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Cost-effectiveness of Implantable Cardioverter-Defibrillators in Children with Dilated Cardiomyopathy

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Abstract

Background—Implantable cardioverter-defibrillators (ICDs) improve survival and are cost-effective in adults with poor left ventricular function. Because of differences in heart failure etiology, sudden death rates, and ICD complication rates, these findings may not be applicable to children.

Methods and Results—We developed a Markov model to compare typical management of childhood dilated cardiomyopathy with symptomatic heart failure to prophylactic ICD implantation plus typical management. Model costs included costs of outpatient care, medications, complications, and transplantation. Time horizon was up to 20 years from model entry. Total costs were \$433,000 (ICD strategy) and \$355,000 (typical management). Although quality adjusted survival was greater in the ICD group (6.78 vs. 6.43 quality adjusted life-years, QALYs), the incremental cost-utility ratio was \$281,622/QALY saved with the ICD strategy. In sensitivity analyses, the ICD strategy cost less than the \$100,000/QALY benchmark for cost-effectiveness only when the annual probability of sudden death exceeded 13% or when strong, sustained benefits in QOL due to the ICD were assumed.

Conclusions—Prophylactic ICD use in children with dilated cardiomyopathy, poor ventricular function, and symptomatic heart failure does not appear to be cost-effective. This is likely due to lower sudden death rates in this population.

Keywords

pediatrics; heart failure; cost effectiveness

INTRODUCTION

Prospective studies in nearly 7,500 patients have established indications for the use of implantable cardioverter-defibrillators (ICDs) for primary prevention of sudden death in adults with left ventricular dysfunction.^{1–8} ICDs have also been shown to be cost-effective in these adult heart failure populations.^{9–11} This has lead some to consider ICDs in children with end-

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DISCLOSURES

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stage heart disease;¹² however, extrapolation of adult heart failure treatment recommendations to children is problematic due to important differences between these populations. Prospective studies in children to address this issue are not feasible due to the relative infrequency of heart failure in pediatrics. Also, because children with ICDs constitute only about 1% of all ICD recipients,¹³ pediatric data on ICD use are limited to small case series or retrospective cohort summaries of children and young adults with heterogeneous underlying diagnoses. Although much about the characteristics of children with ICDs, rates of ICD-related complications, and risk factors for complications have been learned from these reports, these studies lack the ability to draw conclusions about the suitability of ICDs in specific pediatric sub-populations. In particular, there are no data which indicate a survival benefit with routine use of ICDs in children with depressed ventricular function.¹⁴ While Dubin et. al. have reported ICD implantation to be an effective bridge to transplantation in 28 children and young adults, this report included patients with structural heart disease and lacked an appropriately matched group of patients awaiting transplantation without an ICD.¹²

Because of limitations in studying this small but important group of patients, we employed decision analysis to examine this clinical question. We hypothesized that ICD therapy would be cost-effective in some children with dilated cardiomyopathy and mildly symptomatic heart failure. Thus, the aim of our study was to delineate the circumstances in which ICD therapy in children with systolic heart failure might be considered cost-effective. This research technique utilizes computerized decision models to synthesize the available literature, incorporating all the major possible outcomes of a decision.¹⁵

METHODS

We created a decision analytic model (figure 1) to compare costs and survival in a hypothetical cohort (age 10–15 years) with dilated cardiomyopathy and symptomatic heart failure receiving outpatient medical management with or without an ICD. The model adhered to the recommendations of the Panel on Cost-Effectiveness in Health and Medicine by examining costs from a societal perspective and applying a 3% annual discount to both costs and health benefits.¹⁶ We constructed the model using TreeAge Pro Suite 2008 (release 1.2.1; TreeAge Software, Inc., Williamstown, MA).

Model Overview

Patients were tracked monthly and could remain stable, die suddenly (arrhythmic) or non-suddenly, or decompensate and require hospitalization with immediate listing for cardiac transplantation (i.e., United Network for Organ Sharing (UNOS) Status 1A candidate). Hospitalized patients were tracked for up to 12 months during which time they could remain hospitalized awaiting transplantation, receive transplantation, or die suddenly (arrhythmic) or non-suddenly. After 12 months, all inpatients were either transplanted or dead (non-sudden death). Costs and survival were also followed after transplantation. Patients could be followed for up to 20 years from model entry.

In the ICD arm, the model assumed implantation of a transvenous, single lead ICD for primary prevention of sudden (arrhythmic) death. Patients who received an ICD had a small probability of death (0.1%) at implantation and were also at risk each month for inappropriate ICD discharge, lead malfunction, and pocket infection.

Clinical Assumptions

Base-case estimates and ranges of all clinical parameters, costs, and utilities are shown in Table 1. We estimated the probabilities of clinical decompensation, death, transplantation, and post-transplant survival from various data sources that we believed were most representative of the

target population. We estimated the probability of sudden death in outpatients from the cumulative incidence of sudden death in 2,392 children listed for cardiac transplantation from 1993 – 2003.¹⁷ Likewise, the probability of non-sudden death as an outpatient was estimated from data depicting the natural history of 620 children listed as UNOS status 2 (least urgent listing status) for cardiac transplantation.¹⁸ Both of these model probabilities declined annually, consistent with the data describing these events. Although no good data describe the probability of arrhythmic versus non-sudden death in hospitalized children awaiting cardiac transplantation, there is reliable data which depict the multiple, competing outcomes after listing for transplantation (death, alive waiting, and transplantation) in children listed UNOS status 1.¹⁹ Thus we estimated sudden death to be 20% of the total deaths in this setting and derived monthly probabilities for non-sudden death, sudden death, and transplantation, assuming that at the end of 12 months of waiting for transplantation as inpatients, all would have died or been transplanted.

The base-case model assumption of ICD efficacy in reducing sudden death was based on composite adult data from primary prevention trials.^{2,4,5,7,8} ICD generator replacement frequency was also based on adult data.^{20,21}

Costs

All costs were adjusted using the gross domestic product deflator method and reported in 2006 US dollars.²² Outpatient care costs considered in the model include: drug costs for heart failure medications (enalapril 7.5mg twice daily, furosemide 20mg daily, spironolactone 25mg daily, and digoxin 125 mcg daily); every 4 monthly cardiology office visits with echocardiogram, electrocardiogram, phlebotomy (electrolytes, blood urea nitrogen, B-type natriuretic peptide level, liver transaminases, and complete blood count), and ICD interrogation (if applicable); annual chest radiography; and annual 24-hour ambulatory electrocardiography. Technical and professional fees were considered, as appropriate. All of the above cost data were derived using an institutional cost-to-charge ratio of 0.44. Costs of inpatient pre-transplant care, perioperative transplant care (including organ recovery and surgical fees), and both short and long-term post-transplant related care were adapted from Dayton et al., in their study of cost-effectiveness of pediatric cardiac transplantation.²³

ICD risks and complications

Risks and scenarios for ICD-related complications in the model were restricted to: 1) inappropriate ICD discharge with assessment in and discharge from the emergency department; 2) lead malfunction requiring emergency department visit, lead replacement, and 3 day hospitalization; and 3) pocket infection requiring emergency department visit and a total of 7 days hospitalization for generator removal, initiation of intravenous antibiotics (total duration 4 weeks), and subsequent generator replacement. Event probabilities were extrapolated from the multicenter, pediatric ICD registry¹³ and costs derived from institutional data.

Quality of life measures (utilities)

Utilities measure quality of life on a scale from 0 to 1, where 0 represents death and 1 represents perfect health. Our model assumed that one year of life as an outpatient with dilated cardiomyopathy and mildly, symptomatic heart failure equaled 0.71 year of ideal health. This estimate was based on data from adults with stable heart failure²⁴ but was also made in the context of utility data in children after cardiac transplantation, which classifies one year of life in this state as being equal to 0.87 year of perfect health.²⁵ We estimated a utility of 0.5 for children receiving inpatient care for decompensated heart failure, realizing that this classification encompasses a broad clinical spectrum from those who are in the intensive care unit on mechanical circulatory support to those on a medical ward receiving a single inotrope infusion.

We also subtracted utility (disutility) from patients for specific lengths of time depending on the specific health states they experienced. Disutilities were associated with ICD-related complications, generator replacement and the first year after transplantation. After reviewing adult and pediatric literature regarding ICD impact on quality of life, no ICD-specific quality of life benefit or disutility was assumed in the base-case model.^{26–32}

Sensitivity Analyses

To account for model assumptions and uncertainties, we performed one-way sensitivity analysis on each variable. Estimates were varied widely in these analyses to account for the relative uncertainty of some data. Two-way sensitivity analyses were performed on selected variables. A probabilistic sensitivity analysis, where all model parameters were varied simultaneously (ranges listed in Table 1) was performed using random draws from parameter distributions and 1000 recalculations of cost-effectiveness ratios for parameter sets drawn.

In three separate analyses, the model was modified to account for: a) a greater proportion of sudden death relative to non-sudden death, and to allow for b) hospital discharge of listed patients on home inotropic therapy while awaiting transplantation, and c) listing and transplantation of outpatients. For the last of these analyses, patients faced the same risks described for the primary model with the added possibility of being transplanted as an outpatient. The cumulative incidence of transplantation was estimated at 0.1% at 1 month, 1% at 6 months, 3% at 12 months, 6% at 24 months, 10% at 36 months, and 20% at 48 months, with a constant probability of transplantation as an outpatient of 0.9%/month thereafter.

RESULTS

Base-case Analysis

Total per patient costs were \$433,000 for the ICD strategy and \$355,000 for typical management. Quality adjusted survival was greater for the ICD strategy relative to typical management (6.78 years vs. 6.43 years). Under base-case assumptions, the incremental cost utility ratio for the ICD strategy, as compared to typical management, was \$281,622 per quality-adjusted life year (QALY) gained.

Sensitivity Analyses

In all but two assessments, the ICD strategy exceeded the \$100,000/QALY benchmark that is typically considered cost-effective. The ICD strategy cost less than \$100,000/QALY only when the annual probability of sudden death as an outpatient exceeded 13% or when the ICD improved the patient's quality of life by a utility of ≥ 0.11 . When an equivalent decrease in the patient's quality of life from the ICD was assumed (disutility of 0.11), the ICD strategy was more costly and less effective (dominated) than typical management. The ICD strategy was also dominated when associated with a reduction in the risk of sudden death of $< 1.7\%$, relative to the typical management strategy. On the other hand, when 100% reduction in the relative risk of sudden death was assumed (i.e., ICD prevented all episodes of sudden death), the ICD strategy cost \$197,628/QALY. The model was moderately sensitive to the cost of the ICD, the frequency and cost of ICD generator changes for battery end of life, and the probabilities of heart failure decompensation, death at ICD implantation, non-sudden death, and death after transplantation (table 2). Except for the probability of ICD-related infections, variations in disutilities, costs, and probabilities of ICD-related complications had minimal impact on results.

In two-way sensitivity analysis at a willingness to pay of \$100,000/QALY, typical management was favored over the ICD strategy at all times when the annual probability of sudden death was $\leq 9\%$, even when the ICD provided complete protection from sudden death (figure 2). The

results of the probabilistic analysis show that the ICD strategy was exceedingly unlikely to cost less than \$100,000/QALY and would be favored only at a willingness-to-pay > \$389,000/QALY gained.

In our supplemental analysis varying the proportion of sudden death we found that the even if 100% of deaths were sudden, the ICD strategy was not cost-effective (\$134,000/QALY gained). When the possibility of discharge on home inotropic therapy while awaiting transplantation was varied we found that the cost-utility ratio exceeded \$200,000 even when 90% of inpatients were discharged on an inotrope. Finally, when the model allowed for the possibility of listing and transplantation of outpatients we found that per patient total costs and quality adjusted survival of the ICD strategy was \$400,000 and 7.19 years versus \$317,000 and 6.86 years for typical management and the incremental cost-utility ratio for the ICD strategy was \$256,419/QALY. Sensitivity analyses on this modified model showed findings similar to the primary model.

DISCUSSION

In our analysis, prophylactic ICD implantation in children with dilated cardiomyopathy and symptomatic heart failure has a cost-effectiveness ratio above \$100,000/QALY gained. Although there is no absolute threshold below which a therapy is considered to be cost-effective, ratios greater than \$100,000/QALY are usually not considered cost-effective.³³ These findings were consistent, despite wide variations in model parameters to account for uncertainties in model assumptions. Our results contradict the findings of cost-effectiveness studies in adults with ejection fractions <30–35% in whom prophylactic ICD implantation has generally been found to be cost-effective.^{9–11} The difference in findings is most likely explained by inherent differences in the adult and pediatric heart failure populations; particularly, the etiologies of left-ventricular dysfunction.

In the absence of congenital cardiac lesions, children with left ventricular dysfunction and heart failure almost exclusively have non-ischemic cardiomyopathies whereas adults with heart failure from left ventricular dysfunction suffer primarily from ischemic cardiomyopathy. The mortality benefit of ICD therapy upon which the cost-effectiveness of ICDs in adults is based was derived from primary prevention trials in adults with predominant ischemic cardiomyopathy.^{2,4,5,7,8} Furthermore, in adults with non-ischemic cardiomyopathy, ICD therapy showed no statistically significant all-cause mortality benefit,^{1,6,34} but was associated with decreased sudden arrhythmic death.^{6,35} This highlights an important element of the analysis: ICD therapy is most likely to benefit patients with a high risk of sudden arrhythmic death. Available data suggest low sudden death rates in children with advanced cardiac dysfunction. In a multi-center registry study of 2,392 children awaiting heart transplantation, freedom from sudden death was 97% at 3 years after listing for transplantation.¹⁷ A separate population-based study of 314 children with dilated cardiomyopathy found that sudden death in those ≥10 years of age was the initial symptom in only 3.5%.³⁶ These data correspond with more generalized findings of a relatively low risk of sudden tachyarrhythmic death in children.^{37,38} In contrast, adults with left ventricular dysfunction have higher sudden death rates (6.1–25.5% over 20–39 months).^{3,5–8} Thus, our finding that ICDs are cost-effective when sudden death exceeds 13% per year is both consistent with adult data yet highly improbable in pediatric heart failure populations.

Another important dissimilarity between adults and children which may also influence the cost-effectiveness ratio of ICD therapy for primary prevention of sudden death are differences in the rates of ICD-related complications. Recent literature suggests that ICD-related complications are relatively common in children. In a number of small case series, inappropriate discharges occurred in 11 – 61% of patients over 24–52 months of follow-up.

^{39–44} These data were confirmed by a 21% inappropriate shock rate over 7.5 years in the recently published multicenter pediatric ICD registry of 443 patients.¹³ Other frequently reported complications were infections, lead dislodgements, and other lead-related problems (e.g., fractures, breach) occurring in 12%, 20%, and 41% of patients, respectively. In direct comparison to adults, children were found to have greater incidences of infections and lead fractures.⁴⁵ In our model, variation of most ICD-related complications had little effect on results.

When considering the cost-effectiveness of ICD therapy, the psychological impact of having an ICD is an important factor to consider. We found that quality of life directly attributed to the ICD strongly influenced whether or not the ICD strategy was cost-effective. Specifically, only when the ICD was directly associated with a health utility benefit of ≥ 0.11 was the ICD strategy cost-effective. Also, when the presence of an ICD was directly associated with a health detriment less than -0.06 , the ICD strategy was more costly and less effective (dominated). Unfortunately, these values are inherently difficult to conceptualize. While it is easy to understand valuing one health state over another, attaching specific values to health states is more complex. Nonetheless, an ICD-related health utility benefit of 0.11 does not seem plausible. Firstly, studies of quality of life in children and young adults with ICDs have shown reasonably good physical functioning, but frequent worries about body image and social interactions, and have concluded that quality of life is adversely affected by ICD implantation.^{28,32} Secondly, while studies in adults have shown mixed conclusions as to whether ICD use is associated with a net health benefit or detriment,^{26,29,46} younger age (<50 years) and the frequency of ICD shocks (a relatively common event in children) are risk factors for poor psychological adjustment.^{47,48} Lastly, a recent, prospective study of quality of life in adults with heart failure who had an ICD or were taking amiodarone found that ICD therapy was associated with a net health benefit of only 0.05 at 3 and 12 months after ICD placement and no health benefit at 30 months.³⁰

Because patients similar to our model cohort would be almost always considered for heart transplantation at some point in their illness, we felt it necessary to include transplantation costs and outcomes. Although cost-effectiveness studies of ICDs in adults have not modeled transplant-related costs and outcomes, this is reasonable because far fewer adults are suitable transplant candidates due to co-morbidities and advanced age. While we chose to consider patients for heart transplantation in our primary model only after clinical decompensation and inpatient hospitalization, we repeated the analysis allowing patients to receive transplantation as outpatients and found no significant differences from the primary model. We also considered the possibility of discharging patients on inotropes while awaiting transplantation and found that it did not substantially change the favorability of pediatric ICD placement.

Limitations

Though we recognize that many children with heart failure from severe dilated cardiomyopathy require inpatient care with inotropic support until transplantation, it has been our experience that a significant proportion, particularly those who are newly diagnosed and in whom no prior medical therapy has been tried, can be successfully weaned and managed with oral medications as outpatients. In our large volume pediatric cardiology practice we follow at least 30 such children with chronic heart failure from dilated cardiomyopathy and many have been followed for years to a decade. Though none of these patients have cardiomyopathies due to muscular dystrophies, a clear limitation of our hypothesized cohort, and of the treatment of children with long-standing dilated cardiomyopathy in general, is that often a genetic or molecular diagnosis is unknown. Thus what is treated as “dilated cardiomyopathy” is likely a heterogeneous mixture of conditions which result in a common phenotype and despite best attempts at diagnosis, more often than not a specific etiology cannot be determined. Therefore it is reasonable to assume

that not all patients would derive the same benefit of an ICD; however, until the field advances to the point that specific diagnoses can routinely be made and associations with arrhythmic death tied to these diagnoses, this remains the clinical reality.

Other limitations include our reliance on estimations for many model parameters. This was necessary because the pediatric heart failure population is relatively small and not as well studied as adults. To overcome this limitation we researched multiple data sources and used the best available data and wide variations in sensitivity analyses to account for uncertainty. Despite these sometimes implausibly wide variations, we consistently found the addition of an ICD for primary prevention was not cost-effective as compared to typical management alone. Although the model was responsive to variations in some parameters, no realistic scenario resulted in an incremental cost-utility ratio <\$100,000/QALY. Additionally, although cost-utility analysis is a well validated technique, modeling and simulation may be subject to inadvertent bias or error and not every plausible clinical scenario can be considered. In this regard we have taken every effort to ensure the accuracy of the model and conform to the standards of cost-utility analyses. And while a prospective study of this issue might yield “real” results, such a study is not practical because of the relative infrequency of events and the small subject population. Finally, it must be stated that these results are applicable only to the population studied and thus are not likely to be applicable to any specific populations in which a high risk of SCD can be anticipated.

CONCLUSION

Unlike findings in adults, prophylactic ICD use in children with dilated cardiomyopathy and depressed left ventricular systolic function does not appear to be cost-effective. This is likely due to lower sudden death rates in children as compared to adults.

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Figure 1. The Decision Model

Patients surviving ICD implantation and those receiving typical management enter the Markov process (encircled “M”). During each month outpatients remain stable, die, or decompensate and require hospitalization with transplant listing. Inpatients awaiting transplantation either receive transplant or die within 12 months.

Figure 2.

Two-way Sensitivity Analysis of ICD Benefit and the Probability of Sudden Death At a willingness-to-pay of \$100,000/QALY, the ICD strategy is never favored below 9% annual probability of sudden death nor at any ICD benefit <50%. ICD benefit most significantly impacts cost-effectiveness between probabilities of sudden death of 9%–16%.

Table 1**Costs, Quality of Life Measures, and Clinical Parameters**

Variable	Base case estimate	Range	References or sources
Typical Management Costs (per month)			
Cardiomyopathy outpatient management	\$288	\$50 – \$2,000	CHP Finance
Heart Failure Medications	\$62	\$0 – \$1,000	49
Additional ICD-related Costs			
ICD management (per month)	\$39	\$0 – \$220	CHP Finance
ICD implantation	\$46,760	\$0 – \$66,000	CHP Finance
Generator replacement	\$29,637	\$6,600 – \$66,000	CHP Finance
ICD pocket infection	\$50,545	\$440 – \$79,200	CHP Finance
ICD lead malfunction	\$13,996	\$220 – \$33,000	CHP Finance
Inappropriate shock	\$1,420	\$9 – \$3,080	CHP Finance
Transplant Related Costs			
Pre-transplant inpatient management	\$126,713	\$0 – 250,000	23
Surgery/inpatient post-transplant ^d	\$82,855		23
Post-transplant months 1–3 (per month) ^b	\$28,623	\$0 – \$50,000	23
Post-transplant months 4–12 (per month) ^b	\$2,108	\$0 – \$10,000	23
Post-transplant months >12 (per month) ^b	\$1,640	\$0 – \$10,000	23
Frequency of ICD generator replacement	5 years	(1.5 – 20 years)	Estimate
Efficacy of ICD in reducing sudden death	0.6	(0 – 1.0)	Estimate
Utilities			
Outpatient Dilated Cardiomyopathy	0.71	(0.5 – 0.95)	24
Dis/utility of ICD	0	(–0.11 – 0.24)	26–32,48
Disutility of ICD pocket infection ^c	0.2	(0 – 0.6)	Estimate
Disutility of ICD lead malfunction ^d	0.12	(0 – 0.5)	Estimate
Disutility of inappropriate shock ^e	0.05	(0 – 0.5)	Estimate
Disutility of generator change ^f	0.1	(0 – 0.5)	Estimate
Pre-transplant inpatient	0.5	(0.2 – 0.95)	Estimate
Post-transplant months 1–3	0.80	(0.5 – 0.8)	Estimate
Post-transplant months 4–12	0.85	(0.55– 0.85)	Estimate
Post-transplant months >12	0.87	(0.4 – 0.98)	25
Probabilities (per month)			
Death with ICD implantation	0.1%	(0 – 5.5%)	13
ICD pocket infection	0.4%	(0 – 10%)	13
ICD lead malfunction	2.2%	(0 – 10%)	13
Inappropriate shock	5.4%	(0 – 25%)	13
Clinical (heart failure) decompensation	10%	(1 – 50%)	Estimate
Sudden death (outpatient)	2.8% ^g	(0.5 – 50%)	19

Variable	Base case estimate	Range	References or sources
Non-sudden death (outpatient)	7.4% ^g	(1 – 50%)	20
Sudden death (inpatient)	5.8% ^h	(0 – 71%)	21
Non-sudden death (inpatient)	22.4% ^h	(0 – 95%)	21
Transplantation	71.8% ^h	(0 – 99%)	21
Death after transplantation	8.6% ^{††}	(0 – 39.5%)	50

Abbreviation: CHP Finance, Children's Hospital of Pittsburgh Finance Department

^a Includes procurement, transplant surgical fee, post-transplant inpatient costs.

^b Medication costs included.

^c One month duration

^d One week duration

^e Two days duration

^f One-half week duration

^g First-year probability

^h Annual probability

Table 2

Effect of Model Parameter Variability on the Incremental Cost-effectiveness Ratio in One-way Sensitivity Analyses

Variable	Variable Range	Incremental Cost- effectiveness Ratio
Cost of ICD	\$0 – \$51, 550	\$148,351– \$294,133
Frequency of ICD generator change	Never – every 18 mo	\$224,678 – \$488,060
Utility of outpatient Dilated Cardiomyopathy	0.5 – 0.95	\$148,350 – \$294,133
Cost of ICD generator change	\$6,600 – \$66,000	\$237,706 – \$350,944
Probability of death with ICD implant	0 – 5.3%	\$277,361 – dominated ^b
Probability of clinical decompensation	1% – 50% ^a	\$251,902 – \$351,856
Probability of non-sudden death	1% – 50% ^a	\$258,879 – \$1,223,040
Probability of death after transplantation	0% – 40% ^a	\$251,189 – \$438,408
Probability of ICD related infection	0% – 10% ^a	\$278,297 – \$368,536
Efficacy of ICD in reducing sudden death	0% – 100%	dominated ^b – \$197,628

Abbreviation: mo, months.

^a Annual probability

^b A strategy is dominated when it costs more and is less effective than the competing strategy.