Cost-Effectiveness of a Microvolt T-Wave Alternans Screening Strategy for Implantable Cardioverter-Defibrillator Placement in the MADIT-II–Eligible Population

Paul S. Chan, MD, MSc,*† Kenneth Stein, MD,‡ Theodore Chow, MD, FACC,§ Mark Fendrick, MD,†
J. Thomas Bigger, MD,‖ Sandeep Vijan, MD, MSc*†

Ann Arbor, Michigan; New York, New York; and Cincinnati, Ohio

OBJECTIVES	This study was designed to compare the cost-effectiveness of implantable cardioverter-defibrillator (ICD) placement with and without risk stratification with microvolt T-wave alternans (MTWA) testing in the MADIT-II (Second Multicenter Automatic Defibrillator Implantation Trial) eligible population.
BACKGROUND	Implantable cardioverter-defibrillators have been shown to prevent mortality in the MADIT-II population. Microvolt T-wave alternans testing has been shown to be effective in risk stratifying MADIT-II–eligible patients.
METHODS	On the basis of published data, cost-effectiveness of three therapeutic strategies in MADIT-II–eligible patients was assessed using a Markov model: 1) ICD placement in all; 2) ICD placement in patients testing MTWA non-negative;, and 3) medical management. Outcomes of expected cost, quality-adjusted life-years (QALYs), and incremental cost-effectiveness were determined for patient lifetime.
RESULTS	Under base-case assumptions, providing ICDs only to those who test MTWA non-negative produced a gain of 1.14 QALYs at an incremental cost of $55,700 when compared to medical therapy, resulting in an incremental cost-effectiveness ratio (ICER) of $48,700/QALY. When compared with a MTWA risk-stratification strategy, placing ICDs in all patients resulted in an ICER of $88,700/QALY. Most (83%) of the potential benefit was achieved by implanting ICDs in the 67% of patients who tested MTWA non-negative. Results were most sensitive to the effectiveness of MTWA as a risk-stratification tool, MTWA negative screen rate, cost and efficacy of ICD therapy, and patient risk for arrhythmic death.
CONCLUSIONS	Risk stratification with MTWA testing in MADIT-II–eligible patients improves the cost-effectiveness of ICDs. Implanting defibrillators in all MADIT-II–eligible patients, however, is not cost-effective, with one-third of patients deriving little additional benefit at great expense. (J Am Coll Cardiol 2006;48:112–21) © 2006 by the American College of Cardiology Foundation

Sudden cardiac death (SCD) from ventricular arrhythmias remains a leading cause of death in patients with ischemic heart disease and left ventricular dysfunction (1). Although antiarrhythmic drug therapy has proved disappointing, recent clinical trials have demonstrated that implantable cardioverter-defibrillators (ICDs) reduce SCD mortality in this high-risk population (2–5). Furthermore, the MADIT-II (Second Multicenter Automatic Defibrillator Implantation Trial) showed that invasive electrophysiologic

testing was not a prerequisite for these high-risk patients to receive benefit from ICDs (3).

Prior cost-effectiveness analyses from clinical trials with ICDs have shown variability in cost-effectiveness estimates (6–8), with the MADIT-I study, which limited ICD implantation to those at high risk based on electrophysiologic testing, showing the most favorable cost-effectiveness estimate ($27,000 per quality-adjusted life-year [QALY] gained). A recent analysis in MADIT-II–eligible patients modeled for patient lifetime showed that ICDs had an incremental cost-effectiveness ratio of $57,300 per QALY compared to medical therapy (9). Nonetheless, therapies that may be deemed cost-effective may remain unaffordable to society if the therapy of interest is expensive and the disease prevalence high.

Recently, the Centers for Medicare and Medicaid Services (CMS) expanded ICD coverage to MADIT-II–eligible patients despite ongoing concerns regarding cost and cost-effectiveness (10). Effective risk-stratification strategies in the MADIT-II–eligible population to determine

Abbreviations and Acronyms

CMS	= Centers for Medicare and Medicaid Services
ICD	= implantable cardioverter-defibrillator
ICER	= incremental cost-effectiveness ratio
MADIT-II	= Second Multicenter Automatic Defibrillator Implantation Trial
MTWA	= microvolt T-wave alternans
QALY	= quality-adjusted life-year
SCD	= sudden cardiac death

which patients derive the largest benefit would improve the cost-effectiveness of ICD therapy (8). Microvolt T-wave alternans (MTWA) testing has been shown to be effective in risk-stratifying MADIT-II–eligible patients (11–13). One study of 129 MADIT-II–eligible patients derived from two prospective cohorts found a 2-year arrhythmic event rate of 0.0% in patients who tested MTWA negative and 15.6% in patients who tested MTWA non-negative (positive and indeterminate) (11). Another recent study of 177 MADIT-II–eligible patients found a 2-year mortality rate of 3.8% in patients who tested MTWA negative and 17.8% in patients who tested MTWA non-negative (12). In the largest study to date involving 537 MADIT-II–eligible patients, a non-negative MTWA test was associated with a greater than two-fold increased risk of all-cause mortality, even after

adjusting for age, left ventricular ejection fraction, a QRS >120 ms on electrocardiogram, clinical variables, and medication treatment (13).

Given the discriminating power of MTWA testing in risk-stratifying MADIT-II–eligible patients, we evaluated the cost-effectiveness of ICD therapy with and without risk stratification with MTWA compared to medical therapy alone using a decision-analytic model.

METHODS

Model design. We used a Markov decision analysis model to evaluate three treatment strategies for a hypothetical 65-year-old cohort with ischemic heart disease and left ventricular ejection fraction ≤30% (Fig. 1) (14). Taking a societal perspective (which includes not only direct medical costs but also accounts for costs and lost productivity from disability) (14), our model tracked short- and long-term outcomes, adverse events (e.g., lead fracture and lead infection with ICD therapy, disability after surviving nondefibrillator resuscitation of cardiac arrest), and the resultant costs and utilities for each treatment strategy. For the cohort, we simulated outcomes with each treatment strategy and followed patients until death.

Target population and model strategies. Three treatment strategies were evaluated in a hypothetical 65-year-old cohort of MADIT-II–eligible patients with ischemic heart
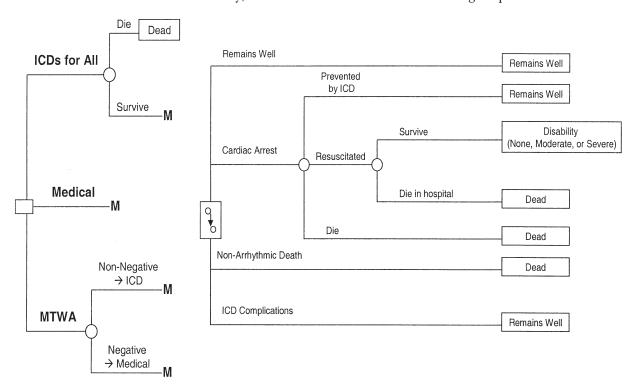

Figure 1. Simplified schematic of Markov model. The **square node at the far left** symbolizes the choice between the three treatment strategies: implantable cardioverter-defibrillators (ICDs) for all, medical therapy, or risk stratification with microvolt T-wave alternans (MTWA) testing. **Circles** represent chance events, and **M** represents the Markov process with multiple health states (well, mildly disabled, moderately disabled, severely disabled) for each treatment option. Patients who survive ICD implantation or who are on medical therapy enter the Markov tree (denoted by **two circles and arrow within a rectangle**), which includes all potential clinical outcomes that occur with each cycle. Patients in the medical therapy arm are not subject to ICD complications and have no cardiac arrests prevented by defibrillator therapy. Patients in the MTWA risk stratification strategy enter the same pathway as those in the ICD-for-all strategy if they test MTWA non-negative and the medical therapy strategy if they test MTWA negative.

Table 1. Model Variables

Input Variables	Base-Case Value (Range for Sensitivity Analysis)	Source (Reference)
Mortality		
Medical therapy, %/yr		11–13,30
Total	10.1 (7.0–13.0)	
SCD	5.2 (3.6–6.6)	
Non-SCD	4.9 (3.4–6.4)	
ICD therapy, %/yr		
Total	6.9 (4.8–8.9)	
SCD	2.0 (1.4–2.5)	
Non-SCD	4.9 (3.4–6.4)	
MTWA risk stratification		11–13,30
Non-negative, %/yr		
Total	12.5 (8.7–16.3)	
SCD		
Baseline	6.4 (4.5–8.3)	
With ICD therapy	2.4 (1.7–3.2)	
Non-SCD	6.1 (3.3–7.2)	
MTWA negative, %/yr		
Total	5.3 (3.7–6.9)	
SCD	2.7 (1.9–3.5)	
Non-SCD	2.6 (1.8–3.4)	
Resuscitation		
Initial resuscitation rate, %	10 (5–30)	16–18
Survive to hospital discharge, %	15 (3–30)	17–20
Post-discharge survival status		21
No disability, %	75 (50–95)	
Moderate disability, %	15 (5–30)	
Severe disability, %	10 (0–20)	
Annual mortality rate, %		21–24
No disability	11 (7–16)	
Moderate disability	18 (15–20)	
Severe disability	30 (20–40)	
ICD complications		
Procedural mortality, %	0.3 (0.0–0.9)	3,26,27
Lead failure, %/yr	3.0 (1.0–5.0)	29,31,38
Lead infection, %/yr	1.0 (0.5–2.0)	25,28,29,31,38
MTWA		
Unable to screen, %	15 (10–20)	3, estimate
Able to screen, %		
MTWA negative	33 (20–40)	11–13,30
MTWA non-negative	67 (60–80)	11–13,30
Costs of care (2004 U.S. $)		
Single event		
ICD		
Initial implantation	35,000 (30,000–50,000)	7,29,31,32
Generator replacement (every 6 yrs)	18,000 (12,000–24,000)	29,32
Lead failure	7,000 (5,000–9,000)	32
Lead infection	51,700 (35,000–70,000)	25,32
Death		
Non-arrest	9,000 (0–18,000)	34,35
Cardiac arrest		
Survived until discharge	24,800 (11,300–46,100)	33
Died before discharge	12,900 (2800–23,600)	33
Annual care		
MTWA screening	400 (300–500)	Cost-accounting
No history of cardiac arrest	10,600 (7,000–20,000)	31,32
Survived cardiac arrest		7,33,36
No disability	18,000 (15,000–21,000)	
Moderate disability	22,000 (19,000–25,000)	
Severe disability	30,000 (20,000–40,000)	

Table 1. Continued

Input Variables	Base-Case Value (Range for Sensitivity Analysis)	Source (Reference)
Utilities for health states		
No history of cardiac arrest	0.88 (0.7–1.0)	8,31,38,39
History of cardiac arrest		40–44
No disability	0.85 (0.7–1.0)	
Moderate disability	0.44 (0.34–0.54)	
Severe disability	0.18 (0.08–0.28)	
Discount rate, %	3 (0–5)	14

Base-case values with the range of estimates for all variables in the Markov model analysis. All variables (rates, costs, and utilities) that are not one-time events are converted to a 3-month cycle rate for model input by the formula: $[(1 + \text{rate})^{(1/\#\text{cycles})} - 1]$.
ICD = implantable cardioverter-defibrillator; MTWA = microvolt T-wave alternans; SCD = sudden cardiac death.

disease and left ventricular dysfunction (ejection fraction ≤30%). Patients who met MADIT-II trial exclusion criteria were excluded from the cohort. The strategies were:

1. Medical therapy, as in the MADIT-II trial.
2. ICDs for all.
3. Risk stratification with MTWA. Given that positive and indeterminate MTWA tests have similar prognostic utility in predicting mortality among patients with ischemic cardiomyopathy (13), we modeled those who would test MTWA non-negative (positive and indeterminate) to receive ICDs and those who would test MTWA negative to receive medical therapy only.

For the analyses, TreeAge Pro (Williamstown, Massachusetts) was used to design the model. The cycle length was three months, the time horizon was lifetime, and costs and utilities were discounted at an annual rate of 3%.

Probabilities and rates. Base-case values, ranges of the estimates, and literature sources for our model variables are shown in Table 1.

MORTALITY RISK. Studies involving MTWA testing in MADIT-II–eligible patients show two-year mortality rates of about 11% to 20% (11–13). For the purposes of this study, we used the survival probability derived from Kaplan-Meier estimates from the largest study of MTWA (n = 768) in patients with ischemic cardiomyopathy by Chow et al. (13). In this study, the three-year survival probability rate with medical therapy was similar to that found in the MADIT-II trial (72.7% for MTWA study and 73.5% for MADIT-II trial) (T. Chow, personal communication, October 2005). Based on this 3-year survival probability, annual mortality rates were modeled to be 10.1%.

In the study by Chow et al. (13), 33% of patients tested MTWA negative, and the age-adjusted mortality hazard ratio was 2.35 for MADIT-II–eligible patients who tested MTWA non-negative relative to those who tested MTWA negative. Based on the annual mortality rate of 10.1%, a 33% rate of a MTWA negative test, and a hazard ratio of 2.35, patients who test MTWA negative and non-negative were modeled to have annual mortality rates of 5.3% and 12.5%, respectively.

Analysis of mortality from the MADIT-II trial showed that 51% of the medical therapy group deaths were from

SCD, and the rate of SCD was reduced by 62% in those implanted with ICDs (1). This translates into a 31.6% all-cause mortality risk reduction for the model (actual relative mortality reduction from MADIT-II trial = 31%). We assumed the benefit of ICD therapy was constant over time, applied these rates to the base-case analysis, and explored different rates of SCD death and ICD efficacy in reducing SCD mortality in sensitivity analysis. We also age-adjusted annual mortality rates for the cohort using life tables from the National Center for Health Statistics (15).

Individuals with an SCD not prevented by ICD therapy in each treatment strategy may receive cardiopulmonary resuscitation in the field. On the basis of published reports, initial resuscitation rates of 10% in the field and survival rates of 15% to hospital discharge were used, for an overall rate of surviving a cardiac arrest not prevented by an ICD of 1.5% (16–20). Moreover, the annual mortality rates of surviving SCD unimpaired, moderately impaired (could live independently), and severely impaired (required institutionalization) were modeled (21–24), and all SCD survivors without severe impairment who did not already have an ICD implanted were assumed to receive one.

COMPLICATIONS OF ICD THERAPY. On the basis of published reports, a procedural mortality risk of 0.3% for ICD implantation, as well as a 3% annual risk for lead fracture and a 1% annual risk for lead infection (with one-half requiring new endocardial systems), were used for the model (3,25–28). Generator replacements were estimated to occur every six years, with a range of four to eight years for sensitivity analysis (29).

MTWA TESTING. Because 8% to 9% of patients in the MADIT-II trial were in atrial fibrillation (3), and because a small percentage of MADIT-II–eligible patients are not able to perform the short duration of exercise required for the MTWA screening test, we estimated that 15% of the unselected MADIT-II population could not be assessed with MTWA testing and would therefore receive an ICD in our model. Among those able to be tested, prior studies have consistently shown that 27% to 35% will test MTWA negative (11–13,30). For our model, we used the estimate of

Table 2. Incremental Cost-Effectiveness Ratios in Base-Case Estimates

	Lifetime Cost	Life-Years	QALYs	ICER (Relative to Medical Therapy)	ICER (Relative to MTWA)
Placing ICDs in all	$157,993	8.2	7.246	$55,800/QALY	$88,700/QALY
Risk stratify with MTWA	$136,449	8.0	7.004	$48,800/QALY	Base-case
Medical management	$80,782	6.7	5.863	Base-case	—

Incremental cost-effectiveness ratios (ICERs) comparing the three strategies for MADIT-II eligible patients are shown. A MTWA risk stratification strategy compared to medical therapy has an ICER comparable to that of hemodialysis ($50,000 per QALY) and would likely be considered cost-effective. An ICD-for-all strategy compared to a MTWA risk stratification strategy would not be considered cost-effective. All ICER results are measured in 2004 U.S. dollars and are rounded off to the nearest $100. Discrepancies in ICER calculations are due to round-off error.

QALY = quality-adjusted life-year; other abbreviations as in Table 1.

33% from the largest cohort study for the baseline probability of testing MTWA negative (13), or 28.7% of the unselected MADIT-II population (after accounting for the 15% unable to perform the test) (13).

Costs. Our model assessed discounted costs (3% annually) in 2004 U.S. dollars from a societal perspective (Table 1) (14). To estimate costs of treatment strategies, Medicare reimbursement rates, inflation-adjusted values from published data, and hospital cost accounting were used (14). All patients had annual costs of $10,600 related to their heart failure and ischemic heart disease (29,31,32). Initial ICD costs utilized inputs from the Duke database (9), which estimated an ICD placement cost of $32,914, or $35,000 after converting to 2004 dollars. For ongoing costs of ICD therapy, ICD generator replacements ($18,000) would occur every six years, and patients with lead fractures and lead pocket infections would incur additional inpatient costs (25,28,32). Patients presenting with SCD not saved by ICD therapy incurred further costs if resuscitation attempts were made (probability = 10%), with the cost dependent upon whether the patient survived until discharge (33–35). Finally, those who survived until discharge after a resuscitated SCD event incurred different annual health care costs depending upon their level of impairment (7,33,36). All cost estimates were standardized to 2004 U.S. dollars by using the Consumer Price Index for all urban consumers (37) and were analyzed across their range of estimates in sensitivity analysis.

Utilities. Quality-of-life adjustments for utility estimates were derived from published data and also discounted at 3% per year. We made a conservative assumption that ICD implantation did not modify the utility of MADIT-II–eligible patients relative to medical therapy and assigned a baseline utility of 0.88 to all patients in the cohort (31,38,39). Health utilities for patients surviving a SCD were estimated from either the SCD or stroke literature for varying degrees of impairment (40–44).

Sensitivity analysis. One-way sensitivity analysis was performed for each model variable across its range of estimates from Table 1. Because varying the mortality hazard ratio for MTWA testing would invariably change the baseline mortality rate, the effect of this variable on incremental cost-effectiveness was examined in two-way sensitivity analyses with the annual mortality rate. Moreover, those variables with the highest uncertainty in the one-way analysis were

further examined in two-way sensitivity analyses. Finally, multivariable sensitivity analysis was conducted using 10,000 second-order Monte Carlo simulations. For each simulation, the distribution of the ranges of every model variable is randomly sampled (to account for the uncertainties of each model variable) in order to generate an incremental cost-effectiveness ratio (ICER) estimate. This analysis assesses the precision of the primary cost-effectiveness estimates from the Markov model by providing a distribution of likely ICER estimates with the 10,000 simulations. We assumed normal distributions for most variables, with the sensitivity analysis covering four standard deviations for the variable's estimate range. For cost and probabilities that were skewed, we assigned log-normal distributions for the analysis.

RESULTS

Table 2 shows model predictions for the three treatment strategies. A strategy involving ICD therapy for all MADIT-II–eligible patients was most effective (7.25 QALYs), followed by risk stratification with MTWA (7.00 QALYs) and medical therapy (5.86 QALYs). Similarly, ICD therapy for all patients was the most expensive ($157,993), followed by risk stratification with MTWA ($136,449) and medical therapy ($80,782). When a risk-stratification strategy with MTWA is compared to the base-case strategy of medical therapy, 1.14 QALYs are gained at an incremental cost of $55,667, representing an ICER of $48,800 per QALY gained. A strategy that implants ICDs in all yields a higher ICER of $55,800/QALY compared with medical therapy. Finally, compared to a MTWA risk-stratification strategy, an ICD-for-all strategy gained an additional 0.24 QALYs at an incremental cost of $21,544, yielding an ICER of $88,700/QALY. This suggests that 83% of the total potential benefit of ICDs can be achieved by implanting ICDs in the 67% of patients who test MTWA non-negative (1.14 incremental QALYs [risk stratification with MTWA]/1.38 incremental QALYs [ICDs-for-all]).

One-way sensitivity analysis. The results of one-way sensitivity analyses for variables with the highest sensitivity are shown in Table 3.

COMPARISON OF MTWA RISK STRATIFICATION WITH MEDICAL THERAPY. Compared to medical therapy, results of one-way sensitivity analyses were relatively insensitive, with the upper ICER estimate range consistently below $62,000

Table 3. Summary Table of One- and Two-Way Sensitivity Analyses

Variables	One-Way Sensitivity Analysis		
	MTWA Screening vs. Medical Therapy	ICDs For All vs. Medical Therapy	ICDs for All vs. MTWA Screening
MTWA mortality hazard ratio (1.0–5.0)	$52,200 to $47,800	N/A	$61,000 to $149,500
SCD proportion of overall mortality (40%–60%)	$55,300 to $44,600	$64,300 to $50,500	$111,400 to $76,400
SCD reduction by ICD (50%–70%)	$56,100 to $45,100	$64,900 to $51,200	$107,800 to $79,700
Cost of ICD ($30,000–$50,000)	$45,700 to $61,200	$52,200 to $70,200	$82,800 to $112,300
Baseline annual mortality (7.0%–13.0%)	$58,100 to $44,800	$67,300 to $50,600	$116,400 to $75,400
Cost of annual care ($7,000–$20,000)	$44,700 to $59,600	$51,700 to $66,600	$84,600 to $99,400
MTWA negative screen rate (10%–50%)	$51,200 to $46,200	N/A	$91,700 to $80,900
Baseline utility for well health (0.7–1.0)	$61,500 to $42,900	$70,300 to $49,100	$111,500 to $78,100
Lead infection risk (0.5%–2.0%)	$47,400 to $55,600	$54,000 to $59,400	$85,100 to $96,000
Discount rate (0%–5%)	$43,100 to $53,100	$48,800 to $61,100	$74,700 to $99,600

Variables	Two-Way Sensitivity Analysis
	ICDs for All vs. MTWA Screening
MTWA mortality hazard ratio × SCD proportion	$55,200 to $190,800
MTWA mortality hazard ratio × ICD efficacy	$55,200 to $188,300
MTWA mortality hazard ratio × ICD cost	$56,800 to $188,900
SCD proportion × ICD efficacy	$68,900 to $136,200
SCD proportion × ICD cost	$71,600 to $134,400
ICD efficacy × ICD cost	$74,500 to $137,500

Variables with the greatest influence on incremental cost-effectiveness ratios when evaluated across the range of estimates from Table 1 are shown for one-way sensitivity analyses. No single variable significantly influenced the incremental cost-effectiveness ratio comparing a MTWA risk stratification strategy with the base case of medical therapy. However, several variables were highly influential when an ICD-for-all strategy was compared with a MTWA risk stratification strategy, and these variables are further examined with two-way sensitivity analysis, using the upper and lower limits of each variable's range of estimates. Dollar amounts are in 2004 US dollars and are per quality-adjusted life-year.
Abbreviations as in Tables 1 and 2.

per QALY. Because varying the MTWA mortality hazard ratio inherently increases the baseline annual mortality rate, this variable was further explored as a two-way sensitivity analysis (Fig. 2). At the base-case annual mortality rate of 10.1%, threshold analysis found that the MTWA hazard ratio would need to be >1.8 to yield an ICER of <$50,000 per QALY. As seen in Figure 2, the ICER for a MTWA risk-stratification strategy compared to medical therapy decreases with a higher baseline annual mortality rate or a higher MTWA mortality hazard ratio.
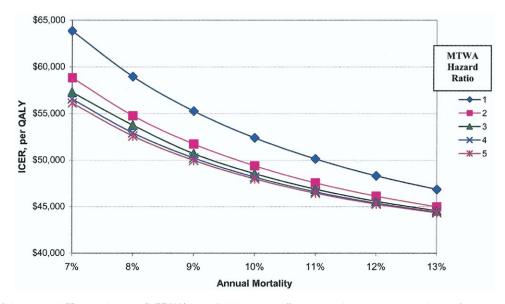

Figure 2. Effect of the microvolt T-wave alternans (MTWA) hazard ratio on cost-effectiveness when comparing a risk stratification strategy with MTWA to medical therapy. As varying the MTWA hazard ratio changes the underlying baseline annual mortality rate, the effect of this variable on cost-effectiveness is performed as a two-way sensitivity analysis. Base-case estimates are for an annual mortality rate of 10.1% and a MTWA hazard ratio of 2.35. The incremental cost-effectiveness of a risk stratification strategy with MTWA compared to medical therapy becomes more favorable as the MTWA hazard ratio or the annual mortality rate increases. ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
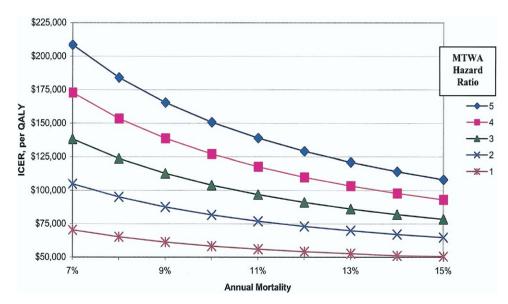
Figure 3. Effect of the MTWA hazard ratio on cost-effectiveness when comparing an ICD-for-all strategy with a MTWA risk stratification strategy. The incremental cost-effectiveness of an ICD-for-all strategy compared to a risk stratification strategy with MTWA becomes more favorable as the annual mortality rate increases or as the MTWA hazard ratio decreases. Abbreviations as in Figures 1 and 2.

COMPARISON OF ICD-FOR-ALL STRATEGY WITH MTWA RISK STRATIFICATION. When an ICD-for-all strategy is compared with a MTWA risk-stratification strategy, results were most sensitive to the mortality hazard ratio for MTWA testing (Table 3). As before, the impact of this variable on incremental cost-effectiveness is best appreciated as a two-way sensitivity analysis with annual mortality (Fig. 3). At the base-case mortality hazard ratio of 2.35 and annual mortality risk of 10.1%, the ICER is $88,700 per QALY. The ICER decreases with a higher annual mortality rate or a less predictive MTWA test. However, even when the MTWA screening test is non-discriminating (hazard ratio = 1), the annual mortality rate would need to be >15% to yield an ICER <$50,000 per QALY.

Other variables with significant impact in the one-way sensitivity analyses included the MTWA negative screen rate, patient risk for arrhythmic death, the cost and efficacy of ICD therapy, baseline annual mortality rate, baseline utility for health, and discount rate used. Finally, when we limited the mortality benefit of MTWA screening to only the first two years, an ICD-for-all strategy yielded an ICER of $76,500 per QALY.

TWO-WAY SENSITIVITY ANALYSIS. Because no single variable exerted significant impact in the one-way sensitivity analysis when compared with a medical therapy strategy as the base case, there remained little variability in two-way sensitivity analyses, with none of the upper-range estimates for the MTWA risk-stratification strategy exceeding $100,000 per QALY gained (results not shown). In contrast, when an ICD-for-all strategy was compared with a MTWA risk-stratification strategy, several variables showed high sensitivity in two-way sensitivity analyses (Table 3).

However, in no instance did the ICER of the ICD-for-all strategy compared to a MTWA risk-stratification strategy fall below $55,000 per QALY gained.

MULTIVARIABLE SENSITIVITY ANALYSIS. Monte Carlo simulations demonstrated that the ICER for the MTWA risk-stratification strategy compared to medical therapy had a 100% probability of being <$100,000 per QALY gained, and a 55% probability of being <$50,000 per QALY gained in the MADIT-II population (Fig. 4). The ICER for an ICD-for-all strategy compared with MTWA risk stratification had a 26% probability of being >$100,000 per QALY gained and a 0% probability of being <$50,000 per QALY gained (Fig. 5).

DISCUSSION

Although ICDs have been found to be efficacious in patients with ischemic cardiomyopathy, the cost-effectiveness and cost-affordability of these life-saving devices over a lifetime remains less certain. Our study found that when MADIT-II–eligible patients are first risk-stratified with MTWA testing, the incremental cost-effectiveness of ICD therapy compared with medical therapy was comparable to that of hemodialysis (~$50,000 per QALY gained), an oft-cited benchmark for cost-effectiveness (45). When ICD therapy was provided to all MADIT-II–eligible patients, compared with medical therapy alone, incremental cost-effectiveness increased moderately, suggesting that its proper comparator would be the MTWA risk-stratification strategy (14). Compared to a MTWA risk-stratification strategy, providing ICDs for all patients generated only a small amount of benefit (0.24 QALY) at a significant price ($21,500) and
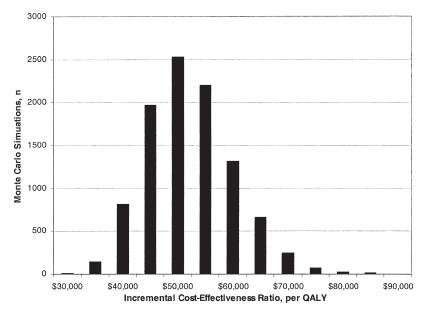
Figure 4. Estimated distribution of the incremental cost-effectiveness ratio of risk stratification with MTWA testing versus medical therapy in the MADIT-II–eligible population. Data were obtained by performing 10,000 Monte Carlo simulations. The cost-effectiveness ratio was less than $50,000/QALY in 5,459 (54.6%) of the simulations, whereas none of the simulations yielded cost-effectiveness ratios above $100,000/QALY. Abbreviations as in Figures 1 and 2.

was therefore cost-ineffective by commonly cited cost-effectiveness thresholds (14).

Sensitivity analyses showed that no model variable exerted significant influence when a MTWA risk-stratification strategy was compared to a medical therapy strategy, implying that the incremental cost-effectiveness estimates are likely to be in the $42,000 to $62,000 per QALY range. When an ICD-for-all strategy was compared with a MTWA risk-stratification strategy, one-way, two-way, and multivariable sensitivity analyses showed that it was unlikely to be cost-effective. Finally, even in the unlikely scenario in which the mortality

benefit of MTWA screening was limited to only the first two years (i.e., time frame of the prospective cohort studies for MTWA), an ICD-for-all strategy would probably still not be considered cost-effective (ICER: $76,500 per QALY).

Despite the recent decision by CMS to expand defibrillator coverage to MADIT-II–eligible patients irrespective of QRS duration, ongoing concerns on the cost implications of this decision persist. One recent study estimates that 32,000 new MADIT-II patients in the U.S. were eligible for defibrillator implantation in the year 2000 (9). Our
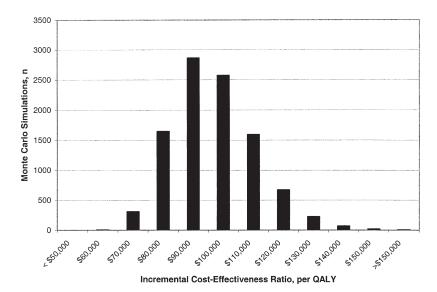

Figure 5. Estimated distribution of the incremental cost-effectiveness ratio of an ICD-for-all strategy versus risk stratification with MTWA testing in the MADIT-II–eligible population. Data were obtained by performing 10,000 Monte Carlo simulations. The cost-effectiveness ratio was above $100,000/QALY in 2,594 (25.9%) of all simulations, whereas no simulations gave cost-effectiveness ratios below $50,000/QALY. Abbreviations as in Figures 1 and 2.

model suggests that the lifetime incremental cost of defibrillator therapy in an ICD-for-all strategy compared to medical therapy is $77,200 per patient (lifetime cost for ICD patient = $157,993; lifetime cost for medical therapy patient = $80,782 from Table 2), which is similar to the incremental lifetime cost of $90,800 determined in another study (9), in order to generate 1.38 QALY per patient. This suggests that an ICD-for-all strategy would, over a lifetime, cost an incremental $2.47 billion ($77,200 × 32,000 patients) and save an incremental 44,160 QALYs (1.38 QALY × 32,000 patients) for 100% penetration of this policy for each year of patients who meet MADIT-II criteria. If an MTWA risk stratification strategy was used instead, the average incremental lifetime cost would be $55,700 to gain 1.14 QALYs per patient, or an incremental lifetime cost of $1.78 billion to save 36,480 QALYs by covering all newly eligible MADIT-II patients annually. This suggests that a MTWA risk stratification strategy would save $690 million (28%) but lose 7,680 QALYs (17%) to cover all newly eligible MADIT-II patients annually compared to an ICD-for-all strategy.

Our study demonstrates that a MTWA risk stratification strategy is a more cost-effective approach to ICD implantation than an ICD-for-all strategy in the MADIT-II–eligible population. Until more effective risk stratification models are developed, this suggests that ICDs may be considered cost-effective in those who test MTWA non-negative at a cost-effectiveness threshold of ~$50,000 per QALY. For those who test MTWA negative, however, given their lower sudden cardiac death risk and the potential for ICD complications, ICDs may not be cost-effective. It remains unclear whether annual screening with MTWA testing in those who screen MTWA negative may further increase the negative predictive power of MTWA testing and therefore be an alternative option for such patients.

We made conservative assumptions for model inputs that likely yielded a more favorable ICER when comparing an ICD-for-all strategy with a MTWA risk-stratification strategy. We used a mortality hazard ratio of 2.35 for MTWA non-negative versus negative patients from the largest study involving MADIT-II type patients to date (n = 537) (13). A higher mortality HR of 4.7, as seen in the study by Bloomfield et al. (12) (n = 177), would have yielded an ICER of $142,400 per QALY (Fig. 3). However, in that smaller study, the mortality HR derived was not age-adjusted and reflected a younger population than that seen in the MADIT-II trial population (mean age = 65 years). Nevertheless, it is likely that the ICER for an ICD-for-all versus a MTWA risk stratification strategy may be higher than $88,000 per QALY, especially as our model conservatively assumed a fixed survival benefit with ICD therapy over patient lifetime, similar annual medical therapy costs for the ICD and non-ICD groups, and low rates of ICD complications, all of which would favor the ICD-for-all strategy.

Our study had several limitations. To date, there have been no published randomized clinical trials with MTWA. Prospective cohort studies may have unmeasured selection bias, although the consistent robust findings across different studies using MTWA to identify patients at high risk for SCD would suggest that, even if such bias existed, there would likely remain significant differences in SCD risk between the MTWA negative and non-negative patient groups. Decision-analytical models also make simplifying assumptions, and we extrapolated the rates for overall and SCD mortality derived from the literature for patient lifetime. These rates may not be linear beyond the study's follow-up periods or may be outside the ranges used for our sensitivity analyses. It was assumed that patients who received ICDs would not have a change in health state utility, although some might argue that an ICD could either increase or decrease (from frequent inappropriate shocks) a patient's health state utility, which would decrease or increase, respectively, the cost-effectiveness estimates comparing a MTWA risk stratification strategy with medical therapy. Our study's cost-effectiveness estimates were generated for a hypothetical 65-year-old cohort and may not be applicable to older or younger MADIT-II–eligible patients. Moreover, these results reflect mean ICERs for the cohort but do not provide patient-specific ICERs based on one's covariate distribution. Finally, we did not model potential uses of biventricular pacers with defibrillators in this population with left ventricular dysfunction, as this would require a more complex model with additional assumptions that are outside the scope of the present study.

Conclusions. Implantable cardioverter-defibrillators in MADIT-II–eligible patients who are risk stratified by MTWA testing are costly but likely cost-effective. Implementing a policy of ICD placement in all MADIT-II–eligible patients compared to a risk stratification strategy with MTWA, however, is not likely to be considered cost-effective, with one-third of patients deriving little additional benefit at great expense.

Reprint requests and correspondence: Dr. Paul S. Chan, VA Ann Arbor Healthcare System, Cardiology (111-A), 2215 Fuller Road, Ann Arbor, Michigan 48105. E-mail: paulchan@umich.edu.

REFERENCES

1. Greenberg H, Case RB, Moss AJ, Brown MW, Carroll ER, Andrews ML. Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). J Am Coll Cardiol 2004;43:1459–65.
2. Moss AJ, Hall WJ, Cannom DS, et al., the Multicenter Automatic Defibrillator Implantation Trial Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med 1996;335:1933–40.
3. Moss AJ, Zareba W, Hall WJ, et al., for the Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–83.

4. Buxton AE, Lee KL, Fisher JD, et al., for the Multicenter Unsustained Tachycardia Trial Investigators. A randomized study of the prevention of sudden death in patients with coronary artery disease. N Engl J Med 1999;341:1882–90.

5. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–37.

6. Hlatky MA, Sanders GD, Owens DK. Cost-effectiveness of the implantable cardioverter defibrillator. Card Electrophysiol Rev 2003; 7:479–82.

7. Mushlin AI, Hall WJ, Zwanziger J, et al. The cost-effectiveness of automatic implantable cardiac defibrillators: results from MADIT. Multicenter Automatic Defibrillator Implantation Trial. Circulation 1998;97:2129–35.

8. Sanders GD, Hlatky MA, Owens DK. Cost-effectiveness of implantable cardioverter-defibrillators. N Engl J Med 2005;353:1471–80.

9. Al-Khatib SM, Anstrom KJ, Eisenstein EL, et al. Clinical and economic implications of the multicenter automatic defibrillator implantation trial-II. Ann Intern Med 2005;142:593–600.

10. Phurrough S, Salive M, Baldwin J, Chin J. Decision Summary: implantable cardioverter-defibrillators (CAG 00157R2). Available at: http://www.cms.hhs.gov/mcd/viewncd.asp?ncd_id=20.4&ncd_version =2&basket=ncd%3A20%2E4%3A2%3AImplantable+Automatic+ Defibrillators. Accessed October 1, 2003.

11. Hohnloser SH, Ikeda T, Bloomfield DM, Dabbous OH, Cohen RJ. T-wave alternans negative coronary patients with low ejection and benefit from defibrillator implantation. Lancet 2003;362:125–6.

12. Bloomfield DM, Steinman RC, Namerow PB, et al. Microvolt T-wave alternans distinguishes between patients likely and patients not likely to benefit from implanted cardiac defibrillator therapy: a solution to the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II conundrum. Circulation 2004;110:1885–9.

13. Chow T, Kereiakes DJ, Bartone C, et al. Prognostic utility of microvolt T-wave alternans in risk stratifying patients with ischemic cardiomyopathy. J Am Coll Cardiol 2006;47:1820–7.

14. Gold M, Siegel J, Russell L, Weinstein M. Cost-Effectiveness in Health and Medicine. New York, NY: Oxford University Press; 1996.

15. National Vital Statistics Reports: United States Life Tables, 2002. Hyattsville, MD: National Center for Health Statistics, Centers for Disease Control and Prevention; 2002.

16. Stiell IG, Wells GA, DeMaio VJ, et al. Modifiable factors associated with improved cardiac arrest survival in a multicenter basic life support/defibrillation system: OPALS Study Phase I results. Ontario Prehospital Advanced Life Support. Ann Emerg Med 1999;33:44–50.

17. Ladwig KH, Schoefinius A, Danner R, et al. Effects of early defibrillation by ambulance personnel on short- and long-term outcome of cardiac arrest survival: the Munich experiment. Chest 1997;112:1584–91.

18. Cobb LA, Fahrenbruch CE, Walsh TR, et al. Influence of cardiopulmonary resuscitation prior to defibrillation in patients with out-of-hospital ventricular fibrillation. JAMA 1999;281:1182–8.

19. Lombardi G, Gallagher J, Gennis P. Outcome of out-of-hospital cardiac arrest in New York City. The Pre-Hospital Arrest Survival Evaluation (PHASE) Study. JAMA 1994;271:678–83.

20. Becker LB, Ostrander MP, Barrett J, Kondos GT. Outcome of CPR in a large metropolitan area—where are the survivors? Ann Emerg Med 1991;20:355–61.

21. Bunch TJ, White RD, Gersh BJ, et al. Long-term outcomes of out-of-hospital cardiac arrest after successful early defibrillation. N Engl J Med 2003;348:2626–33.

22. Ezekowitz JA, Armstrong PW, McAlister FA. Implantable cardioverter defibrillators in primary and secondary prevention: a systematic review of randomized, controlled trials. Ann Intern Med 2003;138: 445–52.

23. Connolly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. Eur Heart J 2000;21:2071–8.

24. Hardie K, Hankey GJ, Jamrozik K, Broadhurst RJ, Anderson C. Ten-year survival after first-ever stroke in the Perth community stroke study. Stroke 2003;34:1842–6.

25. Ferguson TB Jr., Ferguson CL, Crites K, Crimmins-Reda P. The additional hospital costs generated in the management of complications of pacemaker and defibrillator implantations. J Thorac Cardiovasc Surg 1996;111:742–51;discussion 751–2.

26. Rosenqvist M, Beyer T, Block M, et al. Adverse events with transvenous implantable cardioverter-defibrillators: a prospective multicenter study. European 7219 Jewel ICD Investigators. Circulation 1998;98:663–70.

27. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004;350:2151–8.

28. Mela T, McGovern BA, Garan H, et al. Long-term infection rates associated with the pectoral versus abdominal approach to cardioverter-defibrillator implants. Am J Cardiol 2001;88:750–3.

29. Owens DK, Sanders GD, Heidenreich PA, McDonald KM, Hlatky MA. Effect of risk stratification on cost-effectiveness of the implantable cardioverter defibrillator. Am Heart J 2002;144:440–8.

30. Chow T, Schloss E, Waller T, et al. Microvolt T-wave alternans identifies MADIT-II patients at low risk of ventricular tachyarrhythmic events (abstr). Circulation 2003;108:IV323.

31. Sanders GD, Hlatky MA, Every NR, et al. Potential cost-effectiveness of prophylactic use of the implantable cardioverter defibrillator or amiodarone after myocardial infarction. Ann Intern Med 2001;135: 870–83.

32. Chen L, Hay JW. Cost-effectiveness of primary implanted cardioverter defibrillator for sudden death prevention in congestive heart failure. Cardiovasc Drugs Ther 2004;18:161–70.

33. Groeneveld PW, Kwong JL, Liu Y, et al. Cost-effectiveness of automated external defibrillators on airlines. JAMA 2001;286:1482–9.

34. Disch DL, Greenberg ML, Holzberger PT, Malenka DJ, Birkmeyer JD. Managing chronic atrial fibrillation: a Markov decision analysis comparing warfarin, quinidine, and low-dose amiodarone. Ann Intern Med 1994;120:449–57.

35. Cheng CH, Sanders GD, Hlatky MA, et al. Cost-effectiveness of radiofrequency ablation for supraventricular tachycardia. Ann Intern Med 2000;133:864–76.

36. Larsen G, Hallstrom A, McAnulty J, et al. Cost-effectiveness of the implantable cardioverter-defibrillator versus antiarrhythmic drugs in survivors of serious ventricular tachyarrhythmias: results of the Antiarrhythmics Versus Implantable Defibrillators (AVID) economic analysis substudy. Circulation 2002;105:2049–57.

37. U.S. Department of Labor Bureau of Labor Statistics. Consumer Price Index: All Urban Consumers. U.S. Department of Labor Bureau of Labor Statistics; 2004. Available at: http://www.bls.gov.proxy.lib.umich.edu/ data/. Accessed May 26, 2005.

38. Owens DK, Sanders GD, Harris RA, et al. Cost-effectiveness of implantable cardioverter defibrillators relative to amiodarone for prevention of sudden death. Ann Intern Med 1997;126:1–12.

39. Tsevat J, Goldman L, Soukup JR, et al. Stability of time-tradeoff utilities in survivors of myocardial infarction. Med Decis Making 1993;13:161–5.

40. Gage BF, Cardinalli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. JAMA 1995;274:1839–45.

41. Nichol G, Stiell IG, Hebert P, Wells GA, Vandemheen K, Laupacis A. What is the quality of life for survivors of cardiac arrest? A prospective study. Acad Emerg Med 1999;6:95–102.

42. Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. Arch Intern Med 1996;156:1829–36.

43. Granja C, Teixeira-Pinto A, Costa-Pereira A. Quality of life after intensive care—evaluation with EQ-5D questionnaire. Intensive Care Med 2002;28:898–907.

44. Samsa GP, Matchar DB, Williams GR, Levy DE. Cost-effectiveness of ancrod treatment of acute ischaemic stroke: results from the Stroke Treatment with Ancrod Trial (STAT). J Eval Clin Pract 2002;8:61–70.

45. Stange PV, Sumner AT. Predicting treatment costs and life expectancy for end-stage renal disease. N Engl J Med 1978;298:372–8.