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## **Companion Meeting**

# **CARDIAC DISEASES AT RISK OF SUDDEN DEATH IN THE YOUNG**

### **Chairpersons:**

**Jagdish Butany, Toronto, Canada**

**Gaetano Thiene, Padova, Italy**

***Sunday March 8, 2009***

***h.08:30 – 12:00***

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Is prevention of sudden cardiac death feasible?

# The burden of phenomenon

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Sudden cardiac death is a tragic, unexpected, end-result of a variety of cardiovascular disorders that affect men and women of any age, nationality or ethnic group. The incidence of sudden death in any population varies depending on many factors: gender, age, nationality, ethnic group, screening methods to detect sudden death, and attempts to prevent or avert sudden death pharmacologically, surgically, and/or by the use of external or implantable devices. The fact that sudden death is often the first manifestation of the cardiovascular disease makes sudden cardiac death particularly difficult to prevent. Furthermore, the greatest number of these deaths occur in people considered to be at “low-risk” for such an event.

According to different sources, in the United States, there are over 300,000 sudden cardiac deaths per year. The majority, perhaps 90% or more, occur in individuals greater than 35 years old, and are due to atherosclerotic coronary artery disease.

Fortunately, sudden death in the young (less than 35 years old) is a rare event that accounts for only 1 to 2% of sudden deaths. In one study of sudden death in the young (<25 years old) in Australia, Puranik found that in about 1/3 of cardiac deaths the heart was structurally normal, suggesting that the etiology was a genetic syndrome. Myocardial infarction (25%) and myocarditis (12%) were next most common. Only 6% of deaths were attributed to hypertrophic cardiomyopathy (HCM).

These percentages are in sharp contrast to those in young athletes that die suddenly. In young athletes however, there are variations depending on the region in which the individuals live and other factors to be discussed. In the USA, for example, HCM is consistently named as the most common cause of sudden cardiac death while in northern Italy, arrhythmogenic right ventricular dysplasia/cardiomyopathy is most common. Indeed, estimates will vary depending on the gender (sudden death is much more common in young males), age (more common in college athletes than high school athletes), level of activity (competitive vs recreational athlete), and definition of sudden death.

Data compiled by O’Connor et al indicate that the incidence of non-traumatic sudden death in high school and college athletes is 7 and 1 per million per year in males and females, respectively. In US air force recruits 17 to 28 years old, the incidence is 1:735,000 and in Rhode Island joggers less than 30 years old, 1:280,000 per year.

The most common entities associated with sudden cardiac death in the young are cardiomyopathies (particularly HCM), coronary anomalies, obstructive coronary artery disease, myocarditis, valvular disease, channelopathies, and aortic disease that lead to dissection or rupture. Some of these entities will be discussed in greater detail by subsequent speakers.

The above discussion begs the following questions: can sudden death in the young be prevented by screening studies? What would it cost? Is it worth it?

The answer to the first question is - it depends. The consensus of opinions is that history and physical examination alone are ineffective in detecting individuals at high risk of sudden death. Glover and Maron found that in high school and collegiate athletes that experienced sudden cardiac death, history and physical examination led to a correct diagnosis in less than 1% of cases. On the other hand, the group from the Veneto region of northern Italy found that by adding an EKG to the screening evaluation the detection of HCM increased 4 fold. Furthermore, during the course of their pre-participation screening program, the Italian group observed a decrease in the incidence of sudden cardiovascular death in athletes from 4.19 to 0.40 per 100,000 person-year. Overall, during the 26 year period of the program, there was an 89% decrease in the incidence rate of sudden cardiovascular death in young competitive athletes 12-35 years old.

The Veneto group estimated the cost of screening at 40-45 US dollars per person. It has also been estimated that about 200,000 competitive athletes would need to be screened to identify one athlete who would die during competition.

Is it worth it? Who can place a value on a human life to a family, community, or society.

#### **BULLET POINTS:**

- Sudden cardiovascular death is a rare but catastrophic event in young men and women throughout the world
- Sudden death is difficult to prevent since it may be the first and last manifestation of cardiovascular disease and the greatest number of deaths occurs in “low-risk” groups
- The most common causes of cardiovascular deaths in the young are cardiomyopathies, coronary anomalies, obstructive coronary artery disease, myocarditis, valvular disease, channelopathies, and aortic disease that lead to dissection or rupture.
- Appropriate pre-participation screening of competitive athletes can reduce the incidence of sudden cardiovascular death in the young
- Whether or not measures to try to prevent these rare deaths are indicated or cost effective are matters of discussion and controversy

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# The risk of coronary sudden death in the young: a pathology overview

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In contrast to the adult, coronary disease is an infrequent cause of sudden death in the young. As might be expected, coronary disease in the young is frequently caused by congenital anomalies, as opposed to acquired conditions such as atherosclerosis in the adult. In addition, the type of coronary atherosclerosis that is seen in young patients, when it does occur, tends to differ from that seen in patients over 40 years of age.

The largest group of sudden cardiac death under the age of 20 is unexplained arrhythmia in the absence of morphologic abnormality in the heart at autopsy. In the state of Maryland, sudden cardiac death in the < 20 age groups occurs in approximately 2/100,000 population yearly, which is compared to a rate of over 100 per 100,000 for sudden infant death syndrome. Of sudden cardiac deaths occurring < 20 years, a coronary etiology is found in less than 10%, in the form of anomalous origin of the coronary arteries. Therefore, the risk of sudden coronary death in individuals under age 20 is quite small, <0.2/100,000 incidence, and is due to ectopic origin of coronaries. Other major causes of sudden cardiac death in this age range include structural congenital heart disease and myocarditis.

In the age range of 20-40 years, the incidence of sudden cardiac death is about four times greater than in the <20 year-old age group, with a higher rate of coronary disease. The rate of congenital coronary artery anomalies and idiopathic arrhythmias remains about the same as in the age range <20 years, but the proportion of these as the overall total drops significantly, to <5% and about 20%, respectively. The most common cause of coronary disease is atherosclerosis, with a small number of idiopathic coronary artery dissections at a similar to rate to anomalous origin. The overall most common cause of sudden cardiac death in the 20-40 year-old age range is cardiomyopathy, slightly higher than coronary atherosclerosis.

There are 3 anomalies that represent most sudden coronary deaths under age 20 years. The left main coronary artery arises from the pulmonary trunk in 1/50,000 to 1/300,000 autopsies, representing 0.25 to 0.5% of congenital heart disease. There is a female predominance of 2:1. Most cases are identified in the first year of life, and sudden death occurs in approximately 40% of cases. Sudden death usually occurs at rest, but may occur after strenuous activity in older children. The aberrant artery arises in the left pulmonary sinus in 95% of cases. Typically, the artery appears thin-walled and vein-like, and the right coronary artery, while normal in location, is tortuous. The heart is typically enlarged, with extensive scarring and thinning of the anterolateral left ventricular wall and anterolateral papillary muscle. Dilatation of the left ventricle with endocardial fibroelastosis is common, and the gross appearance of the heart may mimic dilated cardiomyopathy.

The second anomaly, which is the common coronary anomaly resulting in sudden death in adults, is an aberrant left main arising in the right coronary sinus of Valsalva. There is a male/female ratio

of 4:1 - 9:1. Sudden death occurs in up to 2/3 of patients with this anomaly, 75% of which occur during exercise. Most patients are adolescents or young adults, although death may occur as young as 1 month of age. There are often premonitory symptoms of syncope or chest pain, but stress electrocardiograms and stress echocardiograms are often negative. The ectopic ostium is typically near the commissure, and in some cases actually lies above the commissure between the right and left sinuses. Often, the ostium is somewhat malformed and slit-like, and an ostial ridge is present. The proximal artery lies within the aortic media and may be compressed during diastole. In most cases, and virtually all cases of sudden cardiac death, the aberrant artery passes between the aorta and the pulmonary trunk. In a minority of cases, the left main travels anterior to the pulmonary trunk, posterior to the aorta, or posterior to the right ventricular outflow tract within the ventricular septum.

The third anomaly that may cause sudden cardiac death in the young is ectopic origin of the right coronary from the left sinus of Valsalva. The ostium supplying the right coronary artery may have similar features as anomalous left ostia located in the right sinus. Namely, there may be upward displacement, location near the commissure, and slit-like ostia with ostial ridges. Most deaths are exertional, and occur between the ages of 20 and 35. The majority of patients with this anomaly live a normal life span, but up to 1 in 3 die suddenly.

Coronary artery dissection accounts for approximately 0.5% of sudden deaths in patients 20-40 years old. Most patients are young women, sometimes in the post-partum period, and one patient with Marfan syndrome has been reported. In cases studied clinically, patients have presented with chest pain, electrocardiographic evidence of acute myocardial infarctions, and contrast dye within the false lumen at catheterization. Over 90% of cases causing sudden death involve the left anterior descending coronary artery. Histologically, the dissection plane is in the outer media with infiltrates of eosinophils, lymphocytes, neutrophils and macrophages in the adventitia. The etiology is obscure; although an intimal tear and medial perforation can be found if extensively sought after, clear-cut histologic features of medial dysplasia are usually absent. In about 50% of cases, an acute and/or healed infarction in the area perfused by the dissected artery is seen, generally in the anterior wall of the left ventricle.

Coronary atherosclerosis in patients younger than 40 generally occurs after age 20. Autopsy studies show that, in comparison to patients with severe coronary atherosclerosis dying after age 40 years, there are few lipid-rich plaques, and most thrombi are erosions with ongoing organization of thrombus.

Rare causes of sudden coronary death that may occur in the young include coronary vasculitis, coronary thrombosis secondary to coagulopathies, coronary artery dysplasia, and coronary embolism. Coronary vasculitis comprises Kawasaki disease in children < 6 years, isolated (idiopathic) coronary arteritis, and coronary arteritis associated with ascending aortitis (Takayasu disease).

**BULLET POINTS:**

- Coronary disease is a rare cause of sudden cardiac death under the age of 40 years. The underlying etiology is ectopic origin of the coronary arteries.
- The three most common forms of anomalous coronary artery that causes sudden death are, in ascending order of mean age at presentation, ectopic origin of the left main in the pulmonary trunk, ectopic origin the left main in the right sinus of Valsalva, and ectopic origin of the right coronary in the left sinus of Valsalva.
- Spontaneous coronary artery dissection is the third most common cause of sudden coronary death, after coronary atherosclerosis and anomalous origin, in individuals aged 20-40 years. The etiology is unknown.

- Rare causes of sudden coronary death in the young included coronary arteritis, dysplasia, embolization, and idiopathic thrombosis.
- Coronary atherosclerosis in the young may cause sudden cardiac death and differs from typical atherosclerosis in paucity of lipid rich plaques and frequency of acute plaque erosions.

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# Cardiomyopathies and sudden death

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Cardiomyopathies are among the leading causes of sudden death in young people. Both hypertrophic and arrhythmogenic cardiomyopathies carry a significant risk of sudden death, even in individuals who have not experienced prior symptoms of contractile dysfunction. This talk will focus primarily on the arrhythmogenic cardiomyopathies, a general term that includes arrhythmogenic right ventricular cardiomyopathy (ARVC), the most common clinical form of this group of diseases. Arrhythmogenic cardiomyopathies are characterized clinically by a high incidence of ventricular tachyarrhythmias and increased risk of sudden death which may occur early in the disease process, typically before significant ventricular remodeling or contractile dysfunction develop. These cardiomyopathies are characterized pathologically by cardiac myocyte degeneration and replacement by fibro-fatty scar tissue. It is now recognized that many patients with arrhythmogenic cardiomyopathy have mutations in genes encoding proteins of the desmosome including desmoplakin, plakoglobin, plakophilin and the desmosomal cadherins desmoglein and desmocollin. We have observed deficient localization of the desmosomal protein plakoglobin ( $\gamma$ -catenin) in a great majority of patients with ARVC. This observation suggests that altered subcellular distribution of plakoglobin may be a final common pathway in disease pathogenesis. It also provides the basis for a sensitive and specific diagnostic test for the disease. We have also observed remodeling of gap junctions in virtually all patients with ARVC. This observation supports the hypothesis that genetic defects in desmosomal proteins may not only cause myocyte injury eventually leading to cardiac myocyte degeneration and fibro-fatty tissue replacement, but also contribute to development of anatomic substrates of sudden death by remodeling gap junctions and altering electrical conduction.

## **BULLET POINTS:**

- Arrhythmogenic cardiomyopathy includes ARVC (the most common form) in which RV free wall involvement is prominent and also LV-dominant and biventricular forms in which other ventricular regions are affected.
- The term “dysplasia” is not appropriately applied to these diseases.
- ARVC is a leading cause of sudden death in young adults (<35 years of age).

- One or more mutations in a desmosomal protein can be identified in ~50% of patients with ARVC. The remaining patients may have mutations in other, as yet unidentified, proteins related to desmosomes or signaling pathways activated by desmosomal proteins.
- The pathogenesis of ARVC is probably related to a combination of altered cellular biomechanical behavior and altered signaling via wnt/catenin pathways.
- Gap junction remodeling occurs in ARVC. It is plausible to suggest that it contributes to conduction abnormalities and arrhythmias but this has not been rigorously established.

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# Sudden cardiac death with “normal” heart: molecular autopsy

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Several culprits may be identified at postmortem in young sudden death (SD) victims, including coronary artery, either acquired or congenital, myocardial, valve, conduction system and congenital heart diseases. However, in up to 20% of cases, the heart is grossly and histologically normal (unexplained SD or “mors sine materia”) and inherited ion channel diseases have been implicated (long and short QT syndromes, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia). These channelopathies are nowadays regarded as inherited cardiomyopathies with isolated electric dysfunction, and are due to defective proteins of sodium and potassium ion channels at the sarcolemma level or receptors for intracellular calcium release. Long QT syndrome, in both autosomal and recessive forms, is characterized by prolonged QT interval, mostly due to potassium channel dysfunction in terms of delay of intracellular potassium current during repolarization. On the opposite, in short QT syndrome, a hereditary disease with autosomal dominant transmission, the potassium reentry is accelerated during repolarization. Both conditions are at risk of SD: the more the length or shortness of the QT interval, respectively, the higher the risk of ventricular fibrillation.

Brugada or Martini-Nava-Thiene syndrome is an inherited autosomal dominant cardiomyopathy, featured by non ischemic ST segment elevation, due to delayed sodium exit during repolarization. Whether there are structural alterations associated with Brugada syndrome is still a matter of controversy.

At difference from the previous ones, catecholaminergic polymorphic ventricular tachycardia presents with normal ECG at rest; ventricular arrhythmias arise only during effort or emotion, when the heart frequency exceeds the threshold of 120-130 beats/min. It is also an inherited disease with autosomal dominant pattern. Molecular investigations disclosed mutations in genes coding the calcium receptors (ryanodine receptor 2 and calsequestrin), located in the membrane of the smooth sarcoplasmic reticulum and in charge of calcium release for electromechanical coupling. Unfortunately, the stress test, which should trigger the ventricular arrhythmias thus unmasking the disease, may result false negative, so that only mutation screening in the family may detect asymptomatic carriers and allow preventive strategies.

Overall, 30-40% of the diseases at risk of SD in the young are genetically, potentially recurrent cardiac disorders, and they include both structural and non structural heart diseases which can account for SD as first clinical manifestation in previously asymptomatic apparently “healthy” people. Thus, autopsy may still represent the first opportunity to make the proper diagnosis and the employment of molecular biology techniques even at postmortem may be of help, particularly to solve the puzzle of “mors sine materia”. Molecular autopsy, carried out in a large cohort of SD

cases, was able to achieve the diagnosis in one third of otherwise unexplained SD cases (14% RyR2, 16% KCNQ1 or KCNH2, 4% SCN5A).

Archived formalin-fixed, paraffin embedded tissue (FF-PET) is the easy way of storage and transport, and thus is typically the only source of DNA available for procurement. However, postmortem genetic testing can be performed only using “DNA-friendly” autopsy material such as EDTA-preserved blood or fresh frozen tissue. More in details, 10 ml of EDTA blood and 5 g of heart and spleen tissues should be frozen and stored at –80°C.

In conclusion, the employment of molecular techniques at autopsy is becoming nowadays an essential tool in the setting of unexplained cardiac SD. To this aim, proper sampling of blood and tissues has been recommended in the guidelines for autopsy investigation proposed by the Association for European Cardiovascular Pathology.

#### **BULLET POINTS:**

- Up to 20% of SD cases in the young present a grossly and histologically normal heart (unexplained SD or “mors sine materia”)
- 30-40% of the diseases at risk of SD in the young are genetically, potentially recurrent cardiac disorders
- Autopsy investigation of cardiac SD in the young should always include sampling for molecular investigation
- “DNA-friendly” autopsy material such as EDTA-preserved blood or fresh frozen tissue is recommended for genetic screening purposes

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# How to identify patients at risk

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Cardiovascular disease that predispose to sudden death in the young include structural heart diseases and primary electrophysiologic disorders in the absence of any structural heart disease. The most common structural heart diseases include hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia/cardiomyopathy, anomalous origin of a coronary artery, various congenital heart diseases, cardiomyopathy and myocarditis. Primary electrophysiologic disorders include ventricular preexcitation, long QT syndrome, short QT syndrome, Brugada Syndrome, and catecholamenergic polymorphic ventricular tachycardia (CPVT).

Patients with structural heart disease and prior cardiac arrest or sustained ventricular tachycardia are particularly at risk for sudden cardiac death. Patients with a family history of premature sudden death, prior syncope especially exercise induced syncope, spontaneous or exercise induced ventricular arrhythmias, and certain genotypes associated with sudden death can be identified as being at high risk of sudden death.

Genetic syndromes that predispose to sustained ventricular tachycardia or fibrillation, which represent the focus of this presentation, include Wolf Parkinson White Syndrome, the long and short QT syndromes, Brugada Syndrome, idiopathic ventricular fibrillation, and catecholamenergic polymorphic ventricular tachycardia. These primary electrical conditions typically exist in the absence of any underlying structural heart disease and predispose to cardiac arrest. While controversy still exists with regard to risk factors for sudden death with these conditions, there is consensus that those with prior cardiac arrest are at very high risk for recurrent arrhythmic events. The long-QT syndromes represent a complex spectrum of electrophysiologic disorders characterized by a propensity for development of malignant ventricular arrhythmias, especially polymorphic VT. Because this is a primary electrical disorder with most patients having no evidence of structural heart disease or LV dysfunction, the long-term prognosis is excellent if arrhythmia is controlled. Long-term treatment with beta-blockers, permanent pacing, or left cervicothoracic sympathectomy may be helpful. ICD implantation is recommended for selected patients with recurrent syncope despite drug therapy, sustained ventricular arrhythmias, or sudden cardiac arrest. Furthermore, use of the ICD for primary prevention of SCD may be considered when there is a strong family history of sudden cardiac death, or when compliance or intolerance to drugs is a concern. The clinical manifestations of a long-QT mutation may be influenced by the specific gene involved and the functional consequences of the mutation in that gene. Risk stratification of patients with long-QT syndrome continues to evolve with data from genetic analysis increasingly for clinical decision making.

The Brugada Syndrome is characterized by ST segment elevation across the right precordial leads in association with a high risk of SCD. While the Brugada pattern ECG most commonly shows J-point segment elevation in leads V1 to V3 and RBBB, the ECG pattern can be intermittent. Less

commonly, the J-point elevation occurs in the inferior leads. Patients with the Brugada Syndrome have a structurally normal heart with a primary channelopathy. This is transmitted with an autosomal dominant pattern of inheritance and over 90% of those affected are male. The genetic basis for the Brugada Syndrome involves the cardiac sodium channel gene (SCN5A). Cardiac events such as syncope or cardiac arrest occur predominantly in the third and fourth decades of life, although presentation with cardiac arrest in neonates or children have been reported. Fever can acutely predispose to cardiac arrest in the Brugada Syndrome. Risk stratification for SCD in patients with the Brugada Syndrome is of clinical importance as implantation of an ICD is the only prophylactic measure able to prevent SCD. As with LQTS, there are no data showing that family history predicts cardiac events among family members with the Brugada Syndrome. Accordingly asymptomatic individuals with the characteristic ECG but without family history are not necessarily at low risk. Additionally, family members of an individual with SCD should not be assumed to be at increased risk of SCD. Patients with a spontaneous Brugada pattern have a worse prognosis than individuals in whom the typical ECG is observed only after pharmacological drug challenge. Patients with syncope and the ECG pattern of spontaneous ST-segment elevation have a 6-fold higher risk of cardiac arrest than patients without syncope and the spontaneous ECG pattern. The role of electrophysiological testing remains controversial in the Brugada Syndrome. While some investigators suggest that EP testing has a useful role in risk stratification, others have not confirmed this observation. EP testing had a low positive predictive value (23%), but over a 3 year period.

Because only a single gene has been linked to the Brugada Syndrome, there is still insufficient information about the contribution of genetic defects in predicting clinical outcome. Mutations in the SCN5A gene do not identify a subset of patients at higher risk of cardiac events. SCD is caused by rapid polymorphic VT or VF frequently occurring at rest or during sleep. Patients with Brugada Syndrome usually do not have ventricular extrasystoles or nonsustained runs of VT at Holter recording. Therefore, the therapeutic approach for these patients is centered on the prevention of cardiac arrest.

CPVT is characterized by ventricular tachyarrhythmias that develop related to physical or emotion stress in the presence of a resting ECG that shows no diagnostic abnormalities at rest. The initial symptoms often manifest during childhood, although late onset cases have been described. CPVT is transmitted by either an autosomal dominant or recessive inheritance pattern. Approximately one-half of the autosomal dominant cases are caused by mutations in the gene encoding the cardiac ryanodine receptor (RyR2). This receptor is responsible for calcium release from the stores of the sarcoplasmic reticulum. Mutations in the gene encoding calsequestrin (CASQ2), a calcium buffering protein in the sarcoplasmic reticulum cause the recessive form of CPVT. Risk stratification for SCD is not possible given the relatively small number of patients reported. Most clinical reports indicate that beta blockers appear to be effective. Patients who have had an episode of VF are considered at higher risk and are usually implanted with an ICD along with beta blocker therapy. The recurrence of sustained VT, hemodynamically nontolerated VT, or syncope with causes other than VT excluded, while receiving beta blockers is considered a marker of higher risk. In such patients an ICD is a commonly used and reasonable approach. EP testing is not useful for management and risk stratification, because CPVT patients are usually not inducible with programmed ventricular stimulation. Both supraventricular and ventricular arrhythmias are usually reproducibly induced by exercise stress. Isolated PVCs generally precede runs of NSVT. With continued exercise, the runs of VT typically increase in duration and VT may become sustained. A beat-to-beat alternating QRS axis that changes by 180°, "bidirectional VT," is the typical pattern of CPVT-related arrhythmias. CPVT patients can also present with irregular polymorphic VT or VF. Beta blockers are generally effective in preventing recurrences of syncope

even when arrhythmias can still be elicited during exercise stress test. If syncope occurs in a patient taking a beta blocker, the implantation of an ICD is recommended.

#### **BULLET POINTS:**

- Sudden death in the young can occur due to structural heart disease or primary electrophysiologic disorders
- Structural heart diseases associated with sudden death in the young include hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia/ cardiomyopathy, anomalous origin of a coronary artery, various congenital heart diseases, cardiomyopathy and myocarditis.
- Genetic syndromes that predispose to sustained ventricular tachycardia or fibrillation include Wolf Parkinson White Syndrome, the long and short QT syndromes, Brugada Syndrome, idiopathic ventricular fibrillation, and catecholaminergic polymorphic ventricular tachycardia
- Patients with a family history of premature sudden death, prior syncope especially exercise induced syncope, spontaneous or exercise induced ventricular arrhythmias, and certain genotypes associated with sudden death can be identified as being at high risk of sudden death.
- Patients at risk for sudden cardiac death with structural heart disease and primary electrophysiologic syndromes include those with prior cardiac arrest, syncope or sustained ventricular tachycardia

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# Is prevention of sudden cardiac death feasible?

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Hypertrophic cardiomyopathy (HCM) has been recognized for 50 years. The risk for unexpected sudden cardiac death was an important component of the initial contemporary description of HCM (Teare; 1958).

Indeed, we now recognize HCM to be the most common cause of sudden death in the young, including trained athletes. While the implantable cardioverter-defibrillator (ICD) was introduced over 25 years ago, it was not systematically applied to HCM until year 2000. The prevention of sudden death has long been an aspiration in HCM.

Early experiences with pharmacologic strategies demonstrated that drugs (e.g., amiodarone) are not absolutely protective against sudden death.

Based on recent substantial experience, the ICD has now proved to be a safe and the only effective therapeutic intervention in patients with HCM, both for primary and secondary prevention of sudden death. The ICD intervenes appropriately to terminate ventricular tachycardia/fibrillation (VT/VF) at a rate of 5.5%/year. The ICD discharge rate is 4%/year for those patients implanted prophylactically due to one or more major risk markers.

Considerable delays up to 10 years may occur before the ICD is required to intervene to abort potentially lethal ventricular arrhythmias.

Primary prevention of VT/VF occurs with similar frequency in high-risk patients with either 1, 2 or  $\geq 3$  noninvasive risk markers. About one-third of patients with appropriate shocks were implanted for only one risk factor.

The ICD has proved reliable despite the extreme and complex phenotype often present in HCM with massive degrees of left ventricular hypertrophy, microvascular ischemia diastolic dysfunction, or dynamic left ventricular outflow tract obstruction.

Failure to convert life-threatening ventricular tachyarrhythmias to normal rhythm is extraordinarily rare.

## **BULLET POINTS:**

- In high-risk HCM patients, ICDs perform in a highly effective fashion, frequently preventing sudden death by terminating primary life-threatening ventricular arrhythmias
- A single marker of high risk can be sufficient evidence to justify consideration for a prophylactic ICD in selected patients with HCM

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