Selective implantation of cardioverter-defibrillators in patients with genetic heart disease and sudden death risk

Genetik hastalığı ve ani kardiyak ölüm risk altında olan hastalarda kardiyoverter-defibrilatörlerin selektif implantasyonu

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ABSTRACT

The implantable cardioverter-defibrillator (ICD) therapy is an established intervention for the prevention of sudden cardiac death (SCD) in patients with significant left ventricular dysfunction. Multiple randomized clinical trials have studied the use of ICD for the primary and secondary SCD. These studies were performed in patients with left ventricular dysfunction from coronary artery disease or dilated cardiomyopathy, and the marker of reduced ejection fraction has emerged for selecting patients who would benefit from ICD therapy. Currently, for most of these patients the decision to implant, or not, is determined by relatively straightforward paradigms.

The same cannot be said for the genetic cardiac diseases associated with SCD - long QT syndrome, Brugada syndrome, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular dysplasia. Indications for ICD in these conditions are very much a work-in-progress.

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Key words: Long QT syndrome, Brugada syndrome, hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, implanted cardioverter-defibrillator

ÖZET

Implante edilebilen kardiyoverter-defibrilatör (ICD) terapisi önemli LV fonksiyon bozukluğu olan hastalarda ani kardiyak ölümün (AKÖ) önlenmesi için oluşturulmuş bir müdahaledir. Birçok randomize klinik çalışmada AKÖ'nün birincil ve ikincil korunmasında ICD kullanımı incelendi. Bu çalışmalar sol ventrikül disfonksiyonu olan koroner arter hastalığı veya dilate kardiyomiyopatisi olan hastalarda yapılmış ve ICD tedavisinden yararlanacak hastaların seçiminde azalmış ejeksiyon fraksiyonu kullanılmaktadır. Şu anda, bu hastaların çoğu için implant kararı, nispeten basit paradigmalar ile belirlenmektedir. Ancak, aynısı genetik kalp hastalıkları ile ilişkili AKÖ için söylenemez: uzun QT sendromu, Brugada sendromu, hipertrofik kardiyomiyopati ve aritmojenik sağ ventrikül displazi. Bu koşullarda ICD endikasyonları konusunda pek çok çalışma hala sürdürülmektedir.

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Anahtar kelimeler: Uzun QT sendromu, Brugada sendromu, hipertrofik kardiyomiyopati, aritmojenik sağ ventrikül kardiyomiyopati, implante edilebilen kardiyoverter-defibrilatör

Introduction

Decisions to employ the implanted cardioverter-defibrillator (ICD) in inherited heart disease with sudden death risk are complicated by the genetic heterogeneity of the phenotypes, the younger age of patients, and the lack of well established strategies for risk stratification. The less common genetic heart diseases are a heterogeneous group of disorders that are not common or large enough to support study in formal randomized clinical trials. Thus, most of the data regarding the use of ICD is made by extrapolation of registry data or guided by expert opinion. Moreover, in genetic disorders like congenital long QT syndrome and Brugada syndrome, the natural history and true incidence of sudden cardiac death (SCD) has not been adequately studied because of referral bias. Patients who present to specialized clinics are likely represent the sickest patients

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and the most affected families with the worst prognosis. In addition, a more representative sample is not likely to emerge since specialized clinics are where data about these conditions is accumulated. Complicating this lack of knowledge, is the research practice of counting appropriate ICD shocks as equivalent to SCD, which has been shown to be incorrect. In randomized trials of patients with left ventricular (LV) dysfunction the incidence of appropriate shock has been roughly 2 times the incidence of SCD in the control groups without ICD implantation (1). This probably occurs because the ICD has intervened for ventricular tachycardia that would have self- terminated. Alternatively, it is possible that the ICD itself is pro-arrhythmic. Thus, in this review we will describe natural history studies from the pre-ICD era, separately from ICD studies that have tabulated appropriate ICD interventions.

The benefit of ICD implantation is the detection of malignant arrhythmia by the device, and the therapies to terminate arrhythmia that may prevent SCD. Recently, considerable attention has attended the substantial adverse consequences of ICD implantation. The cumulative risks of ICD, discussed at the end of this paper, may be more substantial in a young patient with genetic heart disease because of the long duration of ICD implantation. A complete appraisal of the risks of implantation must be weighed against the benefits. Implantation of an ICD is a lifelong decision. This review critically examines what is known, and what is not, about the current indications for ICD in 4 common genetic heart diseases namely long QT syndrome, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy/dysplasia and hypertrophic cardiomyopathy with the challenges that are unique to this patient population.

Long QT syndrome

Congenital long QT syndrome is a genetic disorder that is characterized by prolongation of QT interval on the EKG and predisposition to SCD from ventricular fibrillation. Mutations in potassium-channel genes KCNQ1 (LQT1 locus) and KCNH2 (LQT2 locus) and the sodium-channel gene SCN5A (LQT3 locus) are the most common causes of the congenital long-QT syndrome. The various mutations individually lead to disruption of the normal cardiac myocyte action potential and lead to propensity for ventricular arrhythmias.

Natural History of Sudden Death in Long QT syndrome

Moss et al. (2) used records from 328 families of unknown genotype from the International Long QT Registry to demonstrate the link between QTc and the risk of cardiac events. They reported that in patients the rate of LQTS-related sudden death (before age 50) was 0.9%/year. In contrast, in affected family members sudden death occurred at a rate of 0.2% year. Priori's study described the risks to LQTS patients in a large cohort of 647 patients. Over an observation period of 28 years 87 (13%) of 647 patients had cardiac arrest or had died suddenly before the age of 40 years. Using genotypes of long QT syndrome, LQT3 has the highest risk of cardiac arrest or sudden death (0.6%/yr), LQT2 (0.56%/yr) and LQT1 (0.3%/yr). The mean time of first cardiac event was young, <20 years of age in all genotype subgroups. (Moss found that 57% of patients with SCD died before age 20). Priori et al. (3) proposed a risk model using both QTc duration >500ms, gender, and genotype to risk stratify subtypes by determining the probability of a first cardiac event, defined as the occurrence of syncope, cardiac arrest, or sudden death before the age of 40 years before initiation of therapy. All patients with QTc greater than 500 msec were high risk (>50% chance of events before 40 years) except for females with LQT3 with QTc > 500 msec who were intermediate in risk. In contrast, patients considered to be low risk (<30% chance of events) were males with LQT1 and LQT2 who had QTc < 500 msec. All others fell in an intermediate risk group.

ICD Registries

Zareba et al. (4) examined the influence of various LQT genotypes and found that the risk of cardiac events (syncope, aborted cardiac arrest, or sudden death) was higher among patients with LQT1 than those with LQT2, whereas the percentage of potentially fatal cardiac events was highest among patients with a mutation at the LQT3 locus. Mönnig et al. (5) reported on a 5 yr follow-up of ICD therapy in 27 LQTS patients classified as high risk because of a history of aborted cardiac arrest in 17, syncope on beta blockers in 9, and a strong family history of SCD in 1 patient. Fifty-nine percent (10/17) of patients received a total of 169 appropriate and 3 inappropriate shocks. None of the 9 patients with prior syncope while taking a beta-blocker required a shock. Further, 7 of 17 (41%) patients did not experience any shocks. They concluded that ICD therapy is safe and useful in high-risk LQTS patients and that beta-blockers should always be added to ICD therapy. Vincent et al. (6) reported on the relative value of using prior aborted SCD as a marker for increased risk. Even among these patients considered to be very high risk of SCD, only 19% of patients receiving beta blockers had shocks during follow-up indicating the heterogeneity not only of the genetic disease but also of the variable penetration and presentation of the disease.

Current guidelines (Table 1) allow early implantation of ICD in patients with LQT2 and LQT3 as these genotypes are considered to be at high risk (7). There are important limitations to extrapolating data from registries to the general group of all patients with long QT syndrome. First, the relative infrequency of the disorder, estimated at 1 in 7,000 persons, which leads to reports of small groups. Secondly, these datasets suffer from referral bias. They include patients or relatives with QTc and severe symptoms from specialized centers. However, this highly symptomatic population, from specialized referral centers may represent only tip of the LQTS iceberg. The large majority of affected individuals may be in the base, with low penetrance, asymptomatic, or low-frequency symptomatic, and perhaps may have low mortality.

Survivors of SCD are considered to be at high risk and placement of an ICD is highly recommended. Prior to the identification of genotypes of long QT syndrome, the QT interval duration was the strongest predictor of syncope and risk for SCD (2). A QTc exceeding 500 ms (corresponding to the upper QTc quartile among affected genotyped individuals) identifies

patients with the highest risk of becoming symptomatic by age 40 years (3). It is important to remember that presence of long QT syndrome does not equate the implantation of an ICD. All patients, identified to have prolonged QT syndrome are begun on beta blockers (7). Beta blockers are also effective in patients who have had syncope or aborted cardiac arrest, but there is an appreciable persistent risk of recurrent nonfatal or fatal cardiac arrest among patients who have had aborted cardiac arrest (14 percent at five years). Beta blockers are most effective in LQT1 and least effective in LQT3. Patients who experience syncope or VT while receiving beta blockers should be referred for consultation for ICD implantation.

Brugada syndrome

Brugada syndrome is a genetic disorder that results from a mutation in the gene coding for the alpha subunit of cardiac sodium channel SCN5A (8). Patients with Brugada syndrome at are increased risk of developing ventricular tachycardia and fibrillation. The electrocardiographic (ECG) pattern has been shown to stratify risk of SCD (See graphic examples of ECG patterns in the paper of Aslam Khan et al. in this Supplement.). Type 1 is diagnostic of Brugada syndrome and is characterized by a "coved" ST-segment ≥2mm (concave down) followed by a negative T wave. A definitive diagnosis of Brugada syndrome can be made when a type 1 ST-segment elevation pattern is observed in >1 precordial lead (V1-V3) along with one of the following 1] documented polymorphic VT or VF 2] a family history of SCD at <45 yrs of age 3] similar type of ECGs in family members 4] inducibility of VT/VF during an EP study (though there is doubt about this as the only adjunctive criteria, as described below) 5] unexplained syncope and 6] history of nocturnal agonal respiration (9). Type 2 ST-segment elevation pattern has a "saddleback" (concave up), appearance with a ST-segment elevation of ≥2 mm, a trough still displaying ≥1 mm ST elevation, and then either a positive or biphasic T wave. Type 3 pattern has either a saddleback or coved appearance with an ST-segment elevation of <1 mm. In patients with either a type 2 or 3 pattern, a diagnosis of Brugada syndrome can be made if there is conversion to a type 1 pattern either spontaneously or after administration of a sodium channel blocker like procainamide (10).

Natural history of Sudden Death in Brugada syndrome

Brugada et al. (11) studied 547 patients with an ECG diagnostic of Brugada syndrome and no previous cardiac arrests. The mean age was 41±15 years, and 408 were male. During a mean follow-up of 24±32 months, 45 patients (8%) suffered sudden death or documented ventricular fibrillation. Patients with spontaneously abnormal ECG, a previous history of syncope, and inducible sustained ventricular arrhythmias had a probability of 27.2% of suffering an event during follow-up.

ICD Registries in Brugada syndrome

Sacher et al. (12) studied 220 patients (age 46±12 years, 183 male) with a type 1 Brugada ECG pattern implanted with an ICD in 14 centers between 1993 and 2005. Nearly half of the patients had syncope or had positive EP study. At mean FU follow-up of 3 yrs, no patients died and the incidence of arrhythmic events was less than 3%/yr. Only 8% of patients had appropriate therapy from the device. However, importantly, 20% of patients had inappropriate shocks. The complication rate was 28%, including inappropriate shocks, which occurred in 45 patients from combination of lead failure, T-wave oversensing, and supraventricular arrhythmias in this young cohort of patients. In another retrospective analyses of 47 patients, Sarkozy et al. studied 47 patients (age 44±15 yrs) with Brugada syndrome that underwent primary prophylactic ICD implantation (13). All patients had baseline spontaneous (23

Table 1. Guidelines for ICD implantation in Long QT Syndrome

	Recommendation Class	Level of Evidence
Implantation of an ICD along with use of beta blockers is recommended for LQTS patients with previous cardiac arrest and who have reasonable expectation of survival with a good functional status for more than 1 year	I	A
ICD implantation is reasonable to reduce SCD in patients with long-QT syndrome who are experiencing syncope and/or VT while receiving beta blockers	IIA	B
Implantation of an ICD with use of beta blockers may be considered for prophylaxis of SCD for patients in categories possibly associated with higher risk of cardiac arrest such as LQT2 and LQT3	IIB	B

ICD - implanted cardioverter defibrillator, LQT - long QT interval, SCD - sudden cardiac death

Recommendations and Level of Evidence :

Class of Recommendations

- Class I: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.
- Class II: Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment.
- Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.
- Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
- Class III: Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence

- Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses.
- Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies.
- Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care

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patients) or drug-induced (24 patients) coved type I ECG pattern. All patients were judged to be at high risk because of syncope (26 patients) and/or a positive family history of sudden death (26 patients). During a median follow-up of 47.5 months, 7 patients had appropriate shocks (2.6%/year). However, 17 patients received inappropriate shocks (IS); 8 patients for sinus tachycardia; 6 patients for new onset atrial arrhythmias; and 5 patients for noise oversensing. New onset atrial fibrillation (AF) and age less than 50 years were independent predictors of significantly shorter IS-free survival (p=0.04 and P=0.036, respectively). These studies, with their relatively low appropriate intervention rates and their relatively high complication rates, highlight the need for better risk stratification for implantation of ICD.

Current guidelines (Table 2) recommend ICD implantation for Brugada patients with previous cardiac arrest as these individuals are at high risk for repeat events. For primary prevention, use of electrophysiologic testing using programmed electrical stimulation (PES) has been suggested as a method of identifying a high-risk cohort. Unfortunately, electrophysiologic testing (EP) testing using PES for risk stratification is a very poor marker of future events especially cardiac arrest. Several studies have indicated that PES inducibility is deeply influenced by the protocol used and the variability of ventricular tachycardia (VT) inducibility in patients with Brugada syndrome is high and does not correlate with clinical presentation (14). Further, in an analysis of 200 patients with SCN5A genetic mutation PES failed to demonstrate an association between PES inducibility and spontaneous occurrence of ventricular fibrillation (9).

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is considerably more common, 1:500 prevalence in the general population, than the 2 previously described conditions. Familial HCM is caused by mutations in the genes that code for sarcomeric proteins. In probands a gene-causing mutation can be found in 50% of diagnosed patients. Rare phenocopies are caused by non-sarcomeric protein mutations. Though there are no mutations that have definitely been shown to be associated with a higher incidence of SCD, it has been shown that the presence of any disease-causing mutation portends a poorer prognosis of the combined end-points of mortality and progression to higher grade of disability (15).

The Natural History of Sudden Death in HCM

SCD is a prominent feature of the clinical course of HCM and is its most dreaded complication. Early studies reported an incidence of up to 4% per year of SCD (16). This was shown to be an overestimation, mainly due to referral bias. Subsequent studies, in newly diagnosed individuals from rural communities by Maron et al have shown a yearly overall HCM-related mortality of 1.5% per year with 1%/year due to SCD and 0.5%/year due to heart failure (17). A 1% SCD mortality would not be considered high in an elderly heart failure patient population. It is the young age of HCM SCD that occurs at an average of 40 years of age, that makes this an important management issue especially since it may occur in patients with relatively preserved cardiac functional status and otherwise good life expectancy.

Ability to predict which patients with HCM will experience sudden death has long been a clinical goal. Risk factors for SCD may increase SCD mortality to 2-4%/year (15, 17-21). Risk stratification has received more attention since the advent of SCD prevention with the ICD for both primary and secondary prevention (20). Because patients with HCM may present at young age, and since the risk period for sudden arrhythmic death may be long and cumulative, decision making about primary prevention may be difficult. For primary prevention, risk factors that are observed to stratify risk for SCD in HCM include massive wall thickening (≥30 mm), unexplained syncope, particularly in young patients and within 6 months of presentation, family history of SCD in a first-degree family member-the relative dying at age less than 40 years, ventricular tachycardia-3 or more beats on 24- or 48-hour ECG monitoring, inadequate rise or frank drop in blood pressure with exercise in patients younger than 40 years (19, 20). Nonsutained VT is considered to have limited weight, when it occurs in isolation in patients >30 years of age whereas it is a strong predictor in patients younger than 30 years (19).

Table 2. Guidelines for ICD Implantation in Brugada syndrome

	Recommendation Class	Level of Evidence
ICD is indicated for Brugada syndrome patients with previous cardiac arrest receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year	I	C
ICD is reasonable for Brugada syndrome patients with spontaneous ST-segment elevation in V1, V2, or V3 who have had syncope with or without mutations demonstrated in the SCN5A gene and who have reasonable expectation of survival with a good functional status for more than 1 year	IIA	C
ICD is reasonable for Brugada syndrome patients with documented VT that has not resulted in cardiac arrest	IIA	C
EP testing may be considered for risk stratification in asymptomatic Brugada syndrome patients with spontaneous ST elevation with or without a mutation in the SCN5A gene	IIB	C

EP - electrophysiologic, ICD - implanted cardioverter defibrillator
Recommendations and Level of Evidence as in Table I.
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Table 3. Guidelines for ICD Implantation in Hypertrophic Cardiomyopathy

	Recommendation Class	Level of Evidence
ICD therapy should be used for treatment in patients with hypertrophic cardiomyopathy who have sustained VT and/or VF and who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year	I	B
ICD implantation is reasonable for patients with hypertrophic cardiomyopathy who have 1 or more major risk factor for SCD	IIA	C
ICD therapy may be considered in patients with a familial cardiomyopathy associated with sudden death	IIB	C

ICD - implanted cardioverter defibrillator, SCD - sudden cardiac death, VF - ventricular fibrillation
Recommendations and Level of Evidence as in Table I.
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The problem with current risk stratification schemes is that each risk factor has relatively low positive predictive value for SCD. Absence of any risk factors offers the patient and clinician some measure of assurance that the risk of SCD is low. The presence of 1 risk factor is very common (as high as 50%) in HCM, whereas sudden death is uncommon. Implantation of an ICD in patients with 1 risk factor thus depends on physician judgment and patient choice. There should be discussion with the patient of the benefits and risks of the ICD, and the pros and cons of implantation, and the rationale for the physician's considered recommendation.

ICD Registries in HCM

The ICD is the preferred therapy for HCM patients at high-risk of SCD (Table 3). Randomized trials have not been performed; as a result, the indications for an ICD are derived from observational data that define high-risk populations and from ICD registries. There are no randomized trials to provide evidence of improved survival with an ICD in HCM patients. However, support for the efficacy of ICDs in HCM comes from the known rate of SCD in high-risk patients and from the incidence of appropriate ICD therapies in patients who have had one implanted. Importantly, the data for the risk factors and the perceived high- risk groups comes from retrospective studies and expert opinion. The benefit of ICD implantation in high-risk patients is sudden death prevention with appropriate shock rates of 3.6% per year for primary prevention and 11% per year for secondary prevention (18, 22).

The efficacy of ICD therapies was illustrated by a report of 506 HCM patients from a multicenter registry (22). Overall, 24 percent of patients had ICD implantation for secondary prevention. The remaining patients had implantation for primary prevention due to the presence of one or more of the following four high-risk features: (1) family history of premature HCM-related sudden death, (2) massive left ventricular hypertrophy, (3) nonsustained VT on Holter monitoring, and (4) prior unexplained syncope. At an average follow-up of 3.7 years, 20 percent of patients received appropriate ICD interventions. Overall, the rate of appropriate device activation was 10.6%/year when used for secondary prevention and 3.6%/year when used for primary prevention of SCD. However, a quarter of patients received only inappropriate ICD shock. The study concluded that most of the therapies occurred in patients with 1 risk factor and suggested that ICD could considered for HCM patients with one risk factor (22). However, this study is limited by the equating of appropriate ICD shock with SCD, which we know is an overestimation. The true incidence of SCD with risk factors is lower and closer to that observed in the natural history studies of Elliott et al. and Spirito et al. discussed above (18, 21).

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (AVRC/D) is a genetic disorder characterized by replacement of the myocardium by fibrofatty tissue predominantly affecting the right ventricle. This replacement leads to a predisposition to life-threatening arrhythmias and SCD. This disease affects 1 in 1000 to 1 in 5000 individuals (23, 24). The prevalence of ARVC/D varies across communities making it difficult to gauge the exact prevalence of the disease.

Importantly, 30-50% cases of ARVC/D occur in families (25). The pathophysiology of ARVC/D involves mutant genes coding for the abnormal desmosome proteins that cause the myocytes to undergo apoptosis and be replaced by fatty tissue. These areas can give rise to areas of reentry and fatal ventricular tachycardia. Common presentations include palpitations, dizziness or syncope. However, SCD is unfortunately the presenting symptom in most patients.

Natural History

Information on the natural history and progression of ARVC/D is obtained from the study of asymptomatic family members. In a review of 37 families, 9.6 percent of initially unaffected subjects developed structural signs of disease on echocardiography during a mean follow-up of 8.5 years; almost 40 percent of the affected had symptomatic ventricular arrhythmias (26). Progression from mild to moderate disease occurred in 5 percent of patients, while progression from moderate to severe disease occurred in 8 percent. Only 1 of 49 patients with ventricular arrhythmia who were treated with antiarrhythmic drugs died during a mean follow-up of 8.5 years. The majority of these patients were treated for nonsustained arrhythmias.

ICD Registries

Corrado et al. (27) reported a in multicenter series of 132 ARVC/D patients who had a history of cardiac arrest (10%), sustained VT (62%), syncope (16 percent), and other indications (12 percent). At a mean follow-up of 39 months, appropriate device interventions occurred in 48% and inappropriate interventions occurred in 16%. Overall, survival rate was 96% and freedom from VT/VF was 72%. Dalal et al. (28) reported on the experience of ICD implants ARVC/D. Among 69 patients, 47 had an ICD implanted and 29 patients (62%) received at least one appropriate therapy, at a mean of 4 years after ICD implantation. None of the 47 patients with an ICD died of SCD during follow-up, while two of the 22 without an ICD had SCD. The authors concluded that ICD was beneficial. The appropriate intervention rate in ARVC/D ICD patients is higher than those reported in other genetic diseases discussed in this review.

Current guidelines recommend ICD therapy for survivors of sudden death as they are considered to be at high risk (Table 4). In the absence of prospective data, patients with unexplained syncope, history of cardiac arrest or sustained VT, right ventricular failure, family history of SCD and patients with Naxos disease are considered at high risk and ICD implantation is recommended. Risks and benefits should again be carefully considered in these patients given the young age and need for long term ICD therapy. Of particular importance in patients with ARVC/D is that thin areas of the RV myocardium can be perforated during placement of the RV leads, and the fibrofatty changes in the RV may interfere with sensing of arrhythmias.

Risk of ICD implantation

It is important to understand that although ICD implants have been increasing and are perceived to be beneficial, they are not without risk. Although these devices may prolong life, they come with some unique challenges especially in patients with genetic disorders who tend to be young and need ICDs for much longer duration. The risks of ICDs have been summarized as "6Is" (29).

1. Implantation risks

   Specific risks of ICD implantation are summarized in Table 5. Procedural complications are a major reason for morbidity and mortality in the younger population. Overall risk of early complications after ICD implant was up to 6.7%, with 4.9% requiring invasive treatment. The AVID (Antiarrhythmics versus ICD implant trial) reported a 2.8% incidence of lead fracture, 2.8% of infection and 1.1% rate of pneumothorax (30). Not surprisingly, operator experience was a major factor in the incidence of lead and procedure related complications. Lead dislodgement is another major complication and in the young patients, lead dislodgement can present with inappropriate shock, failure to defibrillate or pace. Cardiac tamponade, pericardial effusion, pneumothorax are uncommon but serious morbidities. Asymptomatic lead perforation may be much more common than appreciated. Hirschl et al. (31) performed CT scans in 100 consecutive chronic device patients (pacemakers, n=72, and ICD, n=28): 9 (15%) of 61 right atrial leads had perforated, along with 6 (6%) of 100 of RV leads. The more recently described extrathoracic, axillary vein approach reduces pneumothorax risk and other lead-related complications. Perioperative strokes and death are rare though devastating complications of lead implant.

2. Infection

   Infection is another important complication of ICD implantation. At least 12000 cardiac device infections occur annually with the US adding to per case treatment of $80000 when an ICD is explanted and a new ICD is inserted (32) ICD related infections may be localized in the form of pocket infection or may present as intravascular lead-associated endocarditis. The relative incidence of pocket infections ranges from 52-90% of device-related infections while intravascular lead-related endocarditis ranges from 10-48% of device-related infections. Not surprisingly, there are wide variations in the different reported series of device-related infections. In the HCM-ICD

Table 4. Guidelines for ICD Implantation in Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

	Recommendation Class	Level of Evidence
ICD implantation is recommended for the prevention of SCD in patients with ARVC with documented sustained VT or VF who are receiving chronic optimal medical therapy and who have reasonable expectation of survival with a good functional status for more than 1 year	I	B
ICD implantation can be effective for the prevention of SCD in patients with ARVC with extensive disease, including those with LV involvement, 1 or more affected family member with SCD, or undiagnosed syncope when VT or VF has not been excluded as the cause of syncope, who are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 y.	IIA	C
Amiodarone or sotalol can be effective for treatment of sustained VT or VF in patients with ARVC when ICD implantation is not feasible	IIA	C
Ablation can be useful as adjunctive therapy in management of patients with ARVC with recurrent VT, despite optimal antiarrhythmic drug therapy	IIA	C
EP testing might be useful for risk assessment of SCD in patients with ARVC	IIB	C

ARVC - arrhythmogenic right ventricular cardiomyopathy/dysplasia, EP - electrophysiologic, ICD - implanted cardioverter defibrillator, SCD - sudden cardiac death, VT - ventricular tachycardia, VF - ventricular fibrillation

Recommendations and Level of Evidence as in Table I.

Table 5. Incidence of ICD implant-related complications

Complication	Incidence Range, (%)	Causes, Risk Factors	Diagnosis	Management
Hematoma	1-10%	Coagulopathy, heparin (UFH, LMWH), warfarin, clopidogrel	Physical exam	Conservative; occasionally incision and drainage
Lead Dislodgement	1-5%	Operator technique, Patient factors	ECG, CXR, Interrogation	Operative repositioning (or replacement)
Cardiac perforation	0.5-10%	Technique, implant location, patient factors, leads	CT, CXR, Echo?	Repositioning with backup of pericardiocentesis/window; conservative, watchful, waiting
Hemopericardium	0.5-1.5%	Same; anticoagulation	BP, PP, Echo	Pericardiocentesis window; repair
Pneumothorax	0-2%	Approach;Technique	CXR; exam	Conservative / catheter drainage / chest tube
Stroke	0.02-0.2%	AF, PFO ASD, VSD, malposition	History, Exam, CT/MRI	Neurologic guidelines
Infection	1-5%			
Pocket infection		Repeat operation; operative technique, operator experience, indwelling catheter, temporary wire, immunosuppression	Exam	IV antibiotics 2-4 wks Complete extraction. Delayed reimplantation (4-10 days, contralateral)
Lead endocarditis		Same	Blood cultures, TEE	IV antibiotics 4-6 wks, Complete extraction, Delayed reimplantation (2-6 weeks, contralateral)
PEA	0.01-0.1%	CHF, pneumothorax, tamponade	Rhythm strip plus fluoroscopy (or BP)	Epinephrine, CPR, vasopressin.
Death	0.016-0.2%	DFT testing (inability to convert VF, PEA); tamponade	-	-

AF - atrial fibrillation, ASD - atrial septal defect, BP - blood pressure, CHF - chronic heart failure, CPR - cardiopulmonary resuscitation, CT - computerized tomography, CXR - chest X-Ray, DFT - defibrillator threshold testing, ECG - electrocardiogram, echo- echocardiography, ICD - implanted cardioverter-defibrillator, LMWH - low molecular weight heparin, MRI - magnetic resonance imaging, PEA - pulseless electrical activity, PFO - patent foramen ovale, PP - pulse pressure, TEE - transesophageal echocardiography, UFH - unfractionated heparin, VF - ventricular fibrillation, VSD- ventricular septal defect
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registry, there was a 3.8% incidence of infection at 3 years (22). These infections almost always need lead and device extraction. In younger patients, the long duration of ICDs and likely need for multiple lead or device replacements increase the risks of device-related infections and complications.

3. Inappropriate shock

Inappropriate shocks are defined as shocks delivered by the ICD for a non VT/VF rhythm. Common etiologies include atrial arrhythmias including sinus tachycardia, atrial fibrillation, electromagnetic interference, myopotential sensing and lead fracture and lead failure. Although modern devices are sophisticated and have discriminators to distinguish atrial and ventricular arrhythmias, they have had only modest success in preventing inappropriate shocks. In the landmark MADIT-II trial, the incidence of inappropriate shocks was 10% at 1 year and 13% at 2 years (33). In a younger cohort of patients - those in the HCM- registry, 27% of patients experienced inappropriate shocks at 3.7 years of follow-up (22). Younger patients with ICD experience sinus tachycardia that can result in inappropriate shocks. Inappropriate shocks are associated with an adverse effect on the quality of life that has important implications for young patients (34).

4. Imperfection

Lead failure and generator failures are important issues. Lead failures can present with inappropriate shocks, sometimes multiple, or failure to deliver needed shock or pacing. Demonstrate that lead survival tends to wane over time. Lead survival ranges from 85-98% at 5 yrs and 60-72% at 8 years (35, 36). Lead failure rate increased with age of the implanted lead with high annual failure rate of 20%/year at 8 years (35), most commonly caused by insulation failure. The failure rates are higher in younger and physically active patients. In younger patients, single ventricular lead is preferred because of lower long- term risk (29).

5. Tricuspid Insufficiency

Lead pacing wires and ICD leads are placed across the tricuspid valve and fixed into the right ventricular apex. In 248 patients that had no tricuspid regurgitation, 4% patients developed severe tricuspid regurgitation 3 months after lead placement (37). These patients may present with signs of severe heart failure. The mechanism of valve injury includes impingement on valve leaflet, entanglement or perforation of the leaflet. In patients who present with refractory right heart failure after ICD, it is important to assess the tricuspid

valve with transesophageal echocardiography as lead induced tricuspid regurgitation is an important correctable cause of heart failure. Tricuspid valve replacement has been performed in this scenario and has reversed heart failure.

6. "Insurance" risk

If the individual never needs the device because sustained malignant arrhythmia does not occurs, then for that individual the risk of device-related complications has outweighed its benefits. ICD implantation is comparable to purchase of a term life insurance policy. If malignant arrhythmia occurs, the policy (ICD) pays by delivering a lifesaving intervention. If, however no arrhythmia occurs, and the patient survives to an old age without ever needing the device, all the effort, money, and risk associated with the ICD was for naught. The patient dies from another unrelated condition without ever accruing the benefit of the ICD. In the genetic syndromes discussed herein this risk is magnified because heart failure death is uncommon and thus the percentage of patients surviving who never need the device is higher than in heart failure populations.

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