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Microvolt T-wave alternans and the selective use of implantable cardioverter defibrillators for primary prevention: A cost-effectiveness study

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Objectives: Implantable cardioverter defibrillators (ICDs) are an effective but expensive treatment for the prevention of sudden cardiac deaths in patients with severe left-ventricular dysfunction. Recent studies suggest that microvolt T-wave alternans (MTWA) predicts mortality and severe arrhythmic events in this population. However, the impact of MTWA on ICD cost-effectiveness is unknown.
Methods: A Markov decision-analysis model evaluated three treatment strategies for primary prevention in patients with severe left-ventricular dysfunction: (i) medical therapy for all; (ii) ICD therapy for all; and (iii) selective ICD therapy based on non-negative (positive or indeterminate) MTWA test results. Incremental cost-effectiveness ratios (ICER) were calculated from the perspective of a third party payer using a 10-year time horizon. Sensitivity analyses examined the robustness of the estimates.
Results: A treatment strategy involving ICD therapy in all patients was associated with an ICER of $121,800/quality-adjusted life-year (QALY) compared with medical therapy, whereas a treatment strategy involving the selective use of ICDs based on MTWA test results was associated with an ICER of $108,900/QALY compared with medical therapy. Sensitivity analyses suggest that, under most scenarios, the selective use of ICDs based on MTWA results does not decrease the ICER to below $100,000/QALY.
Conclusion: MTWA only marginally improves the cost-effectiveness of ICDs for primary prevention in patients with severe left-ventricular dysfunction. There remains a need for improved means to effectively identify which patients will derive the greatest benefit from ICD implantation.

J.M.B. conceived of the study idea, and K.B.F., X.X., and J.M.B. contributed to the study design. K.B.F. and X.X. drafted the manuscript. X.X. conducted the statistical analyses. All authors were involved in revising the article for important intellectual content, interpreting the data, and approved the final version to be published. Drs. Dendukuri and Brophy receive financial support from le Fonds de la Recherche en Santé du Québec. Mr. Filion receives financial support from the Faculty of Medicine of McGill University, the Research Institute of the McGill University Health Centre, and the Department of Medicine of the McGill University Health Centre. Ms. van der Avoort received financial support from the Foundation of the University of Nijmegen and the Faculty of Medicine of the Radboud University Nijmegen Medical Center. The authors have no competing interests to declare.

Keywords: Arrhythmias, Cost-effectiveness, Implantable cardioverter defibrillators, Microvolt T-wave Alternans, Primary prevention

Implantable cardioverter defibrillators (ICDs) are an effective treatment for the primary prevention of arrhythmic events and mortality in patients with severe left-ventricular dysfunction. Data from primary prevention randomized controlled trials (RCTs) suggest that the use of ICDs is associated with a relative risk reduction of 19 percent, whereas observational data suggest the relative risk reduction may be as high as 46 percent (23). However, ICDs are an expensive treatment, particularly in the setting of primary prevention, because many patients will not experience severe arrhythmic events (28;55). Although some previous cost-effectiveness analyses suggest that ICD therapy for primary prevention may be cost-effective (44;47), others suggest the contrary (12;13;42). Consequently, there is a need to identify which patients will derive the greatest benefit from this effective but expensive therapy.

Recent studies suggest that microvolt T-wave alternans (MTWA) predicts mortality and severe arrhythmic events in this population (18;30;53). MTWA is an inexpensive diagnostic test analogous to a traditional treadmill test. Patients with non-negative (either positive or indeterminate) MTWA test results have a threefold increased risk of mortality or severe arrhythmias compared with those with a negative test (53). MTWA has thus been suggested as a method to risk stratify this patient population and identify the patients most likely to benefit from ICD implantation. However, the impact of MTWA on ICD cost-effectiveness is unknown. Therefore, the objective of this study was to examine the effect of MTWA testing on ICD cost-effectiveness in primary prevention among patients with severe left-ventricular dysfunction.

METHODS

Decision-Analysis Model

Our Markov model evaluated three treatment strategies for primary prevention in patients with severe left-ventricular dysfunction: (i) medical therapy for all, (ii) ICD therapy for all, and (iii) selective ICD therapy based on non-negative (positive or indeterminate) MTWA test results (Figure 1). Each treatment strategy had three possible health states (well, nonfatal arrhythmic events, and death). The model used 3-month cycles, and costs and quality-adjusted life-years (QALYs) were projected over a 10-year horizon.

Model Inputs

Data were obtained from the best available evidence, with an emphasis placed on results of previous meta-analyses and RCTs. Expert opinion was used for model inputs for which published data were unavailable or inappropriate.

Transition Probabilities. ICD efficacy data were derived from a recent meta-analysis (23). We assumed that the efficacy of ICD therapy relative to medical therapy is constant over time. We also assumed that ICDs are similarly efficacious in low- and high-risk patients. Pooled baseline mortality rates for the medical therapy group were not reported in this meta-analysis. Consequently, we systematically reviewed the literature to identify RCTs examining the efficacy of ICD therapy for primary prevention in adults with severe left-ventricular dysfunction, and we pooled data from identified studies using a random-effects generalized linear mixed model (17;26) to estimate this annual mortality rate. We then derived age-specific population mortality rates using Canadian major chronic diseases mortality rates (45).

Our model inputs for MTWA testing are based on our recently completed systematic review and hierarchical Bayesian meta-analysis of the predictive ability of MTWA testing in patients with severe left-ventricular dysfunction (53). The effect measure from this meta-analysis was combined with the baseline mortality rate and the proportion of negative and nonnegative MTWA tests to obtain annual mortality rates for each MTWA category.

We calculated the annual rate of nonfatal arrhythmic events by multiplying the initial resuscitation rate by the proportion of patients who survive ventricular fibrillation or tachycardia (15;50). Once patients suffer nonfatal arrhythmic events, they moved to the “arrhythmia” state in our model. We pooled annual mortality rates of the medical therapy control groups of ICD secondary prevention RCTs to obtain the baseline mortality rate for patients in this “arrhythmia” state. These data were combined with efficacy measures for ICD therapy in secondary prevention to estimate the mortality rate in secondary prevention patients with ICDs.

Costs. This economic analysis was conducted from the perspective of the Canadian healthcare system and thus focuses on direct health care costs, including professional fees. For modeling purposes, we categorized costs into two types: (i) transition, or one-time, costs; and (ii) state, or general recurrent, costs. The sum of the transition and state costs represents the total costs. All costs are presented in 2007 Canadian dollars (CAD) and were adjusted by purchasing power parities and consumer price index, healthcare component (43;49). Costs of ICD implantation were derived from our technology assessment conducted at our institution (37). Previous studies suggest that an ICD can last 6 years (35;48;56), at which point a new ICD is implanted. We determined annual general care costs for patients in the “Well-ICD” and “Well-medical” states by adding the cost of anti-arrhythmic medical therapy

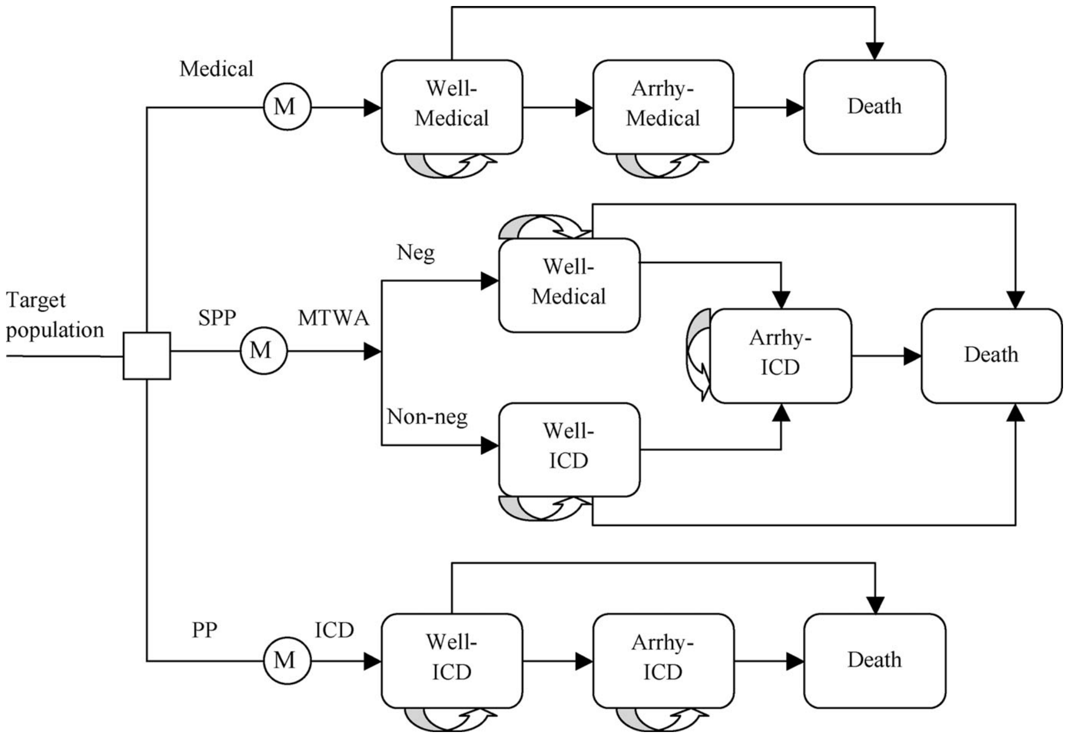

Figure 1. Markov decision analysis model of treatment options for primary prevention. The three treatment strategies are as follows: (i) medical therapy for all, (ii) ICD therapy for all, and (iii) selective ICD therapy based on non-negative (positive or indeterminate) MTWA test results. In this model, square nodes denote decision nodes, round notes with an "M" indicate the Markov model treatment options, square text boxes denote Markov health states, and arrows indicate pathways. Arrhy, arrhythmia; ICD, implantable cardioverter defibrillator; Med, medical thrapy; MTWA, microvolt T-wave alternans; Neg, negative MTWA; Non-neg, non-negative MTWA; PP, primary prevention involving ICD therapy for all; SPP, selective primary prevention based on MTWA test results.

to the Canadian age-specific average annual expenditures per capita (14;42). Cost data for nonfatal arrhythmic events were not available; we approximated these costs with those of atrial fibrillation (21;34;36). Previous studies suggest that the cost of a second ICD implantation and ICD battery replacement are similar to those of initial ICD implantation (37). Consequently, we assumed that all ICD implantations had equal costs.

Utilities. Previous studies have provided conflicting estimates of the effect of ICD therapy on health-related quality of life (13;37). We have, therefore, assumed that patients in the medical therapy and ICD therapy groups have similar quality of life. Estimates for quality of life, assessed using the EuroQoL-5 dimensions (EQ-5D) scale, were obtained from the literature (13). The effect of nonfatal arrhythmic events on quality of life remains poorly understood but was estimated by the decrease in quality of life following defibrillator shocks (13).

Cost-Effectiveness Analysis

Using our decision-analysis model, we compared the cost-effectiveness of the three treatment strategies. Our main outcome measure was the incremental cost-effectiveness ratio (ICER), measured in cost per QALY gained. Our base-case model involved annual discount rates of 3 percent for both utilities and costs (20), which were accrued over a 10-year period. There is no universally accepted maximum willingness-to-pay threshold in Canada and thus, we examined cost-effectiveness at three different thresholds: $20,000, $50,000, and $100,000/QALY (33).

We conducted univariate sensitivity analyses to identify the primary variables influencing our ICERs. We then further examined the effect of these variables in two-way sensitivity analyses. Ranges for sensitivity analyses were primarily based on 95 percent confidence intervals (CI) obtained from the literature. We also conducted probabilistic sensitivity analyses using second order Monte Carlo simulations (10,000 samples). In these probabilistic sensitivity analyses, transition probabilities and utilities were assumed to follow beta distributions (10). Costs, hazard ratios (HR), and relative risks (RR) were assumed to follow gamma distributions (38), and mortality rates were assumed to follow normal distributions. Analyses were conducted using Treeage pro Suite 2007, SAS 9.1, and Excel 2003.

Table 1. Model Inputs

Variables	Value (ranges)	Reference
Transition probabilities		
Annual mortality rates of medical therapy (Baseline)		
Without arrhythmia events	0.096 (0.070–0.120)	(5–7;11;27;29;39;40;51)
After non-fatal arrhythmia events	0.120 (0.084–0.155)	(3;19;32)
Age-specific mortality index (year)		
65–69	1.00	(45)
70–74	1.61	(45)
75–79	2.64	(45)
MTWA test		
The proportion of negative results	0.328 (0.305–0.350)	(8;9;16;25;31)
The proportion of those who cannot be tested	0.15 (0.05–0.3)	(15)
RR of non-negative vs. negative MTWA test	2.6 (1.4–5.8)	(53)
HR of primary prevention by ICD vs. medical therapy	0.81 (0.69–0.95)	(23)
HR of secondary prevention by ICD vs. medical therapy	0.77 (0.65–0.91)	(23)
Annual non-fatal arrhythmia rate	0.0088 (0–0.03)	(15;50)
Initial resuscitation rate per year	0.1	(15)
Survival rate	0.088	(50)
ICD implantation procedure mortality rate	0 (0–0.012)	(23)[a]
Resource costs (2007 CAD)		
MTWA screening	509 (382–636)	(15)
ICD implantation		
Device and electrodes	24,839 (18,630–31,049)	(37)
Implant procedure costs		
Nurses and technician	122 (91–152)	(37)
Surgeon, anesthetist, and cardiologist	1,211 (909–1,514)	(37)
Post implant procedure costs	105 (79–132)	(37)
Follow up of ICD implantation		
Costs per patient visit (technician)	19 (14–23)	(37)[b]
Clinic visit (cardiologist)	54 (41–68)	(37)[c]
ICD complication	553 (415–691)	(37)[d]
Nonfatal arrhythmia	6,737 (5,053–8,421)	(52)
Death from any causes	15,032 (11,274–18,790)	(15)
Average annual expenditures per capital		
65–74 years old	5,229 (3,922–6,537)	(14)
75–84 years old	9,609 (7,207–12,012)	(14)
Amiodarone per year		
Well-ICD strategy	220 (165–275)	(42)
Well-medical strategy	943 (707–1,178)	(42)
Other antiarrhythmic drugs per year		
Well-ICD strategy	105 (79–131)	(42)
Well-medical strategy	25 (19–32)	(42)
After nonfatal arrhythmia events per year	15,672 (11,754–19,590)	(34;36)
Utilities (EQ-5D)		
Well-ICD/Well-Medical State	0.745 (0.5–1)	(13)
Utility loss after non-fatal arrhythmic events	0.11 (0.04–0.18)	(13)

[a] Mortality rate associated with ICD implantation is 0 at the McGill University Health Centre. Consequently, we have used this rate in our base case. In sensitivity analyses, we increased this rate from 0 to 0.012, the rate reported in previous reviews (23).
[b] Follow-up begins at 1 week after implant and consists of one visit every 3 months.
[c] Follow-up begins at 1 week after implant and consists of one visit every year.
[d] The weighted cost per patient of all main possible complications, including lead displacement, infection, pneumothorax, perforation, and bleeding.
CAD, Canadian dollars; EQ-5D, Euro-QoL–5 dimensions (22); HR, hazard ratio; ICD, implantable cardioverter defibrillator; MTWA, microvolt T-wave alternans; RR, relative risk.

RESULTS

Model Inputs

Model inputs are described in Table 1. Efficacy data for ICD therapy and MTWA were obtained from previous meta-analyses (23;53). Our literature review identified 9 ICD primary prevention RCTs (5–7;11;27;29;39;40;51), and pooling of these data revealed an annual mortality rate in the medical therapy group of 0.096/year. Efficacy data were obtained from the meta-analysis by Ezekowitz and colleagues (23),

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who found a HR for all-cause mortality of 0.81 (95 percent CI, 0.69–0.95) among patients randomized to ICD therapy compared with those randomized to medical therapy. From our recent MTWA meta-analysis, we estimated the proportion of patients with negative MTWA to be 32.8 percent. We also approximated that 15 percent of patients are unable to undergo exercise testing (15) and included them with non-negative MTWA patients. The risk of mortality or severe arrhythmic events was 2.6 times greater in patients with non-negative MTWA than in those with negative MTWA (95 percent credible interval, 1.4–5.8) (53). We estimated the quality of life of patients in the 'well' state is 0.745 on the EQ-5D scale (13).

Base Case

The differences in ICER were driven by differences in costs and efficacy (Table 2). A treatment strategy involving ICD therapy in all patients was associated with an ICER of $121,800/QALY compared with medical therapy. A treatment strategy involving the selective use of ICDs based on MTWA test results was associated with an ICER of $108,900/QALY compared with medical therapy. Although neither ICD therapy for all patients or selective ICD therapy were cost-effective compared with medical therapy at willingness-to-pay thresholds of $20,000, $50,000, or $100,000 CAD, selective ICD therapy based on MTWA test results decreased the ICER relative to medical therapy by approximately 10 percent.

Sensitivity Analyses

We examined the robustness of our ICER estimates by varying our model inputs in both one-way and two-way sensitivity analyses (Table 3). The parameters that had the greatest effect of the ICER values were the time horizon, the cost of ICD implantation, the frequency with which ICDs needed to be changed, and the efficacy of ICD therapy (Figure 2). The efficacy of ICD therapy relative to medical therapy had a particularly important effect. Our sensitivity analyses revealed that, under most scenarios, both ICD therapy for all and selective ICD therapy based on MTWA test results were associated with ICERs that were greater than $100,000/QALY. In additional sensitivity analyses, we assumed that all patients who suffered a nonfatal arrhythmic event received an ICD, regardless of treatment strategy. This analysis had similar results as those reported in our base case (data not shown).

We also conducted multivariate probabilistic sensitivity analyses, examining the probability that each treatment strategy was cost-effective while varying the willingness-to-pay threshold from $0/QALY to $200,000/QALY (Figure 3). At a willingness-to-pay of $40,000/QALY, the probability that medical therapy is more cost-effective than the other two strategies was 100 percent. Conversely, ICD therapy for all was cost-effective compared with the other two strategies for willingness-to-pay thresholds of ≥$140,000/QALY. Probabilistic sensitivity analyses also indicated that the probability that the selective use of ICDs is cost-effective compared with medical therapy was 36.6 percent and 1.1 percent at willingness-to-pay thresholds of $100,000/QALY and $50,000/QALY, respectively.

DISCUSSION

Our study was designed to examine the effect of MTWA testing on the cost-effectiveness of ICD therapy for primary prevention in patients with severe left-ventricular dysfunction. We found that both a treatment strategy of ICD therapy for all patients as well as a strategy involving the selective use of ICD therapy based on MTWA test results are not cost-effective compared with medical therapy. Although MTWA modestly improved the cost-effectiveness of ICDs for primary prevention, MTWA testing did not reduce the cost-effectiveness of ICDs to below the willingness-to-pay threshold of $100,000/QALY, the upper limit of the proposed "gray zone" of cost-effectiveness (24). The medical therapy treatment option was the most cost-effective option up to a willingness-to-pay of $140,000/QALY. Consequently, in light of the limited resources available, this economic analysis does not support the unrestricted use of ICDs for primary prevention with the addition of MTWA testing to assist in patient stratification.

Several other diagnostic tests have been proposed for the risk stratification of this patient population. These tests include the use of left-ventricular ejection fraction, ambulatory electrocardiogram (54), QT interval dispersion (46), and electrophysiological testing (2). There remains a need to further investigate the predictive ability and cost-effectiveness of these tests and hopefully identify a cost-effective method to risk stratify this patient population.

Only one other study has examined the effect of MTWA on the cost-effectiveness of ICD therapy. Chan and colleagues (15) also examined MTWA for primary prevention and similarly found that MTWA testing improved the cost-effectiveness of ICD therapy by only a modest $7,000/QALY. Notwithstanding this similarity with our study, the study by Chan et al. had several significant differences with ours. Importantly, they found the baseline ICER for ICD implantation to be $55,800/QALY compared with our result of $121,800/QALY. Their study was conducted using U.S. costs from a societal perspective and, thus, included direct costs and indirect costs, including loss of productivity. Our study was conducted using 2007 CAD from the perspective of a third party payer. Second, their estimates for the predictive ability of MTWA testing were based on a single, large cohort study (16), whereas our MTWA measures our based on a recently completed meta-analysis (53). Third, we have used a more systematic (and conservative) measure of ICD efficacy. This previous study (15), as well as other ICD cost-effectiveness studies (1;41), have used ICD efficacy measures from the MADIT (HR = 0.46) (39) and MADIT-II trials

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Table 2. Results of Primary Cost-Effectiveness Analyses Examining Cost-Effectiveness of Three Treatment Strategies

Treatment Strategy	Lifetime Cost ($1,000s CAD)	QALYs	LYs	ICER (Relative to Medical Therapy) ($1,000s CAD/QALY)	ICER (Relative to Selective ICD Therapy Based on MTWA Test Results) ($1,000s CAD/QALY)
Medical therapy	45.8	4.18	5.63	—	—
Selective ICD therapy[a]	73.8	4.43	5.97	108.9/QALY or 81.3/LYs	—
Primary prevention for all	84.5	4.49	6.05	121.8/QALY or 91.1/LYs	177.4/QALY or 133.3/LYs

[a] The selective ICD therapy treatment strategy involves the implantation of ICDs only in those with non-negative (positive or indeterminate) MTWA test results.
CAD, Canadian dollars; ICD, implantable cardioverter defibrillator; ICER, incremental cost-effectiveness ratio; LYs, life-years; MTWA, microvolt T-wave alternans; QALY, quality-adjusted life-years.

Table 3. One-Way and Two-Way Sensitivity Analyses Examining the Effect of Model Inputs on Estimates of Cost-Effectiveness of Different Treatment Strategies

Variables (range)	Selective ICD Therapy Based on MTWA Test Results vs Medical Therapy ($1,000s CAD/QALY)	ICD Therapy in All Patients vs Selective ICD Therapy Based on MTWA Test Results ($1,000s CAD/QALY)	ICD Therapy in All Patients vs Medical Therapy ($1,000s CAD/QALY)
One-way sensitivity analysis			
Discount rate (0–0.05)	97.4 to 117.2	158.1 to 191.5	108.5 to 130.1
Time horizon (5–15 years)	200.4 to 87.8	361.9 to 120.4	216.2 to 94.1
Cost of ICD (18,630–31,049)	83.6 to 134.1	130.9 to 223.8	92.6 to 151.1
HR (ICD vs. medical therapy) (0.50–0.95)	42.3 to 371.2	68.2 to 670.0	46.9 to 424.3
RR (non-neg vs. neg) in MTWA test (1.4–5.8)	114.1 to 105.6	122.8 to 328.3	116.3 to 131.4
ICD implantation procedure mortality rate (0–0.012)	108.9 to 128.1	177.4 to 275.9	121.8 to 150.2
Baseline annual mortality rate (0.07–0.12)	125.8 to 101.1	226.7 to 151.5	143.1 to 111.4
Utility value in well state (0.5–1)	162.1 to 81.2	263.2 to 132.4	181.2 to 90.8
Frequency of ICD replacement (4–10 years)	144.2 to 75.8	258.0 to 97.9	165.7 to 80.0
MTWA test each 2 years[a]	114.2	148.3	118.7
Two-way sensitivity analysis			
Cost of ICD × HR (ICD vs. medical therapy)	32.7 to 459.5	50.6 to 847.8	36.0 to 528.5
HR (ICD vs. medical therapy) × RR (non-negative vs. negative MTWA) in MTWA test	40.8 to 386.9	47.4 to 1243.7	45.2 to 459.1
HR (ICD vs. medical therapy) × ICD implantation procedure mortality rate	42.3 to 824.2	68.2 to ICD for all dominated	46.9 to 1422.1

[a] We estimated that the proportion of negative results and those who cannot be tested are 0.80 and 0.03, respectively, in subsequent MTWA tests.
CAD, Canadian dollars; HR, hazard ratio; ICD, implantable cardioverter defibrillator; ICER, incremental cost effectiveness ratio; MTWA, microvolt T-wave alternans; QALY, quality-adjusted life-year; RR, relative risk.

(HR = 0.69) (40). In our cost-effectiveness study, we have based our ICD efficacy inputs on the results of a recently completed meta-analysis of all ICD RCTs (HR = 0.81) (23). This discordant measure of efficacy obviously directly increases the ICER associated with its use.

Our study has several important strengths. First, we based our model inputs on the totality of the best available and recent evidence, including several meta-analyses. This includes a recently completed systematic review and meta-analysis of MTWA as a predictor of mortality and severe arrhythmias in patients with severe left-ventricular dysfunction (53). Second, our decision analysis has targeted a clinically important patient population as primary prevention patients represent the majority of the economic burden associated with ICD therapy. Third, our sensitivity analyses demonstrated that, under most reasonable assumptions, our results are consistent.

Our study also has potential limitations. First, as is true with all decision-analyses, our model is based on a certain set of assumptions. However, our sensitivity analyses revealed that our results are robust under all reasonable situations. Second, it has been suggested that patients with negative MTWA should be retested every 1–2 years (4). However, to our knowledge, no study examining the utility of MTWA testing included retesting (53). We, therefore, did not include retesting in our base-case model. We did, however, include retesting every 2 years in our sensitivity analyses. This retesting resulted in additional ICD implantation in the selective

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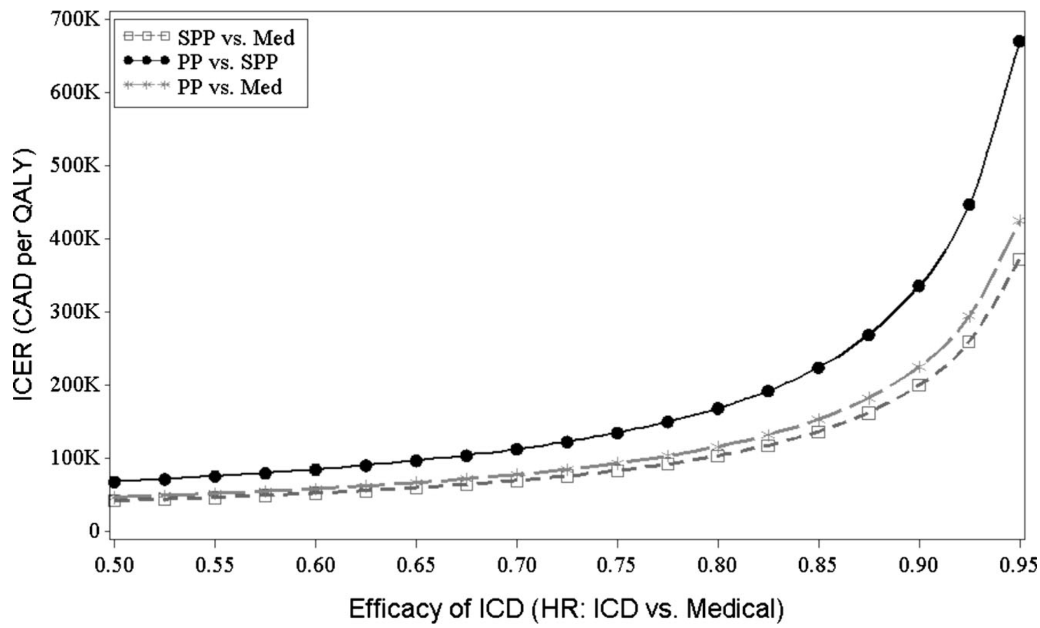

Figure 2. Sensitivity analysis examining the effect of efficacy of implantable cardioverter defibrillators on the cost-effectiveness of three treatment strategies. The three treatment strategies are as follows: (i) medical therapy for all, (ii) ICD therapy for all, and (iii) selective ICD therapy based on non-negative (positive or indeterminate) MTWA test results. CAD, Canadian dollars; ICD, implantable cardioverter defibrillator; Med, medical therapy; PP, primary prevention involving ICD therapy for all; SPP, selective primary prevention based on MTWA test results.

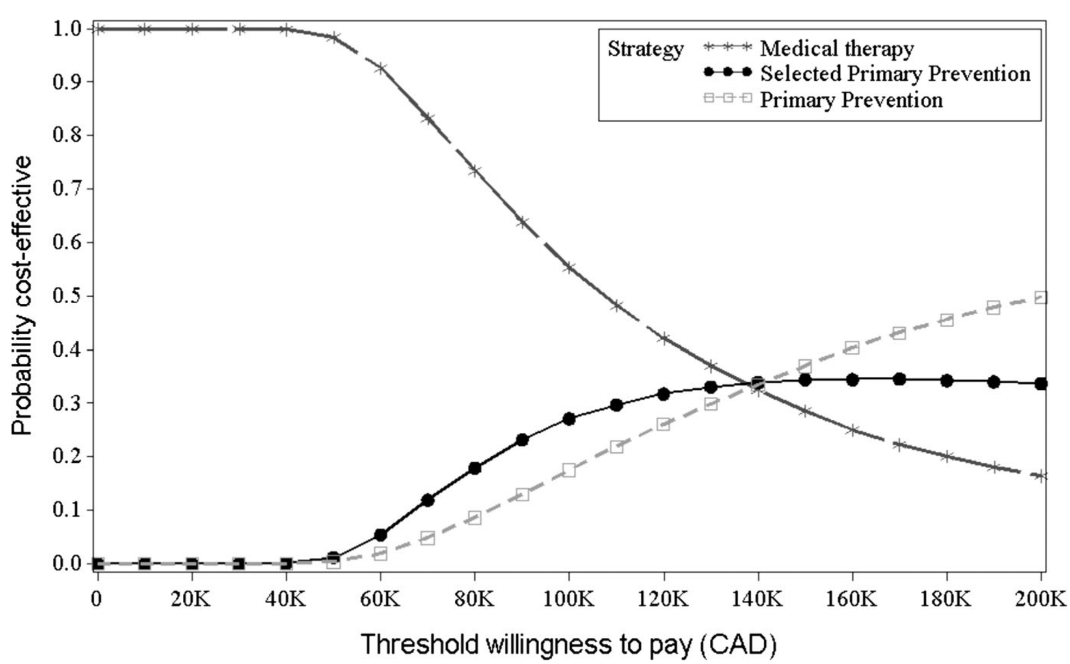

Figure 3. Probabilistic sensitivity analysis examining the effect of the willingness-to-pay threshold on the probability that the treatment strategies are considered cost-effective. The three treatment strategies are as follows: (i) medical therapy for all, (ii) ICD therapy for all, and (iii) selective ICD therapy based on non-negative (positive or indeterminate) MTWA test results. CAD, Canadian dollars.

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primary prevention strategy and higher ICER compared with medical therapy. Thus, our base-case scenario of no retesting represents a conservative assumption. Third, although we used the best available evidence for MTWA efficacy, the quality of this evidence is limited. There remains a need for RCTs to examine the efficacy of MTWA. Finally, this analysis was conducted from the perspective of a third party payer in the context of the Canadian healthcare system, and these results may, therefore, not be generalizable to other healthcare systems.

CONCLUSIONS

MTWA only marginally improves the cost-effectiveness of ICDs for primary prevention in patients with severe left-ventricular dysfunction. Under most scenarios, including the most likely scenario, both ICD therapy for all and selective ICD therapy based on MTWA test results are not cost-effective compared with medical therapy in this patient population. Consequently, there remains an economic need for improved means to effectively identify which patients will derive the greatest benefit from ICD implantation.

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