JACC Vol. 19, No. 6
May 1992:1323–34

REVIEWS

Cost-Effectiveness of the Implantable Cardioverter-Defibrillator: Effect Of Improved Battery Life and Comparison With Amiodarone Therapy

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The implantable cardioverter-defibrillator (ICD) greatly reduces the incidence of sudden cardiac death among patients with recurrent sustained ventricular tachycardia and fibrillation who do not respond to conventional antiarrhythmic therapy. A cost-effectiveness analysis was performed, comparing the ICD, amiodarone and conventional agents. Actual variable costs of hospitalization and follow-up care were used for 21 ICD- and 43 amiodarone-treated patients. Life expectancy and total variable costs were predicted with use of a Markov decision analytic model. Clinical event rates and probabilities were based on published reports or expert opinion.

Life expectancy with an ICD (6.1 years) was 50% greater than that associated with treatment with amiodarone (3.9 years) and 2.5 times that associated with conventional treatment (2.5 years). Assuming replacement every 24 months, ICD lifetime treatment costs (in 1989 dollars) for a 55-year old patient are expected to be $89,600 compared with $24,800 for amiodarone and $16,100 for conventional therapy, yielding a marginal cost/effectiveness ratio for ICD versus amiodarone therapy of $29,200/year of life saved, which is comparable to that of other accepted medical treatments. If technologic improvements extend average battery life to 36 months, the marginal cost/effectiveness ratio would be $21,800/year of life saved, and at 96 months it would be $13,800/year of life saved. Patient age at implantation did not significantly affect these results.

If quality of life on amiodarone therapy is 30% lower than that with the ICD, the marginal cost/effectiveness ratio decreases by 35%. If the quality of life for patients receiving drugs is 40% lower than that of patients treated with an ICD, use of the defibrillator becomes the dominant strategy.

(J Am Coll Cardiol 1992;19:1323–34)

Sudden cardiac death remains the major cause of death in the United States, with an estimated 400,000 persons affected annually (1). In the majority of these deaths, the mechanism is ventricular tachycardia that degenerates to ventricular fibrillation. Although approximately 25% of these patients survive the initial hospital stay without substantial neurologic impairment (2), the recurrence rate is high: 1-year mortality rates of 25% to 40% have been reported (3,4) in patients who have not had pharmacologic therapy guided by invasive or noninvasive techniques.

In an attempt to improve treatment efficacy, electrophysiologic studies have been used to guide drug therapy; however, most patients continue to have inducible arrhythmias despite treatment with conventional antiarrhythmic agents (5–12) and remain at high risk for sudden death. Amiodarone has been advocated in such patients, with 60% to 90% remaining free of recurrent clinical events in the year after initiation of treatment (13–19).

The implantable cardioverter-defibrillator (ICD) offers an alternative approach to survivors of out of hospital cardiac arrest who do not respond to conventional therapy (20). However, the costs of the ICD are high. The early devices cost $13,000, require a thoracotomy for initial placement and must be replaced on average every 18 to 24 months. Furthermore, as the indications for implantation continue to expand, concern over rapidly escalating health care costs has been focused on new expensive technologies such as the ICD. Increasingly, proponents of such therapies are asked whether their benefits can be justified in light of their costs (21). Of course, any such evaluation must be in the context of the costs and benefits of available alternatives.

For this reason, we performed a cost-effectiveness analysis of the ICD, comparing it both with conventional antiarrhythmic drug therapy and with amiodarone therapy in patients with recurrent sustained ventricular tachycardia or fibrillation refractory to conventional drug therapy. Our analysis used actual inpatient and outpatient costs as well as physician fees generated for patients receiving an ICD or

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Manuscript received October 8, 1990; revised manuscript received November 4, 1991, accepted December 19, 1991.

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0735-1097/92/$5.00

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amiodarone therapy for these conditions at a tertiary hospital between 1985 and 1988. The analysis included an assessment of the impact of future technologic improvements to battery systems that have already increased the longevity of the ICD. We also assessed the extent to which changes in assumed quality of life with amiodarone therapy (relative to the ICD) could change the results of our analysis.

Methods

We constructed a Markov or "state transition" decision model to compare the implantable cardioverter-defibrillator (ICD), amiodarone and conventional drug therapy in three cohorts of patients who were assumed to be identical with the exception of the therapy for their recurrent ventricular arrhythmias. The Markov model assumes that each patient is in one of a limited array of health states at any point in time and that the likelihood of that patient moving from one state of health to another is governed by various fixed and time-dependent transition probabilities (22). We used DecisionMaker software (23) to simulate the prognosis of each cohort and "monitored" their progress at monthly intervals, tracking relevant events, total survival time and costs associated with each therapy.

Assumptions. In structuring the decision tree to model this problem, we made several simplifying assumptions: 1) All patients are subject to four forces of mortality: a) a sudden cardiac death rate that is modified by both amiodarone and the ICD; b) a nonsudden cardiac death rate, reflecting variables such as ventricular function; c) a noncardiac death rate, as would affect members of the population at large; and d) complications of the ICD or amiodarone. 2) The case rate for sudden cardiac death is based on patients treated with conventional therapy whose arrhythmias were not effectively suppressed during repeat electrophysiologic testing. 3) There is no crossover between patient groups. Thus, patients treated with conventional therapy or amiodarone who survive a recurrence of sudden cardiac arrest do not receive ICD implantation. In addition, no crossovers from the amiodarone group to the ICD group were allowed if a patient on amiodarone therapy developed an amiodarone drug reaction. 4) Equal quality of life is assumed for all patients with long-term survival; however, this assumption was subjected to sensitivity analysis.

The decision model. A complete description of the decision model is contained in the Appendix. Briefly, there are three patient cohorts: patients receiving an ICD, amiodarone or conventional drug therapy (Fig. 1). Patients in each cohort may die during initial hospitalization. If they survive, they enter the Markov process, where each month they are exposed to the four forces of mortality described. In addition, all patients may experience nonlethal cardiac illnesses (such as exacerbations of heart failure) that require hospitalization. All patients are seen routinely for cardiac outpatient visits. Patients on amiodarone therapy may experience both lethal and nonlethal complications of the drug that may require hospitalization and discontinuation of amiodarone. Patients treated with the ICD may experience complications associated with the device (for example, infection and lead failure) that require hospitalization and repeat operation. In addition, patients who experience an ICD discharge may require an outpatient visit or hospitalization. Finally, patients with an ICD who survive long enough will eventually require a short hospital stay for ICD battery replacement.

Medical rates and probabilities used in the model. We reviewed published reports describing therapy and outcomes for patients treated with an ICD, amiodarone or conventional antiarrhythmic therapy. For probabilities for which no data were available, the opinions of experienced clinical electrophysiologists were used. Mortality data from each study were transformed into an average yearly mortality rate (24). Age- and gender-related mortality rates were taken from U.S. life expectancy tables (25).

Inpatient costs. Twenty-one patients who underwent ICD implantation between October 15, 1986 and November 11, 1988 and 43 patients who received amiodarone therapy between September 18, 1985 and May 20, 1988 for recurrent ventricular tachycardia or fibrillation formed the basis of our estimates of the costs of hospital treatment. All patients received their initial treatment and follow-up care at the New England Medical Center.

Each patient's inpatient costs for every admission, including those for ICD replacement, were available on the New England Medical Center's Clinical Cost Manager cost-accounting system (26), which separates the fixed costs of each unit of service (including overhead such as heating, lights and custodial services) from the variable costs of adding units of similar service (that is, laboratory tests, chest radiography, nursing care and medications given) (27). Variable costs better reflect the actual costs of care for a specific condition and were used in this analysis. The costs of electrophysiologic testing and inpatient medications and the purchase prices of the ICD generator, intracardiac electrodes and patches were added to patients' variable hospital costs to produce the final cost total.

Inpatient costs for the "conventional therapy" group were derived from those of the amiodarone cohort. We assumed that their initial and follow-up hospitalization costs would be similar because they come from the same group with persistently inducible arrhythmia as did the amiodarone-treated patients. However, because they were not exposed to the risks of amiodarone, they would not be admitted for amiodarone toxicity.

Outpatient costs. To help ensure complete acquisition of outpatient costs, all outpatient services for follow-up clinic visits were obtained from New England Medical Center's computer billing records, including office visits, laboratory services and procedures. Actual variable costs were used for laboratory tests, chest radiographs, pulmonary function tests, exercise tolerance tests, electrocardiograms (ECGs) and Holter monitor recordings. Pharmacy costs for amiodarone (400 mg/day) were used as an approximation of these costs for all amiodarone-treated patients. No additional drug

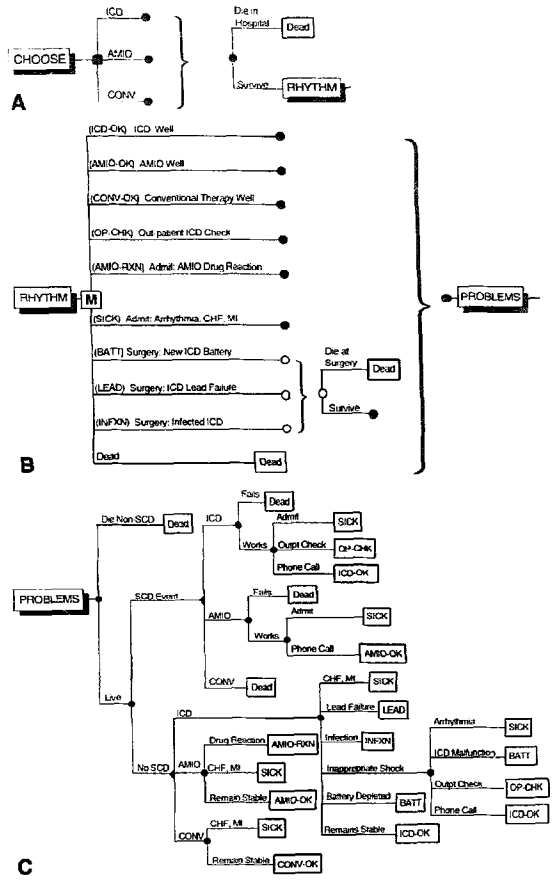

Figure 1. Decision model used for the cost-effectiveness analysis. **A,** The initial CHOOSE node (**solid square**) leads to one of the three therapeutic options (implantable cardioverter-defibrillator [ICD], amiodarone therapy [AMIO] or conventional antiarrhythmic drug therapy [CONV]). For all three options, if patients survive the initial hospital admission, represented by a chance event node (**solid circle**)), they go to the RHYTHM Markov subtree. **B,** The RHYTHM Markov subtree, representing the health states in which patients may exist during each monthly cycle. M denotes the Markov node. During each cycle, patients at solid circles will experience the risks defined in the PROBLEMS subtree (**C**). Patients in the three surgical health states (**open circles**) experience PROBLEMS unless they die at operation. **C,** The PROBLEMS subtree. Each terminal branch ends in a health state listed in the RHYTHM subtree, to which patients return to begin the next monthly cycle. Admit = hospital admission; BATT = battery; CHF = congestive heart failure; INFXN = infection; MI = myocardial infarction; OK = stable, doing well; OP-CHK = outpatient visit to check patient and ICD; RXN = adverse drug reaction; SCD = sudden cardiac death.

costs were added for any of the patients. Baseline clinic charges for the "conventional treatment" group were the same as for the amiodarone group, except the former group did not incur costs for the laboratory tests, such as lung diffusing capacity or thyroid function studies performed as part of surveillance for amiodarone toxicity, nor were they charged for amiodarone.

Physician services. Billing records from the New England Medical Center's medical practice groups were examined to determine the medical, surgical and anesthesiology charges billed to and collected from both ICD- and amiodarone-treated patients for inpatient physician care. For each patient group, the average amount billed per patient multiplied by the average fractional amount actually collected yielded the "recovered

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inpatient physician costs" for physician services for all admissions, including those for generator replacement. This figure was used to represent inpatient physician costs in our model. Outpatient billing records were similarly examined to calculate the average "recovered outpatient physician costs" of office visits. All inpatient, outpatient and physician costs incurred in fiscal years 1985 through 1988 have been inflated by 6%/year to represent all costs in 1989 dollars.

Modeling ICD battery life. We used two models to simulate the need for ICD generator replacement. In the simplest model (model 1), each patient still alive at the end of the estimated average battery life of his or her ICD received a replacement battery. In the baseline case, all surviving patients received a replacement every 24 months. In the more complex model (model 2), we derived a monthly battery failure rate based on reported estimates of average battery "life expectancy" exactly analogous to human life expectancy (24). Thus, in model 2, generator replacement times vary on the basis of a constantly declining exponential probability of generator survival.

The rate at which ICD batteries require replacement is a major determinant of the overall cost of treating patients with an ICD. Battery life for an individual patient is a function not only of battery technology, but also of frequency of ICD discharges. Thus, battery life will vary as patient characteristics vary and as energy storage technology improves. In the early reports (28–34) on the ICD, the mean ICD battery life varied from 13 to 22 months. However, in newer ICD models, the mean battery life has increased to ≥36 months and devices now undergoing clinical investigation may have nominal longevities of as long as 6 to 8 years. Thus, for our baseline analysis, we used a conservative estimate of mean battery life of 24 months, but subjected this variable to sensitivity analysis in which battery life was varied from 18 to as long as 96 months.

Discounting. Future costs were discounted at 5%/year to reflect the fact that deferring expenses allows unused resources to be invested and yield returns before future expenses must be paid. Similarly, the benefits derived from treatment (namely, future years of life saved) were also discounted to reflect the potential future productivity of these patients and to maintain internal consistency in our analysis (27,35).

Quality of life adjustments (utilities). In any decision the ultimate choice is driven by the value attributed to each possible outcome. Our baseline analysis assumes all survival to be equally valuable, regardless of treatment received. Deductions from full life expectancy were made for the short-term morbidity associated with surgery or hospitalization. One week was deducted for elective ICD generator replacement. Two weeks were deducted for initial electrophysiologic testing at the beginning of amiodarone therapy and for surgery required to implant the ICD, treat a major postoperative infection or replace defective ICD patches. We also performed sensitivity analyses in which it was assumed that quality of life with an ICD was either better or worse than that on medical therapy.

Data Summary

Medical Rates and Probabilities in Reported Studies

Nonsudden cardiac death rate. Table 1 shows abstracted data from the largest available studies of patients treated with conventional therapy, the ICD or amiodarone in which it is possible to separate sudden and nonsudden cardiac death rates as well as noncardiac death rates. Among patients treated with conventional therapy, Wilber et al. (11) reported the outcome of 166 survivors of sudden cardiac arrest referred for electrophysiologic studies from 1978 to 1985 (including 10 patients who ultimately received an ICD), and Swerdlow et al. (10) described their experience with 239 survivors of sudden cardiac arrest referred for electrophysiologic studies between 1976 and 1982. Among patients treated with the ICD between 1981 and August 1986, Winkle and Thomas (20) summarized the U.S. experience for 949 patients listed in a central registry. Other reports describe the experiences of individual institutions (28–30,32). Some of these patients are probably also listed in the central registry, so that duplication could not be avoided. For patients treated with amiodarone, eight studies (13–15,17,36–40) report on those treated between 1977 and 1985. Follow-up times are substantially shorter in these reports and the patients tend to be older than patients in the ICD- and conventionally treated groups.

Average yearly nonsudden cardiac mortality rates are quite variable among studies, but tend to be lower in patients treated with the ICD and higher in those treated conventionally or with amiodarone: the weighted average yearly mortality rate for the ICD group was 5.54%/year, but was 9.02%/year for amiodarone-treated patients and 9.27%/year for conventionally treated patients. The reasons for this variation in nonsudden cardiac death rates are not completely clear. Although patients receiving the ICD were on average slightly younger than those treated with amiodarone (weighted mean 58 vs. 60 years old), left ventricular ejection fraction was similar. More important, ICD-treated patients often undergo simultaneous coronary artery bypass grafting or left ventricular aneurysmectomy, which may have an independent favorable impact on the mortality rate from heart failure or myocardial infarction. Also, ICD treatment is a relatively recent development, paralleling the increasing use of more aggressive treatments for acute myocardial infarction, such as thrombolytic therapy and coronary angioplasty. Patients treated with the ICD may have received these therapies, bringing with them reductions in the nonsudden cardiac mortality rate. In addition, selection bias may have occurred, so that patients with multiple or more severe noncardiac illnesses (for example, obstructive lung disease) and a shorter life expectancy were not offered treatment with an ICD.

Yearly sudden cardiac death rates (Table 2). Virtually all patients selected for amiodarone or ICD therapy have already been treated unsuccessfully with conventional antiarrhythmic drugs guided by serial electrophysiologic testing. Five studies (5,9–12) provide data from which to calculate yearly survival

Table 1. Reported Yearly Mortality Rates From Nonsudden Cardiac Death

First Author	No. of Pt	F/U	Average Age (yr)	EF (%)	Yearly Average Mortality	Pt-yr of Mortality
Conventional Therapy						
Wilber (11)	166	7 yr	56	41	0.072	11.952
Swerdlow (10)	239	3 yr	56	37	0.107	25.573
Total	405					37.525
Weighted average yearly mortality rate = (37.525/405) × 100% = 9.27%						
Amiodarone						
Manolis (36)	86	18 mo	64	30	0.1776	15.274
Horowitz (38)	100	13.2 mo	61	24	0.0873	8.73
McGovern (14)	42	10 mo	61	30	0.0586	2.461
Yazaki (39)	54	24 mo	63	29	0.0189	1.021
Waxman (17)	51	9 mo	?	?	0.1669	8.512
Veltri (40)	13	24 mo	59	32	0.0835	1.086
Heger (15)	45	13 mo	52	?	0.0419	1.886
Nademanee (13)	96	15 mo	56	?	0.0516	4.954
Total	487					43.896
Weighted average yearly mortality rate = (43.924/487) × 100% = 9.02%						
Implantable Defibrillator						
Manolis (30)	77	3 yr	60	35	0.0171	1.317
Winkle (20)	949	4 yr	58	33	0.055	52.195
Winkle (32)	270	5 yr	58	34	0.0564	15.228
Kelly (28)	94	4 yr	56	33	0.039	3.666
Mirowski (29)	52	3 yr	56	33	0.144	7.488
Total	1,442					79.894
Weighted average yearly mortality rate = (79.894/1442) × 100% = 5.54%						

EF = ejection fraction; F/U = follow-up; Pt = patients; Pt-yr of mortality = (average yearly mortality) × (no. of patients).

rates for the subgroup of patients treated with conventional antiarrhythmic agents, whose ventricular arrhythmia remains inducible at follow-up electrophysiologic testing. Their mortality rate is quite high (21.1%/year). In contrast, the weighted average yearly mortality rate from eight studies (13,14,16, 17,19,36,38,39) among patients treated with amiodarone is 6.64%/year. For patients treated with the ICD, the mortality rate is even lower. Winkle and Thomas (20) report a rate of 1.92%/year; Winkle et al. (32), describing the Stanford experience between 1981 and 1988, report a rate of 1.2%/year, although some of the Stanford patients are probably also listed in the central registry report (20). Manolis et al. (30) recently reported a mortality rate of 2.14%. The weighted mean sudden death mortality rate is thus 1.82%/year.

Efficacy of amiodarone and the ICD for preventing sudden cardiac death. The sudden cardiac death rate patients whose ventricular arrhythmia is persistently inducible by electrophysiologic testing was compared with that of patients treated with amiodarone or the ICD. Efficacy is defined as the fractional reduction in the mortality rate, or [(conventional mortality − treated mortality)/conventional mortality]. Thus, the efficacy of amiodarone is [(21.14% − 6.64%)/ 21.14%] = 68.6%. Similarly, the efficacy of the ICD is [(21.14% − 1.82%)/21.14%] = 91.4%.

Complications of the ICD. Worldwide surveillance data (33) show a 2.9% probability of dying during the index hospital stay for ICD implantation. Approximately 5% of patients who are "saved" from sudden cardiac death by an appropriate ICD discharge will require a hospital admission and 25% will require outpatient visits, but most will receive only telephone calls for reassurance. The probability that an ICD will deliver a clinically inappropriate shock has been estimated at 3%/month (33,34). Only 10% of patients who receive such a shock will require hospital admission, either for defective hardware or for treatment of newly detected supraventricular tachycardia. The rate of lead failure has been reported (20,32,33) to be 2%/year, and the rate of ICD infection approximately 3%/year.

Complications of amiodarone therapy. There are varying reported in-hospital mortality rates during initiation of amiodarone therapy. The largest series reported to date (19), which reflects the University of California, San Francisco experience in 462 patients, reports a 5.4% mortality rate.

Reported studies show that a large number of patients taking amiodarone have recurrent nonfatal arrhythmia recurrences. In fact, only about 20% of amiodarone-treated patients have a follow-up electrophysiologic study in which arrhythmia is completely noninducible; the other 80% have "modified inducible" or fully inducible arrhythmia (14,37–40). In addition, recent data from Herre et al. (19) demonstrate that just over 50% of all arrhythmia recurrences among amiodarone-treated patients are nonlethal. Thus,

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Table 2. Reported Yearly Mortality Rates From Sudden Cardiac Death

First Author	No. of Pt	Average Age	F/U	EF (%)	Yearly Average Mortality	Pt-yr of Mortality
Conventional Therapy						
Wilber (11)	36	56	7 yr	41	0.2849	10.2564
Swerdlow (10)	102	56	3 yr	37	0.2472	25.2144
Roy (5)	31	55	1.5 yr	?	0.132	4.092
Skale (9)	27	52	2 yr	?	0.1371	3.7017
Kim (12)	27	56	1.5 yr	38	0.1438	3.8826
Total	223					47.1471
Weighted average yearly mortality rate = (47.1471/223) × 100% = 21.14%						
Amiodarone						
Manolis (36)	86	64	18 mo	30	0.0399	3.4314
Herre (19)	427	61	48 mo	36	0.0589	25.1503
Horowitz (38)	100	61	13 mo	24	0	0
McGovern (14)	42	61	10 mo	30	0.1521	6.3882
Yazaki (39)	54	63	24 mo	29	0.0286	1.5444
Waxman (17)	46	?	9 mo	?	0.1269	5.8374
DiCarlo (16)	104	61	16 mo	35	0.1632	16.9728
Nademanee (13)	96	56	15 mo	?	0.0428	4.1088
Total	955					63.4333
Weighted average yearly mortality rate = (63.4333/955) × 100% = 6.64%						
Implantable Defibrillator						
Manolis (30)	77	60	3 yr	35	0.0278	2.1406
Winkle (20)	949	58	4 yr	33	0.0192	18.2208
Winkle (32)	270	58	5 yr	34	0.012	3.24
Total	1,296					23.6014
Weighted average yearly mortality rate = (23.6014/1296) × 100% = 1.82%						

Abbreviations as in Table 1.

although amiodarone saves lives, it does not always do so by preventing all arrhythmia recurrences; rather, it slows the ventricular tachycardia rate or prevents recurrence of the worst rhythm. For these reasons, not all patients for whom amiodarone was "efficacious" in preventing death can simply return to the next Markov cycle in the "well" state; some require further arrhythmia treatment in the hospital. Thus, in our baseline analysis, we assume that 50% of the efficacy of amiodarone in reducing the ventricular arrhythmia mortality rate was due to complete prevention of arrhythmia recurrence. The other 50% of patients were saved from death because the arrhythmia was modified but not abolished and they required hospital admission for further treatment.

The risk of having a drug reaction for which amiodarone must be discontinued is estimated to be 8.1%/year on the basis of the reported follow-up of 1,013 patients (13–17,19,36,38–40). However, the risk of death from amiodarone toxicity among these patients was small—only four deaths were directly attributed to amiodarone toxicity among the 145 patients in whom administration of the drug had to be stopped. Thus, we assume that 2.8% of patients who experience severe amiodarone side effects will die.

Costs

Costs used in the model are listed in Table 3.

Inpatient costs. Patients receiving an implantable cardioverter-defibrillator in our series had a mean age of 62 years and a mean left ventricular ejection fraction of 33%. Their initial hospital stay had a mean duration of 28 days (range 8 to 52) and the mean length of stay in the intensive care unit was 3.3 days (range 1 to 16). Patients treated with amiodarone had a mean age of 64 years and a mean left ventricular ejection fraction of 31%. Their initial hospital stay had a mean duration of 30 days (range 8 to 60) and the mean length of stay in the intensive care unit was 4 days (range 1 to 29). Costs for the index hospital stay for both groups of patients are similar, but total inpatient costs are much higher for the ICD-treated patients because of the high cost of defibrillator equipment.

Inpatient physician services. Records were available for the initial hospital stay of all 21 ICD-treated patients. The average charges billed by surgeons and anesthesiologists for ICD implantation were $7,628/patient, of which 61.5% was actually collected. The average medical charges for these patients were $6,557, of which 60.1% was collected. This

Table 3. Costs and Charges Used in the Model

For Patients With an ICD	$
Index hospital admission	
Hospital variable costs	12,482
Defibrillator generator	13,000
Defibrillator patches (pair)	1,500
Defibrillator sensing leads (pair)	1,300
Physicians' recovered costs, surgery*	4,691
Physicians' recovered costs, medical†	3,942
Generator replacement, hospital admission	1,079
Generator replacement, physicians' recovered costs*	790
Hospital admission for infected implant	17,657
Nonsurgical repeat hospital admission	2,203
Annual recovered outpatient physicians' costs‡	
1st year	468
After 1st year	936
For Patients Receiving Amiodarone and Conventional Therapy	
Index hospitalization	
Hospital variable costs	11,518
Physicians' recovered costs§	2,466
Repeat hospitalization	3,848
Recovered outpatient physicians' costs, per year‡ (5 visits/yr)	332
For Patients Receiving Amiodarone Only	
Hospital admission for amiodarone toxicity	4,810
Monthly pharmacy cost of amiodarone (400 mg/day)	85
Amiodarone-associated laboratory variable costs per year	665

*61.5% collection of charges billed; †60.1% collection of charges billed; ‡78% collection of charges billed; §66% collection of charges billed.

yielded "recovered inpatient physician costs" of $4,691/patient for surgical services and $3,942 for medical services. For generator replacement, recovered costs were $790.

Inpatient billing records for the amiodarone group were available for only nine of the most recently treated patients (admitted from June 12, 1987 to May 20, 1988). The average charges billed by physicians during the index hospital stay for these patients were $3,736, of which 66% was actually collected. The "recovered inpatient physician costs" for this group were thus $2,466 per patient.

Outpatient costs. Routine follow-up visits for ICD-treated patients occurred every 2 months during the 1st year and then monthly until battery replacement was required. The clinic charge for each visit is a flat fee, which covers the costs of ECGs. Our patients on amiodarone therapy were seen on average 5 times/year, charged an average of $85/clinic visit and accumulated $133/visit in variable laboratory costs, including costs of pulmonary function tests, chest radiographs and blood tests. All such tests were performed at baseline. Pulmonary function tests were performed yearly. Chest radiographs and routine chemistry tests were then ordered when clinically indicated. Thyroid function tests were obtained yearly. Outpatient billing records for both groups showed that an average of 78% of physician visit fees was actually recovered.

Results

Baseline Analysis

Using the rates, probabilities and utilities described earlier, the implantable cardioverter-defibrillator (ICD) is effective therapy for patients who have survived sudden cardiac death (Table 4). For a 55-year old patient, treatment with the ICD increases life expectancy over that provided by treatment with amiodarone by >50% (6.1 vs. 3.9 years) and over that anticipated with conventional therapy by almost 150% (6.1 vs. 2.5 years). Treatment with the ICD is also costly. Given the currently reported 24-month ICD generator replacement rate, for a 55-year old patient, the discounted costs of lifetime treatment with the ICD are almost $87,000 compared with just under $25,000 for treatment with amiodarone and about $16,000 for conventional treatment. For

Table 4. Baseline Cost/Effectiveness Ratios*

Therapy	Average LE (QALY)	Average Cost ($)	Marginal Gain in LE (QALY)	Marginal Cost Increase ($)	Marginal Cost-Effectiveness ($ QALY)
Age 45 years					
CONV	2.6	16,200	—	—	—
AMIO	3.96	25,074	1.36	8,874	6,509
ICD	6.43	93,182	2.47	68,109	27,561
Age 55 years					
CONV	2.54	16,156	—	—	—
AMIO	3.85	24,790	1.31	8,634	6,635
ICD	6.07	89,592	2.22	64,802	29,244
Age 65 years					
CONV	2.46	16,071	—	—	—
AMIO	3.64	24,250	1.19	8,179	6,892
ICD	5.46	83,640	1.82	59,390	32,674

*Using model 1 and 24-month average battery life. AMIO = amiodarone therapy; CONV = conventional therapy; ICD = implantable cardioverter-defibrillator therapy; LE = life expectancy; QALY = quality-adjusted life years.

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this reason, the marginal increase in the cost of amiodarone compared with conventional therapy required to save 1 year of life ($6,600) is lower than the marginal cost of the ICD compared with amiodarone ($29,200) to save 1 year of life.

Treatment with the ICD is almost as cost-effective for a 65- as for a 45-year old patient (Table 4). Age has such a small effect on the cost/effectiveness ratio because patients with recurrent sudden cardiac death die predominantly of their heart disease and less frequently from other noncardiac illnesses.

Sensitivity Analysis

We performed sensitivity analyses to examine how a change in one or more of the values used in the baseline case might influence the outcome of the models.

ICD battery life. Average ICD battery life is a particularly important variable because replacement ICD units are expensive and represent a large portion of the expected cost of ICD therapy. Using the simple model (model 1) in which all patients still alive received a new battery every 24 months, we varied this variable from 18 to 96 months, anticipating future improvements in battery technology. Not surprisingly, as battery life increases, the marginal costs of ICD treatment over those of amiodarone for each year of life saved decrease sharply (Fig. 2, model 1). If ICD battery life were 36 months, for example, the marginal cost/effectiveness ratio would be $21,800/year of life saved; at 60 months it would be $16,500 and at 96 months it would be $13,800. There is no realistic battery life, however, at which treatment with the ICD becomes cheaper than treatment with amiodarone (Fig. 2). Thus, therapy with an ICD saves lives, but involves additional resource costs.

Because costs of ICD treatment are so dependent on battery life, we used a more complex model of battery life (model 2) to provide a more refined cost-effectiveness analysis. In the second model, we assumed a constant failure rate, producing an exponentially decreasing battery "survival" curve. Although the marginal cost/effectiveness ratios for both models agree closely (Fig. 2), the more complex model produces slightly higher ratios.

Amiodarone efficacy. The efficacy of amiodarone in preventing mortality from recurrent sudden cardiac arrest was subjected to sensitivity analysis because reported yearly mortality rates with amiodarone treatment vary so widely. However, amiodarone efficacy would have to decline from its baseline value of 69% to 15% for its marginal cost/year of life saved to become higher than that of ICD therapy. Likewise, we varied the estimated frequency with which amiodarone protects patients by making a recurrent arrhythmia hemodynamically tolerable (as opposed to preventing the arrhythmia from occurring) because rehospitalization of these patients could be expected to increase the costs of amiodarone treatment. However, even if *none* of the efficacy of amiodarone was due to complete suppression of arrhythmia and all patients treated with this drug required repeat hospital admission, the marginal cost of the ICD/year of life saved is still almost four times that of amiodarone ($28,900 vs. $7,300).

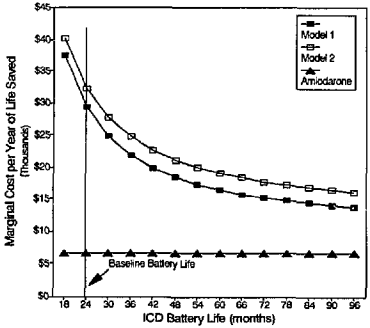

Figure 2. Effect of longer implantable cardioverter-defibrillator (ICD) battery life on marginal cost/effectiveness ratio of the ICD over that of amiodarone therapy. As ICD battery life increases, the marginal cost of the ICD/year of life saved decreases significantly compared with that of amiodarone. Two mathematical models of battery survival are illustrated. In model 1, all surviving patients receive a new battery at each multiple of average battery life. In model 2, batteries fail and are replaced at a constant rate based on an exponentially declining battery "survival" function. Both models demonstrate similar significant reductions in ICD cost/effectiveness ratios as battery survival increases beyond the assumed baseline survival of 24 months. The cost/effectiveness ratio for amiodarone compared with that for conventional therapy is shown for comparison.

Quality of life. Although not formally documented, personal experience suggests that quality of life with the ICD may be better than with amiodarone therapy, both because the ICD is a more effective therapy and thus is reassuring to patients and because patients with an ICD usually take fewer cardiac medications and thus experience fewer drug-related side effects. We therefore progressively reduced the quality of life with amiodarone therapy from the baseline assumption that it is equal to the quality of life with an ICD (100%) to the assumption that it results in 10% of the quality of life achieved with an ICD. In this type of sensitivity analysis, absolute quantity of life does not change from baseline, only the *relative value* attributed to that quantity. Therefore, total costs generated by the model do not change from baseline because they are driven by the absolute quantity of life derived from each therapy. However, the number of quality-adjusted life-years derived from amiodarone treatment progressively declines with each decrement in assumed quality of life on amiodarone therapy. As a result, there is a progressive incremental gain in quality-adjusted life expectancy with ICD therapy over that of amiodarone, whereas

Table 5. Quality of Life on Amiodarone: Influence on Cost-Effectiveness of Implantable Cardioverter-Defibrillator Therapy

Quality of Life With Drugs* (%)	ICD		AMIO		CONV		ICD/AMIO	AMIO/CONV
	Cost ($)	QALE (QALY)	Cost ($)	QALE (QALY)	Cost ($)	QALE (QALY)	Marg C/E ($ QALY)	Marg C/E ($ QALY)
100	89,592	6.07	24,790	3.85	16,156	2.54	29,244	6,635
90	89,592	6.07	24,790	3.46	16,156	2.3	24,875	7,398
80	89,592	6.07	24,790	3.07	16,156	2.04	21,641	8,358
70	89,592	6.07	24,790	2.69	16,156	1.79	19,152	9,604
60	89,592	6.07	24,790	2.3	16,156	1.53	17,176	11,287
50	89,592	6.07	24,790	1.91	16,156	1.28	15,569	13,686
40	**89,592**	**6.07**	**24,790**	**1.52**	**16,156**	**1.02**	**14,237**	**17,379**
30	89,592	6.07	24,790	1.13	16,156	0.77	13,116	23,802
20	89,592	6.07	24,790	0.74	16,156	0.51	12,158	37,755
10	89,592	6.07	24,790	0.26	16,156	0.26	11,331	91,252

*Relative to quality of life with an implantable cardioverter-defibrillator. Marg C/E = marginal cost/effectiveness ratio; QALE = quality-adjusted life expectancy; other abbreviations as in Table 4. Values in boldface show the threshold quality of life on drug therapy below which the marginal cost/effectiveness ratio for the ICD is below that for amiodarone.

total costs do not change, resulting in a progressive decrease in the quality-adjusted marginal cost/effectiveness ratio for ICD therapy. The opposite effect is evident for amiodarone compared with conventional therapy: as quality of life with amiodarone therapy decreases, the relative quality-adjusted cost/year of life on amiodarone therapy increases.

Baseline quality-adjusted life expectancy with amiodarone therapy (Table 5) is 3.9 quality-adjusted life-years but decreases to 2.7 quality-adjusted life-years when the quality of life with drug therapy is only 70% of that with the ICD. As a result, the quality-adjusted cost/effectiveness ratio of the ICD compared with amiodarone decreases by 35%, from a baseline value of $29,200 to $19,200/quality-adjusted life year. At the same time, the marginal cost/effectiveness ratio of amiodarone over conventional therapy increases by 45%. If the quality of life on drug therapy is <40% of that with an ICD (boldfaced values, Table 5), the marginal cost/effectiveness ratio for the ICD becomes less than that for amiodarone ($14,200 vs. $17,400). The overall value of ICD therapy then makes amiodarone an illogical choice even if resources are very limited.

Alternatively, for some patients, the quality of life with an ICD may be worse than that with amiodarone therapy. Some ICD-treated patients must still take antiarrhythmic drugs, may have chronic anxiety after receiving shocks while conscious and alert (occasionally very frequent or inappropriate shocks), or have distorted body images after generator implantation. In such cases, the quality-adjusted cost/effectiveness ratio for the ICD over amiodarone increases with each decrease in ICD quality of life relative to that on amiodarone therapy (Table 6). As the quality of life with an ICD decreases (relative to that with amiodarone), the quality-adjusted cost/effectiveness ratio for the ICD increases from $29,200 to $40,800/year at 90% quality (an increase of 40%). If the quality of life with an ICD is only 70% of that with amiodarone, the quality-adjusted cost/effectiveness ratio increases to $193,000/year of quality-adjusted life saved, an increase of >500%. When the quality of life with an ICD is <65% of that with amiodarone, ICD quality adjusted life expectancy drops below that of amiodarone (3.56 vs 3.85); thus, amiodarone therapy dominates the use of an ICD.

Table 6. Quality of Life With an Implantable Cardioverter-Defibrillator: Influence on Cost-Effectiveness of Implantable Cardioverter-Defibrillator Therapy

Quality of Life With ICD* (%)	ICD		AMIO		CONV		ICD/AMIO	AMIO/CONV
	Cost ($)	QALE (QALY)	Cost ($)	QALE (QALY)	Cost ($)	QALE (QALY)	Marg C/E ($ QALY)	Marg C/E ($ QALY)
100	89,592	6.07	24,790	3.85	16,156	2.54	29,244	6,635
90	89,592	5.44	24,790	3.85	16,156	2.54	40,770	6,635
80	89,592	4.82	24,790	3.85	16,156	2.54	67,291	6,635
70	89,592	4.19	24,790	3.85	16,156	2.54	192,542	6,635
60	89,592	3.56	24,790	3.85	16,156	2.54	D	6,635
50	89,592	2.94	24,790	3.85	16,156	2.54	D	6,635
40	89,592	2.31	24,790	3.85	16,156	2.54	D	6,635
30	89,592	1.68	24,790	3.85	16,156	2.54	D	6,635
20	89,592	1.06	24,790	3.85	16,156	2.54	D	6,635
10	89,592	0.43	24,790	3.85	16,156	2.54	D	6,635

*Relative to quality of life on drugs. D = dominated by amiodarone therapy; other abbreviations as in Tables 4 and 5.

JACC Vol. 19, No. 6
May 1992:1323–34

Discussion

Life expectancy. Our analysis shows that the implantable cardioverter-defibrillator (ICD) prolongs life expectancy in patients who have survived a cardiac arrest from ventricular tachyarrhythmia and, in particular, life expectancy with the ICD is >1.5 times that of patients receiving long-term treatment with amiodarone. The additional years of life gained over amiodarone with the use of the ICD require a resource expense of about $29,200/year of life saved, whereas the more limited gains of amiodarone over those of conventional antiarrhythmic drug therapy cost only about $6,600/additional year gained. If resources available to treat such patients were very limited, more survival could be purchased by giving amiodarone to many patients than by using an ICD in only a few.

Cost/effectiveness ratio. Improvements in battery technology promise to reduce the marginal costs of the ICD substantially. If average ICD battery life is extended to 3 years, the marginal cost of the ICD/year of life saved will decrease by 25%, if battery life is extended to 5 years, costs will decrease by >40% and if it is extended to 8 years, costs will decrease by >50%. Even at currently reported battery life, the marginal cost-effectiveness of treatment with the ICD is similar to the marginal cost-effectiveness of directed electrophysiologic testing for syncope and bifascicular heart block and the procedure is much cheaper than empiric pacemaker insertion for the same condition (41). Its cost/effectiveness ratio is comparable to that of coronary bypass surgery for stable angina pectoris (42) and less than that of hospital-based kidney dialysis (43). As battery technology improves, the marginal cost-effectiveness of the ICD will approach that for treatment of moderate hypertension in middle-aged men (44) and kidney transplantation for end-stage renal disease (45).

Quality of life. In our baseline analysis, we explicitly avoided ascribing differential values to years of life spent in different chronic stable states. There are no data on which to make estimates regarding the differential symptom-free quality of life with an ICD versus the quality of life obtained by taking amiodarone or conventional antiarrhythmic agents. All three strategies require a substantial amount of medical follow-up (and thus expense and inconvenience). The psychosocial adjustment of patients, given the uncertainties of their underlying disease and its treatment, is variable with all three strategies. Our experience has been that patients receiving an ICD feel relieved that their problem has been treated with "state of the art" technology that improves survival maximally. For those taking no antiarrhythmic drugs, the side effects and inconvenience of pharmacologic therapy are obviated. Therefore, we performed sensitivity analyses in which we explored the possibility that quality of life with amiodarone or conventional drugs may be less than that with an ICD. (For technical reasons, we systematically diminished the estimated quality of life for patients taking drugs, rather than increasing the quality of life for patients with an ICD). We discovered a roughly proportional reduction in the marginal cost/effectiveness ratio for the ICD over amiodarone for every decrement in assumed quality of life on drug therapy. When the quality of life was reduced by 30% compared with that with an ICD, the marginal cost/effectiveness ratio decreased by 35%. This reduction in cost/effectiveness ratio is similar in magnitude to that produced by increasing the mean battery replacement interval from 24 to 42 months. If the quality of life with drug therapy is <40% of that with an ICD, it becomes cheaper to purchase quality-adjusted life-years with an ICD than with amiodarone.

Conversely, it may be that for some patients, quality of life with an ICD is worse than that with amiodarone. If so, the marginal quality-adjusted cost/effectiveness ratio for the ICD increases rapidly with each decrement in ICD quality of life relative to that with amiodarone. Thus, if ICD quality of life is only 90% of that with amiodarone, the marginal quality-adjusted cost/effectiveness ratio increases by 40%, and if ICD quality of life decreases to only 70% of that with amiodarone, the ratio increases by >500%.

Limitations. Our analysis has some limitations. The number of patients for whom actual costs were obtained is relatively small. However, these costs, including those for outpatient follow-up and generator replacement, are actual variable costs—not estimates—adding strength to the model. The probabilities of some events in the model (for example, the likelihood that follow-up for an ICD discharge would require an outpatient clinic visit or inpatient admission) are based on expert experience and not reported clinical data. However, altering these variables in sensitivity analyses had no significant effect on the overall outcome.

Our analysis does not model crossovers from amiodarone to ICD therapy, which can occur. In our experience, the actual proportion of such crossovers is extremely low. We believed that a strict comparison of the two treatment strategies would most clearly illustrate the costs and survival differences between them. However, to test the effect of crossovers, we modeled a strategy whereby patients receiving amiodarone who have an amiodarone drug reaction were treated with an ICD. The results showed only a minimal increase in the marginal cost/effectiveness ratio of ICD compared with that of amiodarone therapy ($315 per quality-adjusted life-year saved), thus not altering the basic conclusions of our analysis.

Our techniques for modeling the "survival" of an ICD battery do not fully capture the complexity of actuarial survival curves for such batteries (34). We believe, however, that they adequately capture the effects of changing the battery replacement frequency and its associated expenses.

Comparison with previous studies. The results of our analysis can be compared with work recently reported by Kuppermann et al. (46), who used 1984 data from large Medicare databases and collected total charges, not variable costs, for use in their estimates. They compared ICD treatment with "pharmacologic therapy" not specifically limited to the most effective drug, amiodarone, and did not compare

amiodarone with more conventional antiarrhythmic drug therapy. The pharmacologic therapy group was an amalgam of patients from presumably applicable Diagnosis-Related Group categories; whether these patients underwent electrophysiologic testing could not be determined. They assumed that rates of nonsudden cardiac death were the same for both ICD- and drug-treated groups. Finally, although they created a "1991 scenario," they did not perform sensitivity analyses on expected battery survival of currently implantable systems.

The results of their analysis are also somewhat different from ours. Their base case cost/effectiveness ratio for the ICD of $17,100 (in 1986 dollars) of total charges/year of life saved is still 30% below the $29,200 (in 1989 dollars) of variable costs/year of life saved in the present analysis after correction for inflation of medical costs. Furthermore, because our analysis is based on variable costs rather than charges, our analysis suggests that the cost/effectiveness ratio of the ICD is higher than that calculated previously, perhaps because our analysis compares ICD with amiodarone therapy, a more effective agent than other pharmacologic therapies. Nevertheless, after accounting for methodologic differences, we believe these authors' analysis generally supports our own.

Conclusions. The current study represents an intensive evaluation of the cost and outcome of treatment of life-threatening arrhythmia at one university teaching hospital. It demonstrates the value of combining traditional data collection of patient outcome with *clinically focused* data collection of patient care costs. It illustrates the power of decision analytic modeling to synthesize these data, along with data from existing clinical studies, to provide useful analyses of current medical problems and to assess the potential impact of future improvements in the treatment of these problems. Our results show that treatment of survivors of recurrent sudden cardiac arrest with an ICD substantially increases life expectancy over that obtained by treatment with amiodarone and more than doubles life expectancy obtained by treatment with conventional antiarrhythmic drugs. The marginal cost-effectiveness of treatment with the ICD versus amiodarone is highly dependent on the longevity of the ICD power supply; as battery life improves, cost-effectiveness of the ICD improves dramatically. In any case, even at present levels of battery life, the cost-effectiveness of ICD therapy in these patients is comparable to that of other accepted medical treatments and is not affected substantially by the patient's age.

Appendix

The Decision Model (Fig. 1)

Therapy with the ICD. Patients receiving an implantable cardioverter-defibrillator (ICD) may die during their initial hospital stay or survive, in which case they enter the Markov process in the "ICD Well" state. During each subsequent month they may die of noncardiac causes, nonsudden cardiac causes (for example, heart failure or acute myocardial infarction) or complications of the ICD itself (for example, infection and lead failure) or they may be exposed to the risk of sudden cardiac death. The latter risk is reduced by the efficacy of the ICD. Because the ICD is not completely effective in eliminating death due to a lethal arrhythmia, there remains a small chance during each monthly cycle that patients may experience sudden cardiac death. If sudden death is aborted by the ICD, the patient may simply confer with the physician by telephone, require an outpatient visit or be admitted to the hospital. Patients who do not experience any of these events are still at risk for other complications of heart disease or of the ICD itself during each monthly cycle: they may develop worsening heart failure or myocardial ischemia, lead failure or infection of the ICD or the ICD battery may reach its end of life. The latter three events require hospital admission and surgery. Patients may also experience an inappropriate ICD discharge, which reflects a rhythm disturbance other than ventricular tachycardia/fibrillation. These problems may also lead to hospital admission.

Patients with an ICD who have no complication during a given monthly cycle return to the "ICD Well" state to begin the next cycle. Patients who have a complication requiring surgery, may die at operation or recover, in which case they remain exposed to the other risks discussed. If they develop a medical problem requiring hospital admission, they likewise remain exposed to all the risks of any other patient with an ICD. If they survive the hospital stay without other complication, they return to the "ICD Well" state for the next cycle.

Amiodarone therapy. In contrast, patients on amiodarone therapy enter the Markov process in the "Amio Well" state. During each monthly cycle they may die of the same age-, gender- and race-related causes or nonsudden cardiac causes as a patient with an ICD. In addition, they are exposed to the same baseline risk of sudden cardiac death, reduced by the efficacy of amiodarone to prevent sudden death recurrence. (Some patients for whom amiodarone is effective in preventing death still require hospital admission because amiodarone often prevents sudden death not by eliminating ventricular tachycardia, but by reducing its rate so that it becomes hemodynamically tolerable.) Patients who survive these risks of death, may still require hospital admission for heart failure or myocardial ischemia or they may have an amiodarone drug reaction. If so, they may die or survive, but if they survive, they must stop taking amiodarone and thereby lose its protection against the baseline risk of sudden cardiac death. They then start the next cycle in the "Conventional Therapy Well" state, where they remain exposed to all risks except the risk of an amiodarone drug reaction. Finally, if they avoid all of the problems mentioned, they begin the next monthly cycle in the "Amio Well" state.

Conventional therapy. Patients receiving "conventional therapy," by definition, have persistently inducible ventricular tachyarrhythmias at follow-up electrophysiologic study and thus remain fully exposed to the baseline risk of sudden cardiac death, age- and gender-related mortality and nonsudden cardiac death. If such patients do not die during a monthly cycle, they run a risk of becoming sick and requiring hospital admission. Otherwise they return to the "well" state for the next cycle.

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