the underlying genetic abnormality. The absence of risk factors identifies a low-risk group, and a single risk factor has limited positive predictive value. Stratification based on incorporation of multiple risk factors would likely improve positive predictive accuracy.

Symptomatic patients are generally treated with beta blockers or verapamil. Atrial fibrillation can be especially problematic with sudden clinical deterioration. Amiodarone is most widely used in this context. Medical therapy has not been proven to be beneficial in prevention of disease progression in the asymptomatic individual. Optimal medical therapy and control of comorbidities may reduce the risk of sudden death although this has not been proven.

The ICD has been used in patients with cardiac arrest, sustained VT, or VF with a high percentage of patients receiving appropriate discharge at a rate of 11% per year. ICD implantation in the subgroup for primary prophylaxis on the basis of perceived high risk for sudden death resulted in a lower rate of appropriate discharge of 5% per year. Nonrandomized studies have suggested a role for amiodarone to prevent sudden death, while other studies have suggested symptomatic improvement but no reduction of sudden death. Amiodarone is unlikely to be superior to the ICD for this purpose, and a randomized study comparing the two is unlikely to be done in the light of recent studies favoring the ICD in multiple patient groups. Most asymptomatic patients with HCM have a relatively benign course. The ICD decision is individualized in patients considered to be at high risk for sudden death. Patients with multiple risk factors, especially severe septal hypertrophy (>29 mm) and those with sudden death in close relatives appear to be at a sufficiently high risk to merit consideration of prophylactic ICD therapy.

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is suspected in patients with right ventricular...
It is an ectopic cardiomyopathy that often presents with arrhythmias rather than right heart symptoms. Patients may have simple ectopy, sustained and nonsustained VT, or ventricular fibrillation. ARVC needs to be ruled out when VT originates from the RV outflow region. Idiopathic RV outflow VT is usually not associated with the ECG abnormalities seen with ARVC, is more common in women, and is exercise induced or initiated by isoproterenol more frequently than by programmed stimulation. The ECG in ARVC frequently shows precordial T wave inversion over V1-V3 and a QRS duration greater than 110 msec. Low-voltage potentials following the QRS (Epsilon waves) are characteristic but infrequent and late potentials are observed on the signal-averaged ECG in greater than 50% of individuals. Unfortunately, sudden death is frequently the first manifestation of the disease. A standardized diagnostic scheme has been formulated to establish a clinical diagnosis on a point score basis. The annual incidence of sudden cardiac death has ranged from 0.08% to 9% in several modest-sized cohorts. In an autopsy series of ARVC patients, 24 of 27 patients died suddenly and 3 died of congestive heart failure. Sudden death occurs relatively frequently but not exclusively during exercise or stress. In one Italian series, up to 25% of sudden deaths in athletes were related to ARVC. Sudden death is more probable in individuals with grossly visible RV abnormalities but may occur in those with only microscopic abnormalities and no obvious RV enlargement. RV dilation, precordial repolarization abnormalities, and LV involvement have been associated with sudden death. There may be “malignant” genotypes. Sudden death in family members intuitively suggests a higher risk of sudden death and men may be more at risk of early mortality than women.

The treatment of ARVC is individualized. The ICD has been used in patients with unexplained syncope, sustained VT, or VF with a high incidence of appropriate shocks. Although there are no randomized trials in ARVC, the situation is sufficiently “similar” to other disease states with well-established indications. ICD in individuals with a family history of sudden death or a genetic basis known to be “malignant” is intuitively compelling with data to support this practice. The ICD may be offered to asymptomatic individuals on an individualized basis based on the presence of the above risk factors. Antiarrhythmic agents including class IC agents and amiodarone both alone and in combination with beta-blocking drugs have proved useful for symptomatic ventricular tachycardia. Radiofrequency ablation is useful for eliminating problematic tachycardias but may not prevent sudden death. Ongoing cohort registries may identify risk factors to better predict patients who will benefit from a prophylactic ICD.

The Challenge of Primary Prophylaxis

The ICD is a wonderful tool of undoubted efficacy. Nonetheless, the device remains relatively expensive and results in personal challenges and some morbidity for individuals. Guidelines are helpful but are a just a starting point. It is of dubious wisdom to implant devices in those individuals whose meaningful lifespan is limited by comorbidities where it is arguably at best not useful and may actually just change the mode of death to one less palatable. It takes courage and wisdom to make these judgments in cooperation with patients and their families. It may be useful to conceptualize actual outcomes in a series of 100 patients implanted with a device. For example, the SCD-HeFT clearly demonstrated a 23% risk reduction or an absolute reduction of 7.2 deaths over the 5 years of the study in patients with functional class 2 and 3. In our hypothetical 100 patient cohort followed over 5 years, one might expect approximately 7 or 8 to have their life saved at the end of this time. One might also expect 29 to be dead in spite of the device and 64 to not have used the device appropriately or to have complications and lifestyle issues related to it. Since the annual benefit is relatively low, it takes years for meaningful benefit to be apparent. It would logically follow that extrapolating the results to patients with limited life expectancy due to advanced age and comorbidities is of questionable effectiveness even if such patients may technically be candidates by guidelines (Fig. 1). Conversely, patients relatively well with a low annual risk but otherwise long estimated longevity such as with “less severe” heart failure, the repolarization syndromes, ARVC, and other conditions with a high annual risk of sudden death may benefit from primary prevention strategies.
and hypertrophic cardiomyopathy are at risk for many years and may well benefit. Decisions in these individuals and their families are often fraught with great anxiety, and the ICD can bring reassurance in borderline cases. The key to useful application and expansion of this important technology will be good judgment, clear communication, patient selection, and hopefully further data to provide more focal assessment of risk and benefit.

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