Should patients with congenital heart disease and a systemic ventricular ejection fraction less than 30% undergo prophylactic implantation of an ICD?

Implantable Cardioverter Defibrillator Implantation Guidelines Based Solely on Left Ventricular Ejection Fraction Do Not Apply to Adults With Congenital Heart Disease

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A number of important prospective studies have firmly validated the idea that patients at elevated risk for sudden cardiac death (SCD) can have that risk reduced by the use of implantable cardioverter defibrillators (ICDs). Among patients resuscitated from a potentially lethal cardiac event, ICD placement is termed secondary prevention. Primary prevention is the extension of this protective principle to groups of patients who have yet to experience a cardiac arrest, but who by virtue of specific and carefully defined clinical characteristics are determined to be at elevated risk for this event.

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Given the cost of ICD therapy and the number of patients who may meet primary prevention indications, the potential societal cost of this approach to cardiac risk management is high. In the past decade, this has driven a vigorous debate within the fields of heart rhythm management and health care economics as to the optimal ways to delineate patient groups that will most benefit from ICD therapy. The Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) study1 was a milestone in the evolution of this debate, providing evidence that a large group of patients—those with ischemic cardiomyopathy—could be rapidly and noninvasively sorted on the basis of left ventricular (LV) ejection fraction, with those having severe LV dysfunction realizing a clear survival benefit from ICD therapy.

In this article, I challenge the proposition that MADIT-II and subsequent studies of the efficacy of ICD therapy in patients with acquired LV dysfunction can be applied to patients with moderate to severe systemic ventricular dysfunction in congenital heart disease (CHD). To make this argument, several topical areas must be considered. These include the current state of clinical knowledge of the natural history of CHD in adolescents and adults, the known rates of sudden death in this heterogeneous group, and reported clinical experiences with ICD use in these patients. Congenital heart patients must be compared pathophysiologically and epidemiologically with those ICD-indicated patient groups specifically identified by prospective clinical study. Despite
the high likelihood that ventricular dysfunction and arrhythmogenesis follow a relatively uniform “final common pathway,” at present there is abundant evidence that differences between congenital heart patients and patients with acquired cardiomyopathies are large—certainly larger than some of the clinical differences noted to affect risk and cost-benefit calculations for ICD therapy in the latter group.

Primary Prevention Studies in Acquired Heart Disease

Several large, randomized, controlled trials form the backbone of clinical evidence for ICD efficacy, and the entry criteria defining these study groups have become the basis for clinical ICD indications. Initial studies such as amiodarone versus implantable defibrillator and the Canadian Implantable Defibrillator Study established the therapeutic strategy of secondary prevention, demonstrating the superiority of the ICD over medical therapy in patients with prior cardiac arrest.

Subsequently, the MADIT and the Multicenter Unsustained Tachycardia Trial broadened indications for ICD therapy to include patients with coronary heart disease and abnormal LV function who had not yet suffered an arrest. Although entry into these studies required demonstration of ventricular tachycardia (VT) inducibility, limiting their broad clinical adoption, each demonstrated that ICD implantation resulted in a relative risk reduction of >50% compared with medical therapy.

MADIT-II also enrolled patients with ischemic cardiomyopathy, but with a lower LV ejection fraction threshold (≤0.30) than MADIT and MUSTT, and clinical barriers to study entry were significantly reduced by waiving the requirement for VT inducibility screening. About 1232 patients were followed for 20 months, with control group mortality over that period of 19.8% (≈11.9% per year). A risk reduction of 31% was observed at the time the study was stopped. These strong findings have been extended to patients with nonischemic dilated cardiomyopathy. In the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation, 458 patients with LV ejection fraction ≤0.35, heart failure, and ventricular arrhythmia had a control group mortality of 14.1% more than 2 years. ICD therapy resulted in reduction of mortality to 7.9%, with a significant reduction in sudden death. The SCD in Heart Failure Trial enrolled 2521 patients with LV ejection fraction ≤0.35, comparing ICD therapy to control or therapy with amiodarone. Two-year mortality in the control group was ≈14%, and ICD therapy conferred significant risk reduction regardless of cause of cardiomyopathy.

Similar findings are noted in several other clinical studies more recently published. Although some fail to demonstrate significant benefit for ICD therapy, as the CABG Patch and DINAMIT studies, as a group they show clearly that for patients with measured LV ejection fraction ≤0.30 to 0.35, ICD therapy results in reduced risk of sudden death. In pooled meta-analysis of 10 primary prevention trials, ICD therapy resulted in a highly significant absolute mortality reduction of 7.9%; similar studies have showed relative risk reductions of 50% for secondary and 31% to 34% for primary prevention strategies. The patient populations in these studies are characterized by annual mortalities in their control groups, which range roughly between 6% and 15%. Post hoc analyses of these data have demonstrated that the entire reduction in overall mortality in these studies is due solely to decreases in arrhythmic mortality. This is of particular importance in patients with either very low risk of sudden death, or conversely, those with short life expectancy and/or significant comorbidities, as these patients are quite likely to never use their ICD in follow-up, due to lack of need or competing, nonarrhythmic causes of mortality. This effect of competing risks may be quite significant, and highest in low-risk populations.

Cost-benefit studies of ICD therapy have been applied to these data. From a societal cost perspective (by balancing the expense of this technology against the culturally assigned value of an averted death, or calculation of the cost of a quality-adjusted life-year), ICDs have been found to be cost effective. Sensitivity analyses have shown, however, that assumptions regarding parameters may markedly affect the conclusions drawn from the model. An important factor in the utility function is the sudden death rate of the control group under treatment. Consistent with this is the observation of an inverse relationship among primary prevention studies between hazard ratio and annual death rate with conventional therapy (Figure 1).

Consensus Guidelines for ICD Implantation

Concordant with the findings of these primary and secondary prevention studies, the 2006 guidelines for management of VT and prophylaxis of SCD released jointly by the American Heart Association, the American College of Cardiology, and the European Society of Cardiology classify several ICD indications as I-A or I-B: therapy is clearly indicated and well supported by multiple, methodologically rigorous studies. These include patients with coronary vascular disease or...
studies performed in relatively large subpopulations, defined by common and predictable anatomic forms of CHD and long postoperative survival into adulthood. Practically speaking, this focuses on patients with tetralogy of Fallot (TOF), transposition of the great arteries (TGA), and congenital AS. Together, these account for >25% of congenital heart patients and because of excellent surgical outcomes, likely account for a larger fraction of adults with CHD.

Although atrial tachycardias and AV block contribute to sudden death in these patients, VT is likely the principle culprit. The patients at greatest risk for VT in CHD are those who have undergone a ventriculotomy,29–31 or have evidence of diffuse cardiomyopathy (eg, valvar AS,32,33 failure of the systemic RV in patients with TGA34). In theory, the pathophysiological connections drawn between ventricular arrhythmia, myocardial scarring, and SCD in populations with acquired heart disease will be relevant to these patients.

A large, early survey of SCD in an unscreened CHD population was published in 1998 by Silka et al.27 This geographically based registry examined the prevalence and cause of late sudden death for nearly 3600 patients undergoing cardiac surgery of diverse congenital heart defects (septal defects, patent ductus arteriosus, aortic and pulmonary stenosis, TOF, and TGA) more than nearly 40 years. Deaths were categorized as sudden-arhythmic, sudden-nonarhythmic (eg, stroke, aneurysm), nonsudden cardiac (eg, reoperation or congestive heart failure [CHF]), and noncardiac. The incidence of sudden death was 0.9/1000 patient-years, and of non-SCD 1.6/1000 patient-years. About ¾ of sudden deaths were arrhythmic. This risk was strongly associated with diagnoses of AS and TGA, groups in which the annual incidence of sudden death approached 5/1000 patient-years. Survival curves for sudden death suggest a threshold occur-
Repair reported by Gatzoulis et al. reviewed the surgical, peroperative New York Heart Association status, suggesting that surgical procedures, both of which switch the atrial inflow and result in a systemic RV, have a higher likelihood of sudden death decades later. Patients older, sicker, and more cyanotic at the time of surgery and follow-up, residual hemodynamic lesions and right heart failure, presence of complex ventricular ectopy on monitoring, inducible VT at electrophysiological study and prolongation of the QRS, but these have shown limited predictive power.

Nollert et al. analyzed long-term survival in 490 patients with TOF who survived palliative surgery, performed between 1958 and 1977. Actuarial survival rates in this group at 10-, 20-, 30-, and 36 years were 97%, 94%, 89%, and 85%, respectively, with annualized mortality increasing at \( \approx 2.5 \) per 10 years postoperatively from 0.24% to 0.94% per year; 13 patients (2.7%) died suddenly. A follow-up study in this same group of patients investigated specific risk factors for occurrence of SCD. These included the absence of previous palliation at the time of reparative surgery and higher preoperative New York Heart Association status, suggesting that patients older, sicker, and more cyanotic at the time of surgery had a higher likelihood of sudden death decades later.

A multicenter natural history study of survival after TOF repair reported by Gatzoulis et al. reviewed the surgical, electrocardiographic, and hemodynamic data available on 793 patients, 21 years after surgery. In this group, 33 patients (4.2%) developed monomorphic VT, 16 (2.0%) died suddenly, and 29 (3.7%) had onset of sustained atrial flutter or fibrillation. Risk factors included age at operation and QRS duration on ECG, and the authors contended, as have others, that RV hemodynamic lesions were important pathophysiological risk factors.

Transposition of the Great Arteries
Patients with TGA were widely treated surgically in the 1970s through 1990s using the Mustard and Senning procedures, both of which switch the atrial inflow and result in a systemic RV. This maturing population has also generated significant natural history experience allowing assessment of incidence of and risks for SCD. As in TOF, the incidence of SCD is low, and occurs in the setting of a complex of arrhythmia symptoms. Sinus node dysfunction and atrial reentrant tachycardias are both significantly more prevalent than ventricular arrhythmia and have been implicated as mechanisms of SCD in this group. Several risk factors have been retrospectively associated, including the presence of ventricular septal defect, atrial flutter, and systemic RV dysfunction, particularly when clinical symptoms of heart failure are present.

A multicenter follow-up study reviewed the outcomes of 339 TGA patients up to 30 years postoperatively. Overall mortality was 24%, but more than 2/3 of this was peroperative and total late mortality was 7.7%. Among early survivors, survival at 10, 20, and 30 years after surgery was 92%, 89%, and 79%, respectively. Similar survival rates were noted in 113 patients undergoing the Mustard procedure; SCD incidence of 7% more than 28 years follow-up was observed, without identifiable risk factors. Deanfield et al. noted a sudden death rate of \( \approx 0.6\% \) per year in a prospective follow-up study of 100 adult patients. Puley et al. observed a high prevalence of atrial arrhythmia in adult patients with TGA, but no ventricular arrhythmia. Mortality was \( \approx 1\% \) per year, with systemic RV dysfunction a risk factor for mortality, but sudden death accounted for only \( \frac{1}{3} \) of the total deaths. In 137 late survivors, Dos et al. observed mortality of 5.1% more than 17 years follow-up (\( \approx 0.3\% \) per year), associated with supraventricular arrhythmia and decreased New York Heart Association functional class. Systemic RV dysfunction was seen in only 15% of patients.

Gatzoulis et al. studied the relation between RV function and arrhythmia in these patients. Although the most significant predictor of arrhythmia was QT dispersion, an association was seen between arrhythmia (predominantly atrial) and systemic RV ejection fraction (estimated by nuclear scan): 34% in the arrhythmia group versus 47% in others. Kammeraad et al. performed a multicenter case control design study of 47 patients who had experienced SCD/near-SCD events and found that affected patients were more likely to have had arrhythmia symptoms or CHF, and to have had documented atrial arrhythmia.

Aortic Stenosis
Although the pathophysiology of AS may be more comparable in many respects to acquired cardiomyopathy, less recent data specific to CHD exists documenting the increased risk of late sudden death. This may be because of the fact that the division between congenital and acquired AS is clinically less well defined, and the variety of different therapies applied to the disease, their efficacy and potential for adverse consequences. The second Joint Study on the Natural History of Congenital Heart Defects was published in 1993, and reported that at late follow-up, 25 of 462 patients with AS of varying severity (5.4%) experienced sudden death at approximately 25 years of follow-up. LV end-diastolic pressure was not associated with mortality, but symptoms and elevated systolic outflow gradients were.

Mode of Death in CHD
Additional significant data can be extracted from some of these studies: the percentage of deaths occurring in CHD populations attributable to arrhythmia. The importance of this to the specific question of ICD indications cannot be overstated, as analyses of primary and secondary prevention...
studies in acquired heart disease have isolated the beneficial effects of ICD therapy to arrhythmic events. Patients who undergo ICD implant but never experience an ICD shock are exposed to the expense and risk of therapy but realize no benefit. A registry study of the Canadian Adult Congenital Heart Network published in 1996 reviewed the mode of death in 92 patients. There were 23 patients who died suddenly (25%), but 9 had Eisenmenger syndrome and were thus unlikely to represent arrhythmic deaths. A more comprehensive study presented by Oechslin et al assessed the mode of death in 200 adults with CHD, at a mean age of 37 years. Death was sudden in 26% of patients, with other deaths attributed to CHF, perioperative events, and other cardiovascular and noncardiovascular causes. Thus, sudden death accounts for a lower fraction of mortality in CHD patients compared with those with acquired heart disease, where the fraction of cardiac deaths that are sudden ranges from 50% to 60%.23,55

Risk Stratification in CHD

Multiple series show that electrophysiological study is a significant predictor of arrhythmic events in patients with CHD. Alexander et al analyzed a group of 130 patients with CHD undergoing ventricular stimulation study for clinical indications. TOF, TGA, and AS accounted for 70% of these patients, who had a median age of 18 years. Multivariate analysis showed that inducible ventricular arrhythmia was associated with increased risks of mortality and subsequent arrhythmic events. Khairy et al analyzed the utility of ventricular stimulation in 252 adult patients with TOF. He similarly found that inducible sustained VT (both monomorphic and polymorphic) had a positive and negative predictive values of 55% and 91%, with event free survival rates presented graphically (Figure 2).

Utilization and Adverse Events Associated With ICDs Used in Patients With CHD

Data available on ICD use in CHD are also difficult to analyze: individual studies are mostly small and retrospective. Case series reporting ICD use in children, adolescents and adults with CHD totaling 154 patients have been published in the past decade.59–67 Silka et al previously sur-

Figure 2. Survival curves free of clinical ventricular tachycardia and sudden death in TOF patients who have undergone ventricular stimulation studies, demonstrating the predictive value of that test.43

Figure 3. Effect of LV dysfunction (defined as systolic ejection fraction <0.40) on mortality in TOF patients. Broken line indicates normal or mild-LV dysfunction; solid line, moderate or severe LV dysfunction.58
veyed the Pediatric Electrophysiology Society in 1993 for ICD experience. This report focused on pediatric ICD use (<20 years of age) and was developed from ICD manufacturer databases. Among 177 patients reported, 22 had CHD, principally TOF, TGA, and AS. Most patients were secondary prevention and more than 2.6 years follow-up. 73 patients (59%) received appropriate ICD discharge, and 25 (20%) had inappropriate shocks (Figure 4). Nine deaths occurred after implantation: 5 sudden, 2 due to recurrent arrhythmias, and 2 related to CHF. Abnormal ventricular function was the only significant predictor of mortality. The study concluded that patterns of ICD use in young patients were similar to those seen at the time in adult patients.

Alexander et al. presented results of ICD therapy in 76 patients (median age 18 years), 32 of whom (42%) had CHD (28 with TOF, TGA, or AS). Over 2 years, 22% of the CHD patients received appropriate shocks and 25% experienced inappropriate shocks. No deaths were attributable to ICD placement or device failure, but complications occurred in 29 patients, including lead failure, ICD “storm,” and infection. This rate, similar to other reported pediatric and congenital series, is higher than that observed in adults.64,69 Lead failure was frequent, and more common in the younger patients than in older patients with CHD.

Recently, Berul et al. collected ICD implant and follow-up data from 4 high-volume referral centers. CHD was present in 194 of 443 patients (46%), with the most common diagnosis TOF. Approximately half of implants were considered to be primary prevention. Appropriate shocks were recorded in 32% of secondary and 18% of primary prevention patients, most within 5 years after implant. Inappropriate shocks were recorded in 21% of all patients, usually because of lead failure. Acute implant complications occurred in 55 patients (12%) and chronic complications, mostly lead related, were seen in 116 patients (26%). Eighteen patients died (4 suddenly), and heart transplantation was performed in 16 patients.

Two recent studies specifically address adults with CHD. Yap et al. investigated outcomes and complications of ICDs and predictors of shocks in 64 adult CHD patients, most with TOF. This series suggested that the high rates of complication and inappropriate shock seen in mixed pediatric and congenital series were not solely related to body size, growth, or the specific underlying diagnostic mix common in younger children. Seven patients had procedural and 11 more had late complications, with 20 patients (31%) requiring reintervention. More patients received inappropriate (41%) than appropriate shocks (23%).

Khairy et al. studied surgical, electrocardiographic, non-invasive, and hemodynamic data on 121 adult patients with TOF who have ICDs. Indications for ICD therapy were predominantly primary prevention (56%), but only 2 of 68 patients undergoing primary prevention did so because of low LV ejection fraction. Over 3.7 years, 31% of patients received at least one appropriate shock, with annualized shock rates of 7.7% per year in the primary prevention group and 9.8% per year in the secondary prevention group. Most appropriate shocks were delivered for monomorphic VT, and appropriate shock rate for ventricular fibrillation and polymorphic VT were lower, at 3.6% per year. Appropriate shocks were predicted in multivariate modeling by higher LV end-diastolic pressures and the observation of nonsustained VT. Approximately 25% of the study group received inappropriate shocks. Overall mortality was 2.2% per year and was not different between primary and secondary prevention groups.

A variety of predictors were assessed, and the effect of each on predicted annualized appropriate shock rate is shown in Figure 5.

While confirming the importance of systemic ventricular function, this also highlights the importance of the multiple clinical predictors mentioned above, and implies their covariance. Based on modeling results, a weighted risk score was developed allowing a score of 0 to 12 based on LV end-diastolic pressure (3 points), nonsustained VT, inducible VT, prior palliative shunting, prior ventriculotomy (2 points each), and QRS duration (1 point). This risk stratification schema is demonstrated in Figure 6.

**Psychology of ICD Implantation**

In addition to risk reduction, ICD utility is also determined by the perceived benefit to the patient. Studies of adjustment and coping of small groups of pediatric and congenital patients to life with ICD has revealed high prevalence of anxiety, social isolation, and avoidance of physical activities.73,74 A structured study of a younger ICD population showed that these patients are psychologically resilient but have lower physical function and perceived quality of life than their peers.75 Direct comparison of younger (<50 years) and older patients show that younger patients report greater anxiety, lower quality of life, and problems with emotional function.76
Although ICD patients in general adapt well, younger patients may constitute a subgroup experiencing greater adverse effects on psychosocial well-being and quality of life.

Analysis of Available Data
The thesis of this debate is that LV ejection fraction of \( \leq 0.30 \) is a standalone indication for ICD implantation in grown patients with CHD. As we now see, a literal interpretation of that statement is so difficult to interpret in the context of the diverse anatomy and incomplete data available for adult CHD populations that it becomes restrictive, limiting rather than promoting insight into the problem of risk management in CHD.

Significant similarities and differences exist between acquired and CHD in the pathophysiology of ventricular dysfunction and its relation to arrhythmogenesis and sudden death. Powerful means of risk stratification are critically important to the application of primary prevention strategies—but in CHD, these will not be simple. The protagonist in this debate will argue correctly that much of the natural history research in CHD indicates an important association between ventricular dysfunction and risk of SCD, and some studies cited above identify systemic ventricular dysfunction directly as a measurable risk factor.68,66 Even in these studies, however, ventricular function is assessed in diverse ways, is studied retrospectively, and is only one of several covarying risk factors identified. In fact, the data available indicates that several historical, electrocardiographic, electrophysiological and hemodynamic factors add significant, incremental predictive power in risk stratification, and that risk stratification strategies dichotomized solely by depressed LV (or systemic RV) ejection fraction are too simplistic to guide primary prevention. Of interest, investigators of primary prevention strategies in acquired cardiomyopathy are now themselves reconsidering the use of LV ejection fraction as a single clinical variable for risk stratification, in favor of more refined screening approaches.77–79

It is clear from cost-benefit analyses that the underlying sudden death rate of the population must be quite high to favor ICD implantation. In the CHD populations considered most at risk, the rate of sudden death is 5 to 10 times lower than that observed MADIT-II and similar populations. Appropriate shocks have been observed to occur in primary prevention groups such as the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation Trial at higher frequency than the sudden death rate experienced by the study population,80 as also observed in CHD patients. Although this in part reflects the clinical process of sorting and selecting patients into groups of higher risk based on clinical judgment, it is also undoubtedly a result of overassignment of episodes of nonsustained and/or hemodynamically tolerated arrhythmia as “SCD equivalents.”

From a health policy perspective, calculation of a cost-benefit ratio for ICD implantation in CHD patients is less urgent—despite their numbers, these patients consume only a
small fraction of the resources devoted to this technology. However, it is essence of good care to consider the potential clinical and personal costs of ICD therapy to the patient who may be designated by “guidelines” to receive a device. Several factors alter the experience of living with an ICD younger, congenital populations. Their life expectancy is long and will necessitate many ICD procedures. Vascular access is likely to be problematic, and it is clear that the rate of device associated adverse events and lead failure is higher than that reported in adult populations.\textsuperscript{58,81}

**Summary**

In patients with CHD, depressed ventricular ejection fraction used as a single, dichotomous risk stratifier is not sufficient indication for ICD therapy. It is possible that the trajectory of clinical research followed in the development of ICD implantation guidelines for acquired heart disease may be duplicated in CHD populations and yield useful, disease-specific evidence. However, these patients are significantly different from populations studied in primary prevention studies, in ways known from cost-benefit analysis to strongly affect the utility of this strategy: the untreated death rate of the implanted population, the existence of competing causes for mortality, and the perceived quality of life effect of the treatment. At present, it is clear that assessment of ventricular function should remain one critical input into a multifactorial, patient-specific approach to risk assessment in the CHD population.

**Disclosures**

None.

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**Key Words:** defibrillation ■ epidemiology ■ heart arrest ■ heart defects, congenital

**Response to Triedman**

**Michael J. Silka, MD; Yaniv Bar-Cohen, MD**

Dr. Triedman has summarized the data regarding sudden cardiac death (SCD) in congenital heart disease (CHD) and concludes that although ventricular dysfunction is a risk factor for SCD, it should not be used as a single, dichotomous indication for implantable cardioverter defibrillator (ICD) implantation. In any decision regarding diagnostic testing, a clinician must consider the pretest probability of a given test to determine if additional testing will affect clinical management (posttest probability). This debate is whether the pretest probability or risk of SCD owing to advanced systemic ventricular dysfunction (defined as an ejection fraction (EF) <30%) is sufficient to warrant ICD placement or if additional risk factors are likely to alter that clinical decision. Although Dr. Triedman correctly identifies the low overall incidence of SCD in CHD patients, the crucial question is the risk for SCD in limited numbers of CHD patients with severe ventricular dysfunction. In addressing this, one must consider that severe ventricular dysfunction is an established indication for ICD implantation in other types of heart disease and that patients with a systemic morphologic right or single ventricle may be at even greater risk because of pathologic ventricular remodeling and limited coronary reserve. Based on the available data, we conclude that the risk for SCD in CHD patients with a systemic ventricular EF <30% (the group under study) is sufficiently high to warrant ICD implantation. The inclusion of additional risk factors is reasonable when there is moderate systemic ventricular dysfunction owing to the lower pretest probability for SCD.
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