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# WHICH PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY SHOULD RECEIVE A CARDIOVERTER DEFIBRILLATOR?*

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SUMMARY – Ventricular tachyarrhythmias are the most common cause of sudden cardiac death in hypertrophic cardiomyopathy. Cardioverter defibrillator (ICD) therapy therefore presents a reasonable concept of improving prognosis in selected patients with hypertrophic cardiomyopathy. Recently published studies have confirmed this concept and demonstrated that ICD therapy provides life-saving protection by effectively terminating ventricular tachycardia or fibrillation in patients with hypertrophic cardiomyopathy. Since hypertrophic cardiomyopathy has a low risk of sudden cardiac death in the general population, the decision to implant an ICD depends on the patient symptoms and level of risk. ICD is strongly warranted for secondary prevention of sudden death in patients who have survived cardiac arrest or spontaneous sustained ventricular tachycardia. Because the presence of two or more risk factors confers an annual mortality rate of sudden death of 3%-6% or more, their presence in patients with hypertrophic cardiomyopathy justifies prophylactic therapy with ICD for primary prevention of sudden death. Decisions regarding prophylactic ICD therapy in patients with a single risk factor should be individualized depending on patient age and perceived risk factor severity. A young patient with an extreme left ventricular hypertrophy or a family history of sudden death due to hypertrophic cardiomyopathy should be considered as a candidate for ICD, or should be informed on the potential life-saving protection offered by ICD.

Key words: *Cardiomyopathy – therapy; Defibrillators – implantable; Cardiovascular diseases – complications; Risk factors*

## Introduction

The main goal of therapy with implantable cardioverter defibrillator (ICD) is to reduce the incidence of sudden cardiac death in patients who have survived cardiac arrest due to ventricular fibrillation or hemodynamic unstable ventricular tachycardia[1], or in those who are at a high risk for these arrhythmias[2]. Hypertrophic cardiomyopathy is a genetic cardiac disease with diverse clinical course but with a low risk of sudden cardiac death in the general population[3]. Since sudden cardiac death may occur in asymptomatic or mildly symptomatic patients with hypertrophic cardiomyopathy, the identification of high-risk patients who are potential candidates for ICD therapy is the first step in their management. Unfortunately, most of the clinical features associated with an increased risk of dying suddenly have only modest positive predictive accuracy[4], making the decision to implant an ICD in patients with hypertrophic cardiomyopathy more difficult than in patients with ischemic heart disease.

## Epidemiology and Mechanisms

Sudden cardiac death accounts for about 50% of the mortality in hypertrophic cardiomyopathy but its incidence depends on the study population. Earlier hospital-based clinical investigations have reported on the annual incidence of sudden cardiac death from 2% to

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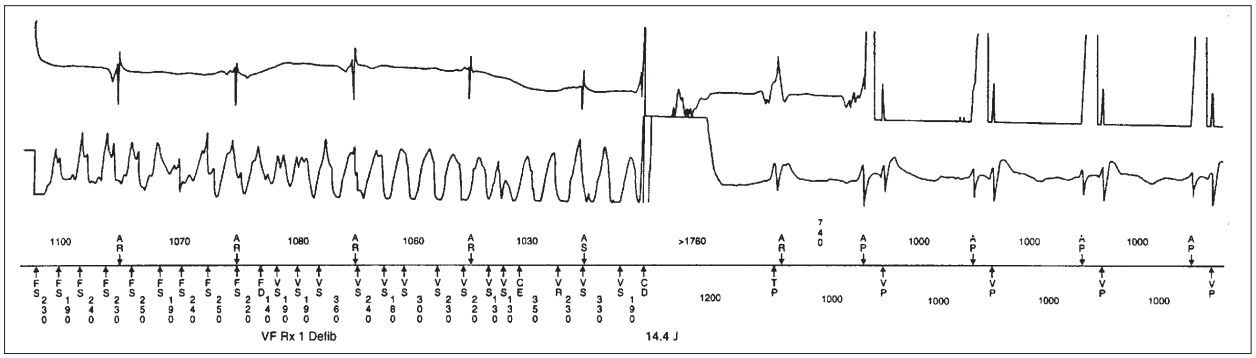


*Fig. 1. Secondary prevention of sudden cardiac death in hypertrophic cardiomyopathy. Continuous recording of stored intracardiac atrial and ventricular electrogram for a patient who had syncope, spontaneous ventricular tachycardia and extreme ventricular hypertrophy. The ICD senses ventricular fibrillation and after programmed interval delivers a defibrillation shock (CD), which restores atrioventricular pacing[10].*

4% in adults, and from 4% to 6% in children and adolescents[5]. In a regionally selected patient population, the annual risk of sudden death was 0.7%[3], and hypertrophic cardiomyopathy did not siginficantly alter the overall life expectancy[6].

In unselected patients with hypertrophic cardiomyopathy studied by Maron et al.[3] the risk of sudden death was not confined to young patients but extended into later phase of life, without statistically significant predilection for any age group. In this study, sudden cardiac death occurred predominantly in patients with no or mild symptoms (NYHA functional class I-II), and most of them died suddenly during or immediately after sedentary or minor physical activities. On the other hand, hypertrophic cardiomyopathy is the most common cause of sudden death in young athletes, accounting for 36% of cases[7].

The available data suggest that ventricular tachyarrhythmias are the cause of sudden cardiac death in the majority of patients with hypertrophic cardiomyopathy. In a study of 32 patients with hypertrophic cardiomyopathy and rhythm recorded at the time of resuscitation from cardiac arrest, 31 had ventricular fibrillation and one patient had ventricular asystole[8]. Stored electrograms from ICD in patients with hypertrophic cardiomyopathy also show ventricular tachycardia rapidly degenerating into ventricular fibrillation before termination of defibrillator charging period (Fig. 1)[9,10]. The efficacy of ICD shocks in restoring sinus rhythm and immediate recovery of patients after ICD intervention[9-12] argue against a catastrophic hemodynamic event preceding ventricular arrhythmias in patients with hypertrophic cardiomyopathy. These data suggest that ventricular arrhythmias in hypertrophic cardiomyopathy are more likely a primary event resulting from electrical instability of an arrhythmogenic substrate (disarray or myocardial scarring) than a secondary phenomenon triggered by myocardial ischemia, outflow obstruction, diastolic dysfunctionn, or supraventricular tachyarrhythmias.

## Risk Stratification

One of the main aims on assessing patients with hypertrophic cardiomyopathy is the identification of individual risk for sudden cardiac death. Clinical parameters currently used to assess the risk level for sudden death in hypertrophic cardiomyopathy[12] are shown in Table 1. Unfortunately, all of these risk factors except for ventricular fibrillation and spontaneous ventricular tachycardia have a low positive predictive value because

*Table 1. Major risk factors for sudden cardiac death in hypertrophic cardiomyopathy*

- Cardiac arrest (ventricular fibrillation)
- Spontaneous sustained ventricular tachycardia
- Familial sudden hypertrophic cardiomyopathy-related death
- Syncope (particularly if recurrent, exertional, or in the young)
- Nonsustained ventricular tachycardia (frequent, repetitive, or symptomatic)
- Abnormal blood pressure response to exercise (in patients aged ≤ 40)
- Extreme left ventricular hypertrophy (maximum thickness ≥ 30 mm)

*Table 2. Relation between the number of risk factors* and sudden death in patients with hypertophic cardiomyopathy (N=368)*

| Number of patients | Number of risk factors | Annual risk of sudden death | Six-year survival |
|---|---|---|---|
| 203 | 0 | 0.8% | 95% |
| 122 | 1 | 1.2% | 93% |
| 36 | 2 | 3.0% | 82% |
| 7 | 3 | 6.0% | 36% |

*nonsustained ventricular tachycardia, syncope, abnormal blood pressure response, family history of sudden death, left ventricular hypertrophy ≥ 30 mm

the majority of patients with one of these factors will never have sudden death. On the other hand, their negative predictive value for sudden death is very high. Therefore, a patient with none of these factors has a favorable prognosis and should be allowed to conduct normal life.

The risk is considered to be higher when two or three of the clinical parameters are associated (Table 2)[4,13]. In children and adolescents with hypertrophic cardiomyopathy, syncope on exertion is an ominous symptom, but the risk is higher when syncope occurs in individuals with a family history of sudden cardiac death due to hypertrophic cardiomyopathy[4]. A similar logic should be used in patients with hypertrophic cardiomyopathy who have nonsustained ventricular tachycardia. In these patients, nonsustained ventricular tachycardia is prognostically significant only when being repetitive or associated with symptoms of impaired consciousness[14]. The use of programmed ventricular stimulation to test inducibility of ventricular arrhythmias in selected patients with hypertrophic cardiomyopathy is controversial[15,16]. Limitations include infrequent success of provocation of the monomorphic ventricular tachycardia and the nonspecificity of rapid polymorphic ventricular tachycardia and ventricular fibrillation. Although the current European guidelines for electrophysiologic procedures indicate no role for electrophysiologic studies in hypertrophic cardiomyopathy[17,] we use this diagnostic procedure in patients who have nonsustained ventricular tachycardia[18]. New possibilities in the risk stratification have been offered by finding that some gene mutations, such as cardiac troponin T and beta cardiac myosin heavy chain mutations causing hypertrophic cardiomyopathy, indicate a particularly high risk of sudden cardiac death[19]. However, caution is warranted before any strong conclusions are derived regarding prognosis based solely on the available epidemiologic genetic data, which are relatively limited and skewed by virtue of selection bias towards high-risk families[20].

## ICD Therapy in Secondary and Primary Prevention of Sudden Cardiac Death

Earlier data on the use of ICD in patients with hypertrophic cardiomyopathy were limited to retrospective studies of secondary prevention in small numbers of patients who had survived cardiac arrest or sustained ventricular tachycardia[11,12,21,22]. Recently, two large studies have been published[9,23] that provide compelling support for the use of ICD for secondary as well as primary prevention in selected high-risk patients with hypertrophic cardiomyopathy. Maron *et al*.[9] have presented the results of a retrospective study that investigated the efficacy of ICD therapy in 128 patients with hypertrophic cardiomyopathy. The mean age of patients was 40 years. In 43 patients, ICDs were implanted for secondary prevention after either resuscitation from ventricular fibrillation, or for sustained spontaneous ventricular tachyardia. In this group of patients, the annual rate of appropriate discharges was 11 percent, with a cumulative rate of 75 percent at 10 years. A strikingly higher rate of interventions occurred in the first four months of implantation, confirming that patients with hypertrophic cardiomyopathy have unstable period. However, there also were substantial rates of recurrent and late events. In this group, the device failed to prevent death in two patients who had end-stage hypertrophic cardiomyopathy with severe systolic dysfunction and heart failure.

Even more important were the results in the remaining 85 patients, who received ICDs for primary prevention. The predominant clinical indications for prophylactic implantation were syncope (n=41), family history of sudden death due to hypertrophic cardiomyopathy (n=39), nonsustained ventricular tachycardia (n=32), and left ventricular wall thickness ≥30 mm (n=10). In addition, 61 patients had two risk factors for sudden cardiac death, and 56 had inducible ventricular tachyardia or fibrillation during programmed ventricular stimulation. In this group of patients, the annual rate of appropriate discharges was 5 percent, which was significantly lower than in the secondary prevention group (Fig. 2). The cumulative discharge rate reached a plateau at approximately 20 percent. By extrapolating from this discharge rate, one could predict that within 10 years almost 50 precent of the ICDs prophylactically implant-

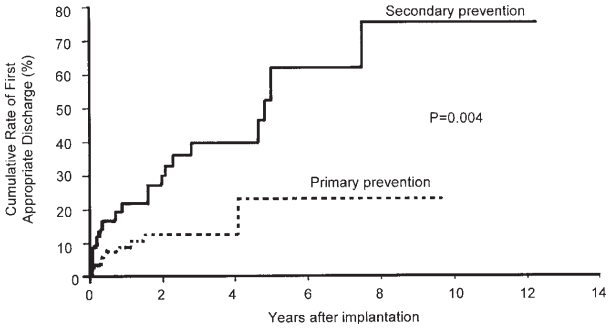


*Fig. 2. Cumulative rates of ICD discharges in 128 hypertrophic cardiomyopathy patients implanted for secondary prevention after cardiac arrest or sustained ventricular tachycardia, or implanted for primary prevention because of risk factors for sudden cardiac death[9].*

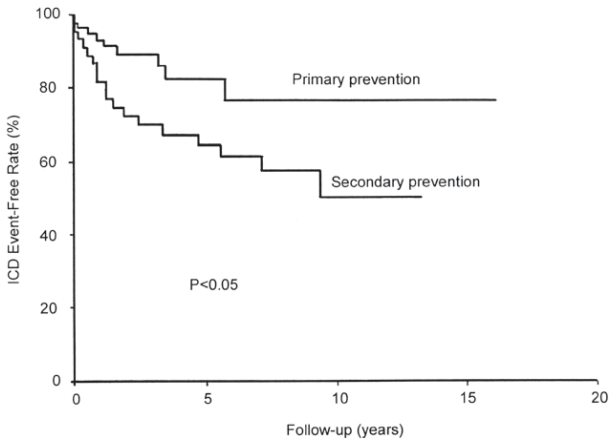


*Fig. 3. Comparison of appropriate ICD intervention-free rates in patients in whom ICDs were implanted for primary and secondary prevention[23].*

ed in young patients would discharge and prevent sudden death. The presence of left ventricular hypertrophy ≥30 mm was found to be the most justified indication for primary prevention of sudden cardiac death (Table 3). The incidence of complications of ICD therapy was also significant. Inappropriate therapies were delivered in 25% of patients, due to sinus tachycardia, atrial fibrillation, or lead dislodgement, fracture, or oversensing. There was one death at the time of implantation, one hemorrhage requiring thoracotomy, and two infections requiring explantation.

Recently, Begley *et al*.[23] investigated the efficacy of ICD therapy in 132 patients with hypertrophic cardiomyopathy. The mean age of patients was 34 years. The indications for secondary prevention were sustained ventricular tachycardia or cardiac arrest in 47 patients, and indications for primary prevention were clinical features

*Table 3. Relation between appropriate implantable cardioverter defibrillator (ICD) intervention and indications for implantation*

| Implantation indications | Number of patients | Appropriate ICD intervention |
|---|---|---|
| ***Secondary prevention*** | | |
| VF or spontaneous VT | 43 | 44% |
| ***Primary prevention*** | | |
| LV hypertrophy ≥30 mm | 10 | 20% |
| Syncope | 41 | 12% |
| Nonsustained VT | 32 | 6% |
| Family history of SD | 3 | 3% |

VF=ventricular fibrillation; VT=ventricular tachycardia; LV=left ventricular; SD=sudden death

associated with an increased risk of sudden cardiac death in 85 patients. In the primary prevention group, the patients had almost four risk factors for sudden death, including syncope (n=38), nonsustained ventricular tachycardia (n=51), more than one sudden death in first degree relatives (n=39), severe left ventricular hypertrophy (n=19), abnormal blood pressure to exercise (n=21), or inducible sustained ventricular tachycardia (n=46). During the mean follow-up of 4.8 years, there were 6 deaths and 55 appropriate interventions in 27 (20%) patients. The annual therapeutic ICD intervention rate was lower in the primary prevention group than in the secondary prevention group (3% *versus* 7%, $p<0.05$). However, survival rates were similar in the two groups (94% for primary *versus* 98% for secondary prevention of sudden death). The cumulative intervention rate at 5 years was also significantly lower in patients in whom ICD therapy was used for primary prevention than in patients who received this therapy for secondary prevention of sudden cardiac death (16% *versus* 26%, $p<0.05$) (Fig. 3). None of the risk factors used was associated with significantly higher rates of therapeutic ICD interventions. Serious complications were recorded in 38 patients, including inappropriate shocks in 30 patients. The complication rates were similar for primary and secondary prevention of sudden death.

Are the results of these studies definitive? At least in case of primary prevention, the answer is no, since there remains the issue of precise identification of patients in whom the risk of sudden death is high enough to warrant this intervention. Clearly, in most patients

with hypertrophic cardiomyopathy, the risk is not high enough to offset the adverse effects of ICD. An international registry should be created to document discharge rates after implantation for each of the risk factors used. The ACC/AHA/NASPE 2002 guidelines have designated ICD for primary prevention of sudden cardiac death as a class IIb indication and for secondary prevention as a class I indication[25].

## Conclusion

Recent studies have demonstrated that ICD provides life-saving protection by effectively terminating ventricular tachycardia or fibrillation in patients with hypertrophic cardiomyopathy. Therefore, patients with prior cardiac arrest or sustained spontaneous ventricular tachycardia without any evident precipitating cause that can be eliminated, have a class I indication for ICD therapy[25].

ICD is strongly recommended for primary prevention of sudden cardiac death in patients with two or more risk factors identified during noninvasive risk stratification, in whom annual rates of sudden cardiac death are 3% to 6% or more[17]. The presence of a single risk factor is of lower positive predictive value and in most patients decisions on prophylactic prevention should be individualized depending on the patient age and perceived risk factor severity. Therefore, a young patient with left ventricular thickness $=30$ mm[12,24] should be considered as a candidate for ICD therapy, or should be informed on the potential life-saving protection offered by ICD.

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Sažetak

## KOJI BOLESNICI S HIPERTROFIČNOM KARDIOMIOPATIJOM TREBAJU KARDIOVERTER DEFIBRILATOR?

*D. Petrač*

Ventrikulske tahiaritmije su najčešći uzrok iznenadne srčane smrti u bolesnika s hipertrofičnom kardiomiopatijom. Stoga liječenje kardioverterom defibrilatorom (ICD) predstavlja prihvatljiv koncept za poboljšanje prognoze u izabranih bolesnika s hipertrofičnom kardiomiopatijom. Nedavno objavljene studije potvrđuju ovaj koncept i pokazuju da ICD djelotvornim prekidanjem ventrikulske tahikardije ili fibrilacije zaštićuje život u bolesnika s hipertrofičnom kardiomiopatijom. Budući da hipertrofična kardiomiopatija ima nizak rizik od iznenadne srčane smrti u općoj populaciji, odluka o liječenju ICDom ovisi o bolesnikovim simptomima i stupnju rizika. Liječenje ICDom je nedvojbeno indicirano u sekundarnoj prevenciji iznenadne smrti u bolesnika koji su preživjeli srčani arest ili spontanu postojanu ventrikulsku tahikardiju. S obzirom na to da prisutnost dvaju ili više čimbenika rizika ima godišnju smrtnost od iznenadne smrti od 3%-6%, njihova prisutnost u bolesnika s hipertrofičnom kardiomiopatijom opravdava profilaktičnu ugradnju ICDa u primarnoj prevenciji iznenadne smrti. Odluka o profilaktičnoj ugradnji ICDa u bolesnika s jednim čimbenikom rizika treba biti idividualizirana s obzirom na dob i uočenu težinu samog čimbenika rizika. Mlađeg bolesnika s ekstremnom hipertrofijom lijevog ventrikula ili obiteljskom anamnezom iznenadne srčane smrti uslijed hipertrofične kardiomiopatije treba razmotriti kao kandidata za ugradnju ICDa i obavijestiti ga o mogućnostima koje ICD pruža u zaštiti života.

Ključne riječi: *Kardiomiopatija, hipertrofična; Kardiomiopatija, hipertrofična – terapija; Defibrilatori – ugradivi; Kardiovaskularne bolesti – komplikacije; Rizični čimbenici*