Cost-Effectiveness of Implanted Defibrillators in Young People with Inherited Cardiac Arrhythmias

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Background: The implanted cardioverter-defibrillator (ICD) has been shown to improve survival in adult patients with high risk acquired cardiac disease, with a cost-effectiveness ratio in the range of \$30,000 to \$185,000 per quality-adjusted-life-year saved. However, data on the benefit and cost-effectiveness of device therapy in high-risk patients with inherited cardiac disorders are limited.

Methods: We developed two separate computer-based analytical models to compare non-ICD with ICD therapy in patients (age range: 10–75 years) with long QT syndrome (LQTS) and hypertrophic cardiomyopathy (HCM). In each disease entity patients were stratified into low-risk (no known risk factors); high-risk (known risk factors [primary prevention]); and very high-risk (prior near-fatal events [secondary prevention]). Net costs were defined as the difference between costs resulting from treatment of the disease and savings due to gained productivity attributable to prevention of sudden cardiac death. Outcome was defined as costs per quality-adjusted life-years saved.

Results: In LQTS, defibrillator therapy was shown to be cost effective in high-risk male patients (incremental cost-effectiveness ratio [ICER] = \$3328 per quality-adjusted-life-year saved), and cost saving in high-risk females (ICER = \$7102 gained per quality-adjusted-life-year saved) and very high-risk males and females (ICER = \$15,483 and 19,393 gained per quality-adjusted-life-year saved, respectively). In HCM, defibrillator therapy was cost saving in both male and female high-risk (ICER = \$17,892 and \$17,526 gained per quality-adjusted-life-year saved, respectively) and very high-risk (ICER = \$22,944 and \$22,329 gained per quality-adjusted-life-year saved, respectively) patients. Defibrillator therapy was not shown to be cost effective in low-risk patients with either LQTS or HCM (ICER in the range of \$400,000 to \$600,000 lost per quality-adjusted-life-year saved). Sensitivity analyses were consistent with the results in each risk group.

Conclusions: In appropriately selected patients with inherited cardiac disorders, early intervention with ICD therapy is cost-effective to cost saving due to added years of gained productivity when the lifespan of an individual at risk is considered.

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Over the past two decades, the implanted cardioverter-defibrillator (ICD) has achieved widespread acceptance for prevention of sudden cardiac death (SCD). Defibrillator therapy has been shown to decrease mortality in high-risk patients with ischemic and nonischemic cardiomyopathy^{1,2} and in patients with aborted cardiac arrest.³ These data have formed the basis for the current published indications for ICD implantation.⁴ Despite advancements achieved in the treatment

of high-risk adult patients with ICDs, to date, there had been limited (but growing) application of the device for the prevention of SCD in patients with less common genetic cardiac disorders, such as long QT syndrome (LQTS), arrhythmogenic right ventricular cardiomyopathy, the Brugada syndromes, and hypertrophic cardiomyopathy (HCM).^{5,6} These syndromes comprise a substantial population of young and otherwise healthy subjects at risk of arrhythmic death. However, guidelines for ICD

therapy in these patients are based on observational studies evaluating relatively small numbers of patients.

The purpose of the present study was to assess the clinical and economic implications of ICD therapy in young subjects with inherited life-threatening cardiac arrhythmias. We chose these two disorders since they represent the most common inherited conditions associated with high risk for SCD. Patients who have normal myocardial structure with a mortality risk related exclusively to the development of sporadic malignant ventricular arrhythmia are represented by LQTS; and patients with a dominant arrhythmogenic risk superimposed on a disordered and abnormal myocardial substrate, which can also cause premature death through a variety of mechanisms, are represented by HCM.

METHODS

Study Design

We used separate computer-based analytical models based on for HCM and LQTS to compare non-ICD with ICD therapy. Annual probabilities of clinical events, including heart failure or stroke (in

HCM) and according to mode of death (including SCD, non-SCD, and noncardiac death) were used to analyze the course of disease in patients with HCM or LQTS. The outcome was defined as costs per quality-adjusted life-years saved. Future costs and benefits were discounted at a rate of 3% per year.⁷ Our analysis also included fiscal aspects outside the health-care system, i.e., earnings from gained productivity attributable to improved survival from the prevention of SCD.^{7,8}

Survival was modeled by adjusting age-specific life-table mortality rates to account for the increased risk due to LQTS or HCM as described in Figure 1. Economic consequences were assessed by accumulating related and unrelated discounted health-care costs and economic productivity. We assessed the probability of related medical events at each age (conditional on survival) and assigned costs to each event type (including death) as shown in Table 1 and described in more detail below. Total health expenditure data from the Medical Expenditure Panel Survey were used to estimate age-specific unrelated health care cost profiles, and estimates from the *Current Population Survey* data published by the Bureau of Labor Statistics were used to calculate age-earnings profiles to account

Figure 1. Estimated rate of sudden cardiac death (percent per year) for low; high; and very high-risk patients with the two inherited cardiac disorders. *In male patients >20 years of age, the estimated risk of sudden cardiac death was reduced by one-half. SCD = sudden cardiac death.

Table 1. Estimated Rate of Events and Associated Costs for ICD- and non-ICD-based Therapy in LQTS and HCM Patients

	Non-ICD Therapy		ICD Therapy	
	LQTS	HCM	LQTS	HCM
Cost of defibrillator	NA	NA	\$17,000	\$17,000 in 25%, additional \$3000 for dual pacing
Cost of initial ICD implantation	NA	NA	\$5000	\$5000
Physician visits (Base cost = \$125)	2/year	2/year	3/year	3/year
Non-ICD related events:*				
Surgery: (Base cost of treatment = \$21,123)	None	Age groups: <40 years: 0.07% per year 40–50 years: 0.4% per year >50 years: 0.1% per year years (one event per patient)	None	Age groups: <40 years: 0.07% per year 40–50 years: 0.4% per year >50 years: 0.1% per year years (one event per patient)
Hospitalization due to heart failure (Base cost of treatment = \$5503)	None	Age groups <40 years: 0.02% per year 40–50 years: 0.05% per year >50 years: 0.05% per year years	None	Age groups <40 years: 0.02% per year 40–50 years: 0.05% per year >50 years: 0.05% per year
Heart failure related death	None	Age groups: <40 years: 0.01% per year 40–50 years: 0.025% per year >50 years: 0.025% per year	None	Ages groups: <40 years: 0.01% per year 40–50 years: 0.025% per year >50 years: 0.025% per year
Stroke (Base cost of treatment = \$6799)	None	≤60 yrs: 0.8%/year >60 years: 1.9%/year	None	≤60 yrs: 0.8%/yr >60 years: 1.9%/yr
Medications	β-blockers in all patients (\$200–300 per year)	β-blockers, calcium channel blockers, disopyramide and diuretics in 30% of patients (\$200–300 per year)	β-blockers in all patients (\$200–300 per year)	β-blockers and/or antiarrhythmic therapy in 70% of patients. Other medications—same as non-ICD (\$ 500–600per year)
ICD-related complications				
Infection (Base cost = \$77,000)	NA	NA	0.5% per implantation procedure (every 5 years)	0.5%/year

(Continued).

Table 1. Continued.

	Non-ICD Therapy		ICD Therapy	
	LQTS	HCM	LQTS	HCM
Generator malfunction (Base cost = \$19,000)	NA	NA	1%/yr	1%/year
Lead problems (Base cost = \$6000)	NA	NA	1% /year	1%/year
Battery replacement (base cost = \$14,000)	NA	NA	Every 5 years	Every 5 years

*Actual costs per year are the base cost times the annual event rate. For example, the cost per year for surgical treatment of HCM in the 40–50 year age group is $(\$21,123) \times (0.004) = \$$ per year.

HCM = hypertrophic cardiomyopathy; ICD = implanted cardioverter defibrillator; LQTS = long QT syndrome.

for economic productivity. Using these data on survival, costs, and productivity, we calculated the expected survival (life expectancy), expected total accumulated discounted costs, and the expected total accumulated discounted earnings by arm (ICD vs non-ICD). The incremental cost-effectiveness ratio (ICER) was calculated by dividing the sum of the difference in costs and the difference in productivity by the difference in discounted life expectancy.

Sensitivity analyses were conducted to determine the stability of the results in the presence of reasonable variations in the data and assumptions.

Study Models

The assumptions for the frequency of disease-related complications, medical therapy, and associated costs by allocation to ICD or non-ICD treatment are shown in Table 1. The assumed rate of SCD for each disease entity by risk stratification is shown in Figure 1. Since the onset of SCD risk for both diseases begins in childhood and continues throughout life, the overall analysis was performed in the age range of 10–75 years. Assumptions for each model were based on reasonable estimates derived from the available literature on LQTS and HCM reporting the incidence of fatal and nonfatal events and appropriate ICD intervention rate. We also included updated data from the International Long QT Registry comprising 4902 patients (Heart Research Follow-Up Program: Rochester, NY) and a multicenter follow-up of HCM patients (the Minneapolis Heart Institute Foundation, MN). Assumptions are considered separately for each of the two disease entities.

Long QT Syndrome

The LQTS is a monogenic channelopathy in which mutation carriers have a variable risk for polymorphic ventricular tachycardia and SCD.^{9–11} β -blockers are considered first-line prophylactic therapy for the prevention of SCD. However, a high rate of cardiac events in patients receiving β -blocker therapy was reported in most studies.^{9–13} The major risk factors predisposing to SCD are categorized in the present study as very high-; high-; and low-risk based on published mortality rates (Fig. 1). The risk of cardiac events in LQTS patients is also affected by age and gender.¹⁴ Accordingly, we estimated that the risk of SCD in those greater than 20 years of age was reduced by one-half in males compared to females.

Very High-Risk LQTS Patients

Risk factors that are associated with the highest annual mortality rate in LQTS include a history of aborted cardiac arrest and/or ECG-documented episodes of torsade de pointes.^{5,12–14} Based on previous follow-up studies and the current analysis of the updated International LQTS registry, the annual risk for aborted cardiac arrest or SCD for base case patients in this risk category was estimated to be 2.5% per year (sensitivity ranges: 2.0–3.0% per year) in females, and in males in the age range of 10–20 years.

High-Risk LQTS Patients

Recurrent syncope during β -blocker therapy and/or QTc prolongation >0.50 second have been

identified as high-risk clinical features associated with recurrent cardiac events in previous long-term follow-up studies and the current updated International LQTS registry.^{5,12–14} Based on these data, we estimated the risk for aborted cardiac arrest or SCD in base case high-risk LQTS patients to be 1% per year (sensitivity ranges: 0.5% to 1.5% per year) in females, and in males in the age range of 10–20 years.

Low-Risk LQTS Patients

The low-risk group includes affected subjects without a history of a prior cardiac event and with a QTc duration ≤ 0.50 second.^{5,12–14} Based on previous studies and the updated analysis, we estimated the annual risk for aborted cardiac arrest or death in base case low-risk LQTS subjects to be 0.05% per year (sensitivity ranges: 0.01–0.1% per year) in females, and in males in the age range of 10–20 years.

Hypertrophic Cardiomyopathy

HCM is a genetic cardiac disease with a heterogeneous presentation and a diverse natural history.¹⁵ Sudden and unexpected death is the leading cause of mortality in HCM patients and is virtually the sole cause of death in young asymptomatic patients.^{15,16} Annual mortality rates as high as 3–6% have been reported from tertiary referral populations, disproportionately comprised of high-risk patients.¹⁷ More recent studies from nontertiary centers report annual mortality rates in a much lower range ($\leq 1\%$), with the overall survival of patients not dissimilar to that of the general adult U.S. population.^{18–21}

In HCM, there are little data supporting the efficacy of prophylactic drug treatment for SCD.²² Also, the frequent adverse consequences associated with chronic use of amiodarone severely limit its application for SCD prevention in young patients with HCM who harbor long periods of potential risk.

Mild-to-moderate heart failure requiring only medications occurs in about 30% of patients; and severe heart failure symptoms, requiring medical symptoms and possibly septal myectomy (either surgery or alcohol septal ablation), occur in about 15% of patients. Such disease progression occurs most commonly in mid life and beyond (mean age,

56 ± 19 years). Most HCM patients with heart failure are treated as outpatients and are rarely hospitalized for this reason (Table 1).^{18,19} Heart failure-related deaths (or heart failure requiring heart transplantation) are uncommon and occur at a rate of about 0.03% per year in HCM patients >40 years.²⁰ Stroke is also a long-term potential complication of HCM patients. The overall incidence of stroke was reported to be 0.8% per year and 1.9% per year for patients >60 years.²¹

Similar to LQTS, the major risk factors predisposing to SCD in HCM subjects are categorized here as very high-, high-, and low-risk (Fig. 1). However, in contrast to LQTS, the annual rate of SCD is not related to gender.^{18,19}

Very High-Risk HCM Patients

Factors associated with the highest risk for SCD in HCM, like LQTS, include prior aborted cardiac arrest and/or prior spontaneous and sustained ventricular tachycardia.²³ Based on prior studies and the relatively high reported intervention rate in patients with these risk factors, we estimated the rate of SCD in this risk category to be 5% per year in the base case (sensitivity ranges: 4–6% per year).

High-Risk HCM Patients

High-risk clinical factors in HCM patients without a prior history of aborted cardiac arrest or spontaneous sustained arrhythmia, include a family history of HCM-related sudden death, extreme left ventricular hypertrophy (maximum wall thickness ≥ 30 mm on echocardiography), syncope (particularly if exertional, repetitive and in the young), multiple-repetitive or prolonged, or non-sustained ventricular tachycardia on serial ambulatory (Holter) ECG, and a hypotensive blood pressure response to exercise.^{18–20,24–26} It has been estimated that patients with one of those risk factors have an overall sudden death rate of 1% per year and those with multiple risk factors have an estimated SCD rate of 3% or more per year.^{25,26} Based upon previous studies in high-risk HCM patients and the rate of appropriate ICD interventions in these patients (5), we estimated the rate of SCD at 2% per year in the base case (sensitivity ranges: 1–3% per year).

Low-Risk HCM Patients

Most studies suggest that asymptomatic patients without risk factors have a low likelihood of SCD.^{18–20,25} In the study correlating left ventricular wall thickness to SCD rate, the cumulative mortality risk 20 years after the initial evaluation was close to zero for patients with a wall thickness of 19 mm or less (25). Other studies have shown a mortality rate of up to 0.5% per year.^{18–20,25} We therefore estimated SCD rate in base case low-risk HCM patients at 0.05% per year (sensitivity range: 0.01–0.1% per year).

ICD Therapy: Estimated Efficacy and Adverse Events in LQTS and HCM

For the decision model, we assumed that ICD prevents only SCD and does not interfere with the progression or natural history of the diseases (e.g., heart failure in patients with HCM), nor change the prognosis of other concomitant noncardiac diseases. We assumed that a single-lead, shock-only ICD would be effective in terminating arrhythmic events in LQTS and HCM, a dual-chamber ICD may be required in 25% of HCM patients when the clinical course is complicated by paroxysmal atrial fibrillation or marked left ventricular outflow obstruction associated with heart failure symptoms.

We estimated life-saving efficacy of ICD therapy in preventing SCD in LQTS and HCM based upon current experience with the device in these two genetic disorders.^{5,6} We employed a conservative estimate that ICD therapy will be effective in preventing SCD in 95% of cases as a base case, and performed sensitivity analysis for 99% and 90% as upper and lower ranges of ICD effectiveness, respectively.

The additional risks of hospital admissions after ICD implantation include: ICD-related infection, 0.5% per implantation procedure; ICD-related lead problems (dislodgement/fracture/migration), 1.0% per year; and generator malfunction, 1.0% per year, elevation, 1.9%.^{2,27–30} We assumed that the ICD-related adverse events are independent of each other. The ICD replacement for battery depletion was assumed to be at 5-year intervals.

Data on Costs

Sources of data on costs for inpatient and outpatient services were derived as follows: Medi-

care cost reports and physician component using diagnostic-related groups (DRGs) for hospitalization and emergency department visits; inpatients physicians' hospital costs and predicted ratio of facility costs for inpatients physicians' services; Medicare rates for outpatient tests and procedures; established Medicare rates for physician/specialist visits; and average wholesale price for medications.

ICD-Related Costs

Defibrillator-related costs include the cost of the device (single lead-shock only in LQTS and in 75% of HCM patients) and initial implantation procedure, physician visits for routine ICD evaluations, ICD-induced adverse events, and device reimplantation after battery depletion. We assumed the implantation procedure would be performed on an outpatient basis in otherwise healthy subjects. The ICD-related cost estimates (Table 1) were based on data from MADIT-II,² a recent analysis by Chen et al.,²⁹ and a study of ICD-related complications by Ferguson et al.³⁰

Drug Costs

The commonly used drugs in LQTS are β -blockers. We assumed β -blocker use in 100% of high-risk patients in the non-ICD group to prevent lethal events and 100% of ICD-treated patients to reduce the frequency of ICD shocks.

In HCM, we assumed that 25% of the high-risk patients would require medical therapy (including β -blockers, calcium channel blockers, disopyramide, and diuretics) to alleviate heart failure symptoms, while current data indicate that 70% of ICD-treated HCM patients require adjunctive medical therapy.

Unrelated Health Care Costs

We used the total health care expenditure data from the 2001 Medical Expenditure Panel Survey data to estimate age-specific-unrelated health care costs. We assumed all LQTS and HCM medical costs that we explicitly modeled were independent of all other health care costs. We specified total health care expenditure models as functions of

5-year age groups, by sex, and used age-specific predictions of total health care costs in our models.

Earnings Profiles

We used Bureau of Labor Statistics estimates of age-specific earnings that were calculated from weekly earnings data in the Current Population Survey (Web site: <http://stats.bls.gov/newsrels.htm> usual weekly earnings of wage and salary workers: second quarter 1999. BLS, US Department of Labor). We used these published earnings' data on 10-year age increments to estimate an earnings' profile that was quadratic in age, and we predicted age-specific earnings from age 18 to age 75. Although women's earnings were lower than men's earnings, we assumed that nonmarket-related productivity, such as child bearing, parenting and household work, accounted for this difference, so we used earnings profiles based on male's earnings to assess productivity for both men and women.

RESULTS

ICD Therapy for Base Case High-Risk Patients (Primary Prevention)

LQTS

The components of costs attributed to the ICD and medical therapy due to the disease in high-risk LQTS patients are summarized in Table 2A. We assumed that the sole cause of disease-related mortality is SCD.

Defibrillator therapy was shown to be cost effective to cost saving for male and female patients in this risk category. A high-risk male patient treated with an ICD would result in 3.7 quality-adjusted-life-years saved as compared to non-ICD therapy, with a stable difference throughout adulthood (Fig. 2A). When the lifetime costs and income were evaluated, ICD therapy was more cost effective after the age of 20, and the cost-effectiveness ratio approached zero throughout adulthood (Fig. 2B), resulting in a lifetime net economic loss of \$12,315 and an ICER of \$3328 per quality-adjusted-life-year saved. High-risk female patients treated with an ICD would have 5.2 quality-adjusted-life-years saved as compared to non-ICD therapy. This would result in a net economic gain of \$36,928 and a positive ICER of \$7102 gained per quality-adjusted-life-year saved.

HCM

The components of costs attributed to the ICD and medical therapy due to the disease in high-risk HCM patients are summarized in Table 2B. SCD is the main cause of death in patients with HCM, while heart failure-related death is associated with a relatively small proportion of disease-related mortality (Table 1). Both causes of disease-related mortality were considered in the estimation of life expectancy with and without ICD therapy.

Defibrillator therapy was shown to be cost saving for both male and female patients in this risk category. High-risk male and female HCM patients treated with an ICD would have 8.5 and 8.8 quality-adjusted-life-years saved, respectively, as compared to non-ICD treated patients. The difference in discounted life-years between ICD and non-ICD patients appears after the age of 10 years and is stable throughout adulthood (Fig. 3A). When the lifetime costs and income of high-risk HCM patients were evaluated, ICD therapy was cost effective in the second and third decades of life, immediately following implantation at the age of 10, and became cost gaining during the fourth decade of life (Fig. 3B). The lifetime net economic gain was \$152,078 (ICER = \$17,892 gained per quality-adjusted-life-year saved) and \$154,227 (ICER = \$17,526 gained per quality-adjusted-life-year saved) for ICD-treated male and female patients, respectively.

ICD Therapy for Base Case Very High-Risk Patients (Secondary Prevention)

LQTS

Defibrillator therapy in LQTS patients with a prior aborted cardiac arrest or sustained spontaneous torsade de pointes resulted in a net economic gain for male and female patients compared to non-ICD therapy (Appendix IA). For a base case male patient in this risk category, ICD therapy results in 7.9 additional discounted life-years saved and a net economic gain of \$122,313, resulting in a positive ICER of \$15,483 gained per discounted life-year saved compared to non-ICD male patients. For a base case female patient with an ICD there would be 10.3 additional discounted life-years saved with a net economic gain of \$199,750, resulting in a positive ICER of \$19,393 gained per discounted life-year saved compared to non-ICD female patients.

Table 2. Costs, Clinical Benefits, and Cost-Effectiveness Ratio of ICD Therapy in Base Case High-Risk Patients

A. LQTS Patients						
	Males			Females		
	Non-ICD Therapy	ICD Therapy	Difference	Non-ICD Therapy	ICD Therapy	Difference
Life saved (years)						
Life expectancy	48.7	58.8	10.1	45.7	61.0	15.4
Discounted life expectancy	24.1	27.7	3.7	23.1	28.3	5.2
Costs (discounted US \$)						
ICD device/replacement	NA	117,228	117,228	NA	119,267	119,267
ICD infections	NA	2449	2449	NA	2449	2449
Lead problems	NA	1821	1821	NA	1856	1856
Generator malfunctions	NA	5269	5269	NA	5370	5370
β -blockers	6015	6933	917	5772	7066	1294
Physician visits	6015	10,399	4384	5772	10,599	4827
Death costs	1230	579	-651	1385	409	-977
Other medical costs [†]	40,054	48,705	8651	51,491	69,515	17,146
Total costs	13,261	144,677	140,067	12,930	14,8142	151,228
Discounted income	602,090	729,842	127,752	56,1718	759,306	188,160
Net economic gain/loss			-12,315			+36,928
Incremental cost-effectiveness ratio (\$/life-year gained)			-3328			+7102

*Estimated sudden cardiac death rate: 1% per year, age 10–20 years; 0.5% per year, age 20–75 years. Estimated ICD efficacy: 95%.

[†]Include costs for medical conditions unrelated to LQTS.

Abbreviations as in Table 1.

B. HCM Patients						
	Males			Females		
	Non-ICD Therapy	ICD therapy	Difference	Non-ICD Therapy	ICD Therapy	Difference
Life saved (years)						
Life expectancy	33.6	57.4	23.7	34.6	59.8	25.2
Discounted life expectancy	18.8	27.3	8.5	19.1	27.9	8.8
Costs (discounted US \$)						
ICD device/replacement	NA	116,231	116,231	NA	118,549	118,549
ICD infections	NA	2449	2449	NA	2229	2229
Lead problems	NA	1790	1790	NA	1830	1830
Generator malfunctions	NA	5180	5180	NA	5295	5295
Medical therapy	6103	6134	30	6193	6271	78
Physician visits	4694	10,223	5528	4764	10,451	5688
HCM-related surgery	508	932	424	525	975	450
Heart failure hospitalizations	26	43	16	27	44	17
Stroke	1066	1620	553	1087	1672	584
Death costs	2165	670	-1495	2098	487	-1611
Other medical costs [†]	27,142	47,384	20,242	39,054	67,261	28,207
Total costs	12,963	142,675	150,948	13,054	145,332	161,536
Discounted income	409,119	712,146	303,027	419,534	735,297	315,763
Net economic gain/loss			+152,078			+154,227
Incremental cost-effectiveness ratio (\$/life-year gained)			+17,892			+17,526

*Estimated sudden cardiac death rate: 2% per year, age 10–70 years. Estimated ICD efficacy: 95%.

[†]Include costs for medical conditions unrelated to HCM.

Abbreviations as in Table 1.

Figure 2. Effect of defibrillator therapy on survival (A) and costs (B) in base case high-risk male long QT syndrome patients (see text and Tables for details). On the Y-axis of Fig B positive numbers denote economic loss and negative numbers denote economic gain. ICD = implanted cardioverter-defibrillator; LQTS = long QT syndrome.

HCM

Patients with HCM who have experienced prior aborted cardiac arrest or sustained spontaneous ventricular tachycardia are at a considerable risk of SCD (estimated at 4–6%). This resulted in ICD being cost saving for both base case males and females with HCM in this risk category (Appendix IB). Defibrillator therapy was associated in 14.4 and 14.9 additional discounted life-years saved in males and females, respectively, com-

pared to non-ICD therapy. The lifetime respective net economic gain was \$330,395 (ICER = \$22,944 gained per discounted life-year saved) and \$332,701 (ICER = \$22,329 gained per discounted life-year saved).

ICD Therapy for Base Case Low-Risk Patients

Current data show that the risk of SCD among LQTS and HCM patients without known risk

Figure 3. Effect of defibrillator therapy on survival (A) and costs (B) in base case high-risk hypertrophic cardiomyopathy patients (see text and Tables for details). On the Y-axis of Fig B positive numbers denote economic loss and negative numbers denote economic gain. ICD = implanted cardioverter-defibrillator; HCM = hypertrophic cardiomyopathy.

factors is similar to the general population, resulting in similar life expectancies for ICD- and non-ICD-treated patients in this risk category. In contrast to the cost-effective or cost-saving results of ICD therapy in high-risk or very high-risk LQTS and HCM patients, the ICER of device therapy for a base case low-risk patient with either disease entity demonstrates costs in the range of \$400,000–600,000 per quality-adjusted-life-years saved (Appendix IA and IB).

Sensitivity Analyses

We performed two-way sensitivity analyses on estimated mortality rates and on ICD efficacy for the three risk categories in each disease entity (Appendix IA and IB).

LQTS

Primary ICD for high-risk patients was shown to be cost effective to cost saving under any

plausible scenario. When the most conservative estimates of SCD rate and ICD efficacy for this risk category were employed, ICD therapy was life saving (1.8 and 2.7 discounted life-years saved for men and women, respectively, compared to non-ICD patients) and cost effective (ICER = \$39,640 and \$16,708 per quality-adjusted-life-year saved for males and females, respectively) when a \$50,000 per quality-adjusted-life-year saved is used as the cost-effectiveness threshold. When the estimated SCD rate and ICD efficacy in the upper range of the high-risk category were included in the analysis, a cost-saving ratio was shown for both males and females (ICER = \$8168 and \$14,984 gained per quality-adjusted-life-year saved, respectively).

Sensitivity analysis did not affect the results of the two other risk categories. In very high-risk LQTS patients, ICD therapy remained cost saving, while defibrillator therapy was not cost effective under all estimates in the low-risk category.

HCM

Defibrillator therapy in high-risk HCM patients was shown to be cost saving for both males and females under all estimates of SCD risk and ICD efficacy analyzed. In the lower ranges analyzed, ICD therapy resulted in 4.6 and 4.8 quality-adjusted-life-years saved in males and females, respectively. The ICER under these conservative estimates showed a positive gain of approximately \$6000 per quality-adjusted-life-years saved in both males and females.

Sensitivity analysis also demonstrated consistent cost-saving ratios among very-high risk HCM patients (ICER in the range of \$21,000–24,000 gained for males and females in this risk category under all estimates analyzed), while ICD therapy in low-risk HCM males and females was not shown to be cost effective even when the upper ranges of SCD and ICD efficacy were analyzed.

DISCUSSION

We evaluated the cost effectiveness of ICD therapy for two inherited cardiac disorders predisposing to premature arrhythmic death. The unique population in the current study allows estimation of quality-adjusted-life-years gained which span throughout the lifetime of the patient at risk. Furthermore, the absolute protection conferred by ICD therapy in the young and otherwise healthy pop-

ulation with genetic cardiac disorders, results in this mode of therapy being able to provide many decades of productive life. This latter ICD effect allowed us to incorporate a societal perspective in the analysis, in which costs of medical and device therapy were balanced by societal gains. These cost-saving benefits correlated to the degree of reduction in arrhythmic death risk. Our analysis indicates that in LQTS and HCM patients risk stratification can delineate patients in whom early intervention with ICD therapy will result in a substantial amount of life-years saved at either minor costs, or cost savings, when the time horizon involves the lifespan of the individual at risk.

Due to the nature of the population, randomized studies for primary prevention in inherited cardiac disorders cannot be performed. Therefore, guidelines for ICD implantation in high-risk patients with genetic cardiac diseases are difficult to establish.⁴ However, available data regarding mortality risk in LQTS and HCM, together with information on ICD-related costs and complications from large-scale studies of adult patients with acquired cardiac disorders, permitted a comprehensive analysis of the survival benefits and associated costs of ICD therapy for the two syndromes. The present analysis shows that young patients with LQTS or HCM, considered to be at high-risk of arrhythmic death, but without a major prior cardiovascular event, benefit from ICD therapy in terms of quality-adjusted-life-years saved. In this risk category ICD therapy was found to be either cost effective (in the case of high-risk male LQTS patients) or cost saving (in high-risk LQTS females and both male and female high-risk HCM patients). The findings persisted after sensitivity analyses, which included reduced ICD efficacy and an estimation of lower mortality rates compared to most studies of high-risk LQTS and HCM patients (in the range of 0.5–1% per year respectively). These results have potential public health and clinical implications in that ICD implantation is likely to be cost effective and often cost saving in a much broader range of at-risk patients than is currently recommended.

The current analysis demonstrates consistent results for the cost effectiveness of ICD therapy in both LQTS and HCM after risk stratification. However, the two inherited cardiac disorders are considered separately below to highlight several important aspects regarding the different clinical course of affected patients.

LQTS

The LQTS represents a group of inherited cardiac disorders in which cardiac morphology is normal and malignant ventricular arrhythmias are the sole cause of disease-related morbidity and mortality. Therefore, among young patients with this inherited disorder, prevention of SCD may lead to normal or near normal life expectancy without additional disease-related morbidity. Previous studies^{5,12-14} and current data from recent analysis of the international LQTS registry indicate that risk stratification for SCD risk in patients with the syndrome is mainly based upon prior clinical history and electrocardiographic findings. Medical therapy with β -blockers was shown to reduce the risk of SCD in high-risk patients, but the risk of arrhythmic mortality is still considerable with medical therapy alone. The results of the present analysis are consistent with this risk-stratification scheme and indicate that, among young patients with this inherited cardiac disorder who have known major risk factors, ICD implantation results in 3.7 to 5.2 quality-adjusted life-years saved, leading to cost-effective-to-cost-saving ratios under all estimates analyzed.

Notably, the majority of LQTS patients have only minor clinical or electrocardiographic risk factors, and among these patients the risk of SCD is similar to or only slightly greater than unaffected subjects in the same age group. Our results indicate that ICD implantation in this population does not contribute substantially to life expectancy and is not cost effective when compared to non-ICD therapy.

HCM

In contrast to LQTS, HCM represents an inherited cardiac disorder in which cardiac morphology is abnormal. This results in an increased risk for SCD and contributes to heart failure and stroke-related morbidity and mortality.¹⁸⁻²¹ However, the latter complications occur in a relatively small proportion of young patients with the disease, while SCD is the major cause HCM-related mortality in all age groups. In addition, drug therapy has not been shown to significantly reduce the risk of SCD in HCM. Accordingly, the present analysis demonstrates that, among male and female HCM patients with known major risk factors, implantation of an ICD at a young age results in a considerable amount of productive life-years gained compared to non-

ICD-based therapy, and is therefore cost saving under all estimates.

Current data indicate that risk stratification for SCD in HCM patients is largely based on noninvasive parameters using clinical history together with echocardiographic findings. Similar to LQTS, the majority of patients with HCM do not have known risk factors for SCD. Among this population, the risk of SCD is probably only slightly greater than unaffected subjects in the same age group. Furthermore, the risk of other disease-related complications, such as heart failure and stroke, is still present in low-risk patients since it is not linked to SCD risk. Therefore, ICD-treated patients in this risk category probably have a similar life expectancy as non-ICD patients, and cost effectiveness of this mode of therapy could not be demonstrated under all estimates analyzed.

It should be noted, however, that a relatively small number of HCM and LQTS patients die suddenly without any of the known risk factors, since not all disease-related risk factors have been identified to date. Thus, careful follow-up is warranted also in low-risk patients.

Cost Effectiveness of ICD Therapy in Young Patients with Inherited Cardiac Disorders as Opposed to Adult Patients with Acquired Heart Disease

In adult patients with high-risk cardiac disease, the ICER for ICD therapy has ranged from \$30,000 to \$185,000 per quality-adjusted-life-year saved,^{29,31,32} with this wide range reflecting variability in mortality risk, the mortality reduction achieved with the ICD, and the duration of ICD therapy in the various reported populations.³³ In ICD-treated adult patients, there are many competing risks for death, and the ICD only prevents SCD. Thus, many clinicians feel the main goal of ICD therapy in adults is to "prolong life," since those whose lives are saved by the ICD usually live, on the average, only months to a few years longer. The situation is very different in young patients with genetic cardiac disorders. In LQTS there are no competing cardiac mortality risks, while in HCM the competing risks are low and their onset is at a considerably later stage than SCD risk. These differences have generated significantly lower cost-effectiveness ratios in the present analysis compared to similar analyses of adult patients with high risk acquired cardiac disease.^{29,31,32} In addition, in

the latter population, the life prolonging effect of ICD therapy is associated with increased costs due to associated morbidity,³¹ while in the former population the added years result in gained productivity.

Limitations

The current conclusions rely on assumptions created for hypothetical models, largely with respect to mortality estimates and risk stratification. The data we have used are derived from current knowledge regarding risk stratification for the two genetic cardiac disorders, including updated analysis from large-scale registries. Risk factors considered in the current analysis included mostly clinical variables, and it is possible that as genetic testing for inherited cardiac disorders improves, more specific risk populations can be delineated. However, we have shown by sensitivity analysis, that ICD therapy is still cost effective in high-risk individuals even when the lower-range assumptions for this risk category (regarding the rate of SCD and ICD efficacy) were considered.

In our analysis we considered a simple, single-lead, shock-only devices to be effective in terminating malignant arrhythmias in young patients with preserved systolic function. It is likely that as technology advances the cost of these simple devices will be reduced and generators will last longer before replacement, reducing the cost of ICD replacement. Thus, the cost effectiveness of ICD therapy in high-risk patients with genetic cardiac disorders is likely to even improve in the near future.

CONCLUSIONS

In both LQTS and HCM, attempts to prevent SCD with drug or surgical therapy have had only limited success.^{12,22,34} Therefore, ICD therapy is the only viable therapeutic option affording the opportunity for normal or near-normal longevity in high-risk patients with these inherited disorders. Our analysis indicates in selected high-risk patients with LQTS and HCM, early intervention with ICD therapy is cost effective and often results in cost savings due to gained productivity. These findings suggest that primary prevention of arrhythmic death for high-risk subjects with either of the two genetic syndromes should include ICD therapy as a first-line measure.

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Appendix IA. Sensitivity Analyses (ICD vs. Non-ICD Therapy)

IA. LOTS Patients						
	Males*			Females		
	Discounted Life-Years Saved (Years)	Net economic Gain/Loss (US \$)	ICER (\$/Life-Year Gained)	Discounted Life-Years Saved (Years)	Net Economic Gain/Loss (\$)	ICER (\$/Life-Year Gained)
A. Very high-risk patients						
Mortality 3.0%/year ICD efficacy: 99%	9.6	+172,251	+17,943	12.3	+258,997	+21,057
Mortality 3.0%/year ICD efficacy: 95%	9.1	+157,972	+17,360	11.5	+237,206	+20,627
Mortality 3.0%/year ICD efficacy: 90%	8.5	+140,644	+16,546	10.6	+211,268	+19,931
Mortality 2.5%/year ICD efficacy: 99%	8.4	+134,252	+15,982	10.9	+218,008	+20,001
Base case:						
Mortality 2.5%/year ICD efficacy: 95%	7.9	+122,313	+15,483	10.3	+199,750	+19,393
Mortality 2.5%/year ICD efficacy: 90%	7.4	+107,755	+14,561	9.5	+177,841	+18,720
Mortality 2.0%/year ICD efficacy: 99%	7.0	+91,980	+13,140	9.4	+169,643	+18,047
Mortality 2.0%/year ICD efficacy: 95%	6.7	+82,398	+12,298	8.9	+154,957	+17,343
Mortality 2.0%/year ICD efficacy: 90%	6.2	+70,655	+11,396	8.2	+137,190	+16,730
B. High-risk patients						
Mortality 1.5%/year ICD efficacy: 99%	5.5	+44,925	+8168	7.5	+112,380	+14,984
Mortality 1.5%/year ICD efficacy: 95%	5.2	+37,714	+7253	7.2	+101,306	+14,070
Mortality 1.5%/year ICD efficacy: 90%	4.9	+28,834	+5884	6.7	+87,799	+13,104
Mortality 1.0%/year ICD efficacy: 99%	3.8	-7492	-1972	5.4	+44,351	+8213
Base case:						
Mortality 1.0%/year ICD efficacy: 95%	3.7	-12,315	-3328	5.2	+36,928	+7102
Mortality 1.0%/year ICD efficacy: 90%	3.5	-18,285	-5224	4.9	+27,780	+5669
Mortality 0.5%/year ICD efficacy: 99%	2.0	-65,922	-32,961	2.9	-36,753	-12,673
Mortality 0.5%/year ICD efficacy: 95%	1.9	-68,342	-35,969	2.8	-40,485	-14,459
Mortality 0.5%/year ICD efficacy: 90%	1.8	-71,352	-39,640	2.7	-45,112	-16,708
C. Low risk patients						
Mortality 0.1%/year ICD efficacy: 99%	0.42	-117,488	-279,733	0.63	-112,947	-179,280
Mortality 0.1%/year ICD efficacy: 95%	0.40	-117,973	-294,932	0.60	-113,697	-189,495
Mortality 0.1%/year ICD efficacy: 90%	0.38	-118,579	-312,050	0.57	-114,633	-201,110
Mortality 0.05%/year ICD efficacy: 99%	0.21	-124,258	-591,709	0.32	-123,273	-385,228
Base case:						
Mortality 0.05%/year ICD efficacy: 95%	0.20	-124,500	-622,500	0.30	-123,648	-412,160
Mortality 0.05%/year ICD efficacy: 90%	0.19	-124,804	-656,863	0.29	-124,116	-427,986
Mortality 0.01%/year ICD efficacy: 99%	0.04	-129,727	-3,243,175	0.06	-131,669	-2,194,483
Mortality 0.01%/year ICD efficacy: 95%	0.04	-129,776	-3,244,400	0.06	-131,745	-2,195,750
Mortality 0.01%/year ICD efficacy: 90%	0.04	-129,837	-3,245,925	0.06	-131,838	-2,197,300

* Mortality rates for males are shown between the ages 10 years and 20 years and were reduced by half at age >20 years.
 HCM = hypertrophic cardiomyopathy; ICD = implanted cardioverter defibrillator; ICER = incremental cost-effectiveness ratio; LOTS = long QT syndrome.

Appendix IB. Sensitivity Analyses (ICD vs. nNon-ICD Therapy)

	IB. HCM patients					
	Males			Females		
	Discounted Life-Years Saved (years)	Net Economic Gain/Loss (US \$)	ICER (\$/Life-Year Gained)	Discounted Life-Years Saved (years)	Net Economic Gain/Loss (\$)	ICER (\$/Life-Year Gained)
A. Very high-risk patients						
Mortality 6.0%/year ICD efficacy: 99%	16.9	+399,902	+23,663	17.5	+402,539	+23,002
Mortality 6.0%/year ICD efficacy: 95%	15.5	+358,826	+23,150	16.0	+360,711	+22,544
Mortality 6.0%/year ICD efficacy: 90%	13.9	+312,144	+22,456	14.4	+313,257	+21,754
Mortality 5.0%/year ICD efficacy: 99%	15.6	+364,988	+23,397	16.1	+367,936	+22,853
Base case:						
Mortality 5.0%/year ICD efficacy: 95%	14.4	+330,395	+22,944	14.9	+332,702	+22,329
Mortality 5.0%/year ICD efficacy: 90%	13.1	+290,460	+22,173	13.5	+292,087	+21,636
Mortality 4.0%/year ICD efficacy: 99%	13.9	+318,023	+22,879	14.4	+321,156	+22,303
Mortality 4.0%/year ICD efficacy: 95%	13.0	+290,054	+22,312	13.4	+292,663	+21,840
Mortality 4.0%/year ICD efficacy: 90%	11.9	+257,252	+21,618	12.3	+259,287	+21,080
B. High-risk patients						
Mortality 3.0%/year ICD efficacy: 99%	11.8	+254,179	+21,541	12.2	+257,225	+21,084
Mortality 3.0%/year ICD efficacy: 95%	11.1	+232,979	+20,969	11.5	+235,623	+20,489
Mortality 3.0%/year ICD efficacy: 90%	10.2	+207,718	+20,365	10.6	+209,907	+19,803
Mortality 2.0%/year ICD efficacy: 99%	9.0	+166,363	+18,485	9.3	+168,786	+18,149
Base case:						
Mortality 2.0%/year ICD efficacy: 95%	8.5	+152,078	+17,892	8.8	+154,227	+17,526
Mortality 2.0%/year ICD efficacy: 90%	7.9	+134,785	+17,061	8.2	+136,614	+16,660
Mortality 1.0%/year ICD efficacy: 99%	5.2	+44,019	+8465	5.4	+44,823	+8,301
Mortality 1.0%/year ICD efficacy: 95%	4.9	+36,800	+7,510	5.2	+37,465	+7,205
Mortality 1.0%/year ICD efficacy: 90%	4.6	+27,919	+6,069	4.8	+28,415	+5,920
C. Low risk patients						
Mortality 0.1%/year ICD efficacy: 99%	0.60	-108,593	-180,988	0.63	-110,741	-175,779
Mortality 0.1%/year ICD efficacy: 95%	0.57	-109,322	-191,792	0.60	-111,484	-185,806
Mortality 0.1%/year ICD efficacy: 90%	0.54	-110,231	-204,131	0.57	-112,412	-197,214
Mortality 0.05%/year ICD efficacy: 99%	0.30	-118,578	-395,260	0.32	-120,950	-377,969
Base case:						
Mortality 0.05%/year ICD efficacy: 95%	0.29	-118,943	-410,148	0.30	-121,322	-404,407
Mortality 0.05%/year ICD efficacy: 90%	0.27	-119,399	-442,219	0.29	-121,786	-419,952
Mortality 0.01%/year ICD efficacy: 99%	0.06	-126,697	-2,111,617	0.06	-129,252	-2,154,200
Mortality 0.01%/year ICD efficacy: 95%	0.06	-126,770	-2,112,833	0.06	-129,327	-2,155,450
Mortality 0.01%/year ICD efficacy: 90%	0.06	-126,860	-2,114,333	0.06	-129,420	-2,157,00

Abbreviations as in Appendix IA.

Michel Mirowski in France, 1950s

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