ORIGINAL ARTICLE

Cost-Effectiveness Analysis of Implantable Cardioverter Defibrillator Therapy for Primary Prevention Patients with Additional Risk Factors in Brazil

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Abstract

Background: Implantable cardiac defibrillators (ICDs) therapy for primary prevention (PP) of sudden cardiac arrest (SCA) is well-established but underutilized globally. The Improve SCA study has identified a cohort of patients called 1.5 primary prevention (1.5PP), based on PP patients with the presence of documented risk factors: non-sustained ventricular tachycardia, frequent premature ventricular contractions, left ventricular ejection fraction < 25%, and pre-syncope or syncope.

Objective: This study evaluated the cost-effectiveness of ICD therapy compared to no ICD among 1.5PP patients in the Brazilian public healthcare system.

Methods: Modified inputs to a published Markov model were applied to compare costs and outcomes of ICD therapy to no ICD therapy from the Brazilian payer's perspective. Mortality and utility estimates were obtained from the IMPROVE SCA trial. Additional effectiveness inputs were sourced from the literature. Cost inputs were obtained from the Brazilian Unified Health System and the Ministry of Health. Costs were discounted at 4.7%; quality-adjusted life years (QALYs) were discounted at 1.45%. This study applied a willingness-to-pay (WTP) value of three times Brazil's gross domestic product (GDP) in 2017, R$105,723 (Brazilian Real).

Results: The total discounted lifetime costs for ICD therapy were R$100,920 compared to R$43,866 for no ICD therapy. Total discounted QALYs for ICD therapy and no ICD therapy were 9.85 and 7.15, respectively. The incremental cost effectiveness ratio was R$21,156 per QALY and less than the R$105,723 WTP threshold. Results from sensitivity analyses were consistent with base case results.

Conclusions: ICD therapy compared to no ICD therapy is cost-effective in the 1.5PP population in Brazil.

Keywords: Cardiovascular Diseases/prevention andcontrol; Defibrillators,Implantable/economy; Cost-Effectiveness Evaluation; Technology Assessment, Biomedical; Death, Sudden Cardiac; Health Evaluation.

Introduction

Evidence for the use of implantable cardioverter defibrillators (ICDs) for primary prevention of sudden cardiac arrest (SCA) in patients with moderately symptomatic heart failure and reduced systolic function has been well-established through multiple randomized clinical trials [1,2] and confirmed in real-world observational evidence.[3] This evidence has led to strong recommendations for ICD use in society guidelines[4,5] and has been leveraged to establish the cost-effectiveness of ICD therapy in multiple healthcare systems.[6,7] Despite this strong evidence base, ICD therapy remains underutilized globally, due at least in part to cost considerations and the lack of reimbursement.[8]

The Improve SCA study has identified a high-risk subset of primary prevention patients called 1.5 primary prevention (PP) based on the presence of at least one of the following documented risk factors: non-sustained ventricular tachycardia (NSVT), frequent premature

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ventricular contractions (PVCs) >10/h, left ventricular ejection fraction (LVEF) <25%, pre-syncope, or syncope.[9] Improve SCA patients with 1.5 PP characteristics were found to have a higher rate of treatment with appropriate therapy than PP patients, and when treated with an ICD, 1.5 PP patients experienced a 49% relative risk reduction in all-cause mortality compared to normal PP patients.[10]

While the cost-effectiveness of ICD therapy for primary prevention patients has been established, the cost-effectiveness of ICD therapy for 1.5 PP patients is not well-known. The 1.5 PP cohort could be used to prioritize health care resources in geographies where such resources are insufficient to cover the full PP population. To that end, this study sought to estimate the lifetime cost and benefits of ICD therapy in the 1.5 PP patient population in Brazil, where ICD therapy is underutilized but may be cost-effective.[11] To the best of our knowledge, this is the first evaluation of the cost-effectiveness of ICD therapy compared to no ICD therapy among 1.5 PP patients from the perspective of the Brazilian public healthcare system.

Methods

An existing Markov decision model was applied to estimate the lifetime cost, quality of life, survival, and incremental cost-effectiveness of ICD therapy versus no ICD therapy for a Brazilian population at risk for SCA (1.5 PP).[6] No ICD therapy was selected as the control, rather than pharmacologic therapy, based on SCD-HeFT study findings that indicated no significant difference in the risk of death between treatment with amiodarone and treatment with a placebo.[1] This evaluation was conducted in the setting of the Brazilian public healthcare system, where health technology assessments are overseen by the National Commission for the Incorporation of Technology (CONITEC).[12] Model inputs are shown in Table 1, and the model analysis was performed in Microsoft Excel, the details of which are described below.

Model Structure

The model follows a simulated cohort of 1,000 patients with a standard indication for PP ICD therapy and at least one 1.5 PP risk factor. The model is structured as a decision tree with two treatment arms, ICD therapy or no ICD therapy, followed by consecutive Markov models (Figure 1). Patients who enter the model in the ICD arm are at an initial risk of operative death or survival. Patients who survive the ICD surgery enter the Markov model in the well state. From the well state, ICD patients stay well or progress to ICD complications, sudden cardiac death, non-sudden cardiac death, non-cardiac death, or unknown death. Patients remain in the same state or progress to a different state at the beginning of each cycle, except for the complication state. Patients who experience an ICD complication remain in the complication state for only one cycle, then progress to continued ICD therapy or discontinued ICD therapy. In the event of therapy discontinuation, ICD patients stay well without ICD treatment or progress to sudden cardiac death, non-sudden cardiac death, non-cardiac death, or unknown death. Patients in the no ICD arm enter the model in a healthy state and remain well or progress to sudden cardiac death, non-sudden cardiac death, non-cardiac death, or unknown death.

Patients incur costs and effects by progressing through the model in monthly increments over a lifetime (420 months); a lifetime perspective allows the model to account for all costs incurred by patients that survive without a sudden cardiac arrest event. Patients in both treatment arms incur monthly inpatient and outpatient costs. In the ICD therapy arm, patients also incur the cost of the device and ICD implant procedure. ICD patients who remain alive long enough to require a device replacement incur additional device and procedure costs at the time of replacement. ICD patients may receive an inappropriate shock or other ICD-related complication that incurs a cost and affects treatment adherence. After experiencing an inappropriate shock or other ICD-related complication, patients remain in the ICD therapy arm, receiving ICD treatment, or progress to discontinued use of ICD therapy. In this study it was assumed that ICD patients who discontinue their use of ICD therapy have the same mortality risk as patients in the no ICD arm.

Clinical Data

Clinical inputs to the model were based on Improve SCA clinical study results, the United States (US) National ICD registry, literature, and administrative claims-based analyses. Improve SCA[10] is the largest ICD study conducted in emerging markets and has enrolled patients from 17 different countries. The non-randomized study tracked outcomes in patients with primary, secondary, and 1.5 PP indications for ICD therapy. The probability of implant-related operative death (0.0002) was based

Table 1 – Model Input Parameters

Model Parameters	Base Case Value	Standard Error	Distribution	Reference
Monthly Risk of Mortality (ICD Therapy)				
Sudden cardiac death	0.0007	0.0003	Beta	(10)
Non-sudden cardiac death	0.0014	0.0004	Beta	
Non-cardiac death	0.0005	0.0003	Beta	
Unknown death	0.0013	0.0003	Beta	
Monthly Risk of Mortality (No ICD Therapy)				
Sudden cardiac death	0.0028	0.0005	Beta	(10)
Non-sudden cardiac death	0.0021	0.0004	Beta	
Non-cardiac death	0.0010	0.0004	Beta	
Unknown death	0.0014	0.0004	Beta	
ICD-Related Probabilities				
Initial operative death	0.0002	0.00002	Beta	(13)
Continue ICD therapy after shock	0.0034	0.0002	Beta	(2,14,15,19,35,36)
Discontinue ICD therapy after shock	0.0001	0.00007	Beta	
Lead replacement (initial implant)	0.0004	0.0005	Beta	(18,22)
Lead replacement (replacement implant)	0.0008	0.0009	Beta	(23)
Lead dislodgement (initial implant)	0.018	0.0012	Beta	(18,22)
Lead dislodgement (replacement implant)	0.005	0.0009	Beta	(23)
ICD infection (initial implant)	0.0244	0.0049	Beta	(17)
ICD infection (replacement implant)	0.0432	0.0064	Beta	(20)
Costs, 2018 Brazilian Reals (R$)				
ICD implant procedure (initial)	R$1,738			(37)
ICD implant procedure (replacement)	R$1,738			
Lead replacement	R$827			
ICD generator removal	R$742			
ICD lead dislodgement	R$742			
ICD inappropriate shock	R$500			
ICD infection	R$30,000			
Monthly inpatient cost	R$166			
Monthly outpatient cost	R$354			
Utility				
Annual utility of heart failure patient	0.837	0.007	Beta	(10)
ICD complication state	0.7408	0.0112	Beta	

Abbreviations: ICD, Implantable Cardioverter-Defibrillator

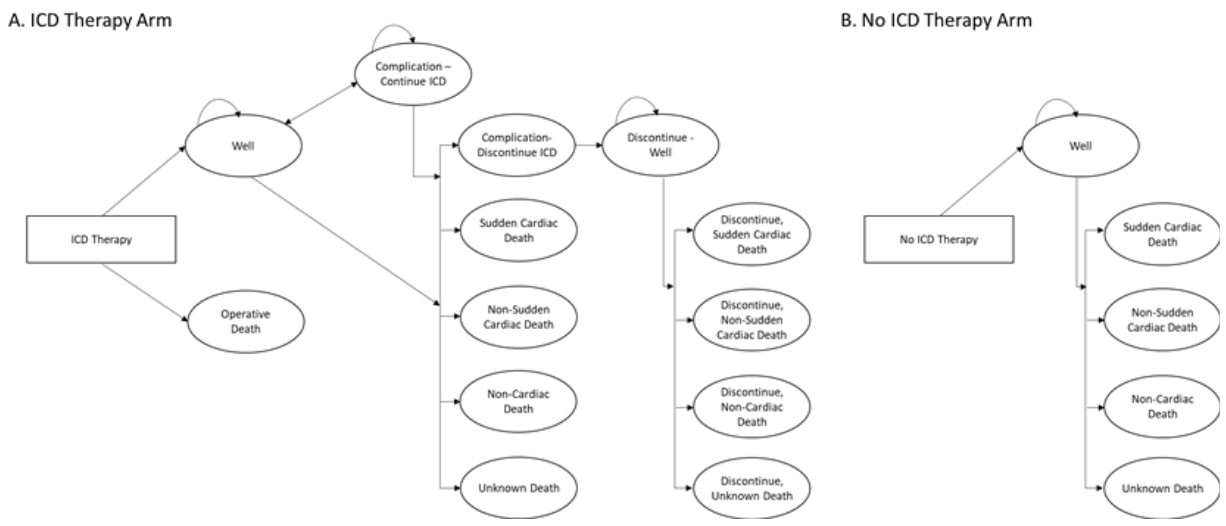

Figure 1 – Model schematic. Model states are represented by ovals; arrows indicate transitions between states. ICD, implantable cardioverter defibrillator. Panel A shows model states in ICD therapy arm. Panel B shows model states in the control arm.

on the US National ICD Registry and applied only to the ICD treatment arm.[13] The probabilities of sudden cardiac death, non-sudden cardiac death, non-cardiac death, or unknown death were based on results from the Improve SCA study. Inappropriate shock probability was derived from a weighted average based on the MADIT RIT, ADVANCE III, PROVIDE, and PainFree SST clinical trials that demonstrated a reduction in inappropriate shock rates due to device programming. [2,14-16] Probabilities of lead failure or dislodgement after initial implant were based on studies of annual incidence of lead failure and ICD lead dislodgement at one year after implant, 0.45% and 1.8% respectively.[17,18] Probability of lead dislodgement or replacement after ICD replacement was based on data from the REPLACE registry, which reported a 1% combined dislodgement and replacement rate.[19]. It was assumed that half of the combined rate reported in the REPLACE registry could be attributed to lead failure (0.5%) and half could be attributed to lead dislodgement (0.5%). The one-year probability of lead infection after initial implant (1.22%) and device replacement (2.16%) was also estimated by means of a retrospective data analysis based on administrative claims from a large US insurance company.[20] The lifetime risk of lead infection after the first year of an initial or replacement implant was double the value of the one-year claims-based probability.[17,18]

Economic Data

Device related costs and long-term health care use costs associated with heart disease were modeled over a lifetime. To represent the perspective of the Brazilian public healthcare system, several cost inputs to the model were based on the medical procedure price list published by the Brazilian Unified Health System in 2017.[21,22] The 2017 costs were updated to 2018 Brazilian Reals (R$) using the Brazil-specific average inflation rate based on the consumer price index, 3.66%. The cost of inappropriate shock was derived from an analysis of procedures commonly performed at encounters for shocks.[23] Long-term inpatient and outpatient costs were estimated from a publication on the costs of heart failure in Colombia .[24] To obtain ICD-specific costs, the long-term inpatient costs were multiplied by the average number of hospitalizations per year for patients recommended for ICD therapy based on the SCD-HeFT trial. Costs were discounted at 4.7%; quality-adjusted life years (QALYs) were discounted at 1.45%, according to CONITEC guidelines.[25].

Health-Related Quality of Life

Quality of life was based on an analysis of EQ-5D data collected in the PainFree SST clinical trial. Brazil-specific utilities were derived by mapping each

patient's EQ-5D state, using country specific societal preferences.[26] The baseline utility for both treatment arms was assumed to be the same. Patients who experienced an ICD-related complication received a short-term utility decrement of 0.096, which is equivalent to 3.5 days.[27]

Construction of the ICER (w/WTP) and Sensitivity Analysis

Total lifetime costs and quality-adjusted life years (QALYs) between ICD therapy and no ICD therapy were simulated to calculate the incremental cost effectiveness ratio (ICER). Both undiscounted and discounted results were calculated to best represent the time value of costs and outcomes. One-way sensitivity analysis and probabilistic sensitivity analysis were conducted to assess the impact of model inputs and parameter uncertainty. A willingness-to-pay (WTP) threshold value of R$105,723 was used for this model. Our WTP value reflects an amount equal to three times the per capita gross domestic product (GDP) in Brazil in 2018, as recommended by the World Health Organization (WHO).[28]

Results

Base case scenario

Table 2 shows the results of the base-case scenario. ICD therapy for 1.5 prevention resulted in a benefit of 11.79 (discounted) and 13.41 (undiscounted) life-years saved, while no ICD therapy resulted in a benefit of 8.54 and 9.46 life-years saved, respectively. Measured in QALYs, the discounted benefit from ICD therapy is 9.85 and 7.15 from no ICD therapy, resulting in an incremental effectiveness of 2.70 QALYs. Discounted costs from ICD therapy and no ICD therapy account for R$100,920 and R$43,866, respectively. The ICER for ICD therapy is R$21,156 per QALY; ICD therapy for 1.5 prevention is cost-effective at R$105,723, three times the Brazilian GDP per capita WTP threshold in the base case scenario. Moreover, ICD therapy is *highly* cost-effective at the R$35,241 threshold of one GDP per capita.

Sensitivity analyses

Results of the one-way sensitivity analyses show that costs per QALY are more responsive to the

Table 2 – Base case scenario results

Base Case Scenario Results		ICD therapy	No ICD Therapy
Undiscounted	Aggregated costs	R$139,120	R$59,008
	Differential cost	R$80,112	
	Effectiveness (life-years saved)	13.41	9.46
	Effectiveness (QALY saved)	11.20	7.91
	Differential effectiveness (QALY)	3.28	
	ICER (costs per QALY saved)	R$24,413	
Discounted	Aggregated costs	R$100,920	R$43,866
	Differential cost	R$57,055	
	Effectiveness (life-years saved)	11.79	8.54
	Effectiveness (QALY saved)	9.85	7.15
	Differential effectiveness (QALY)	2.70	
	ICER (Costs per QALY saved)	R$21,156	

Abbreviations: ICD: Implantable Cardioverter-Defibrillator; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio.

discount rate, age at implant, and conventional mortality (Figure 2); however, the low values of the discount rate resulted in a change in costs per QALY, which proved to be substantially lower than those resulting from the high value. No values of the one-way sensitivity analysis are under the incremental costs per QALY above the WTP thresholds of one or three times the Brazilian GDP per capita.

Figure 3 shows the simulated costs per QALY of the probabilistic sensitivity analysis, where each dot corresponds to the resulting cost per QALY of a model iteration, and the continuous line shows the WTP threshold of R$105,723 per QALY. Results show a mean cost per QALY of R$21,258 (median cost per QALY of R$21,250, 95-percent Credible Interval [R$15,293 – R$46,619] per QALY) after 1,000 iterations; 99.8% and 92.9% of the simulations result in costs per QALY below the three (long-dashed lined in Figure 3) and one (short-dashed line in Figure 3) times GDP per capita WTP threshold, respectively.

Discussion

Our results indicate that ICD therapy is highly cost effective for 1.5 PP patients in the Brazilian healthcare system, which at an ICER of R$21,156 per QALY is less than one-third the WTP value of R$105,723 (three times GDP per capita). This finding is robust, with a sensitivity analysis indicating that the cost effectiveness is preserved in virtually all reasonable variations of model inputs.

Prior estimates of the cost effectiveness of ICD therapy have been performed in the broader primary prevention population. Mark et al.[7] performed an analysis of the randomized SCD-HeFT trial and found ICD therapy to be economically attractive at $41,530/QALY (at a WTP of $100,000) in the US healthcare system. An analysis in the healthcare system of a European country using a meta-analysis of six randomized PP trials and the same model used in this study showed similar results.[6]). The cost-effectiveness of ICD therapy has also been confirmed in

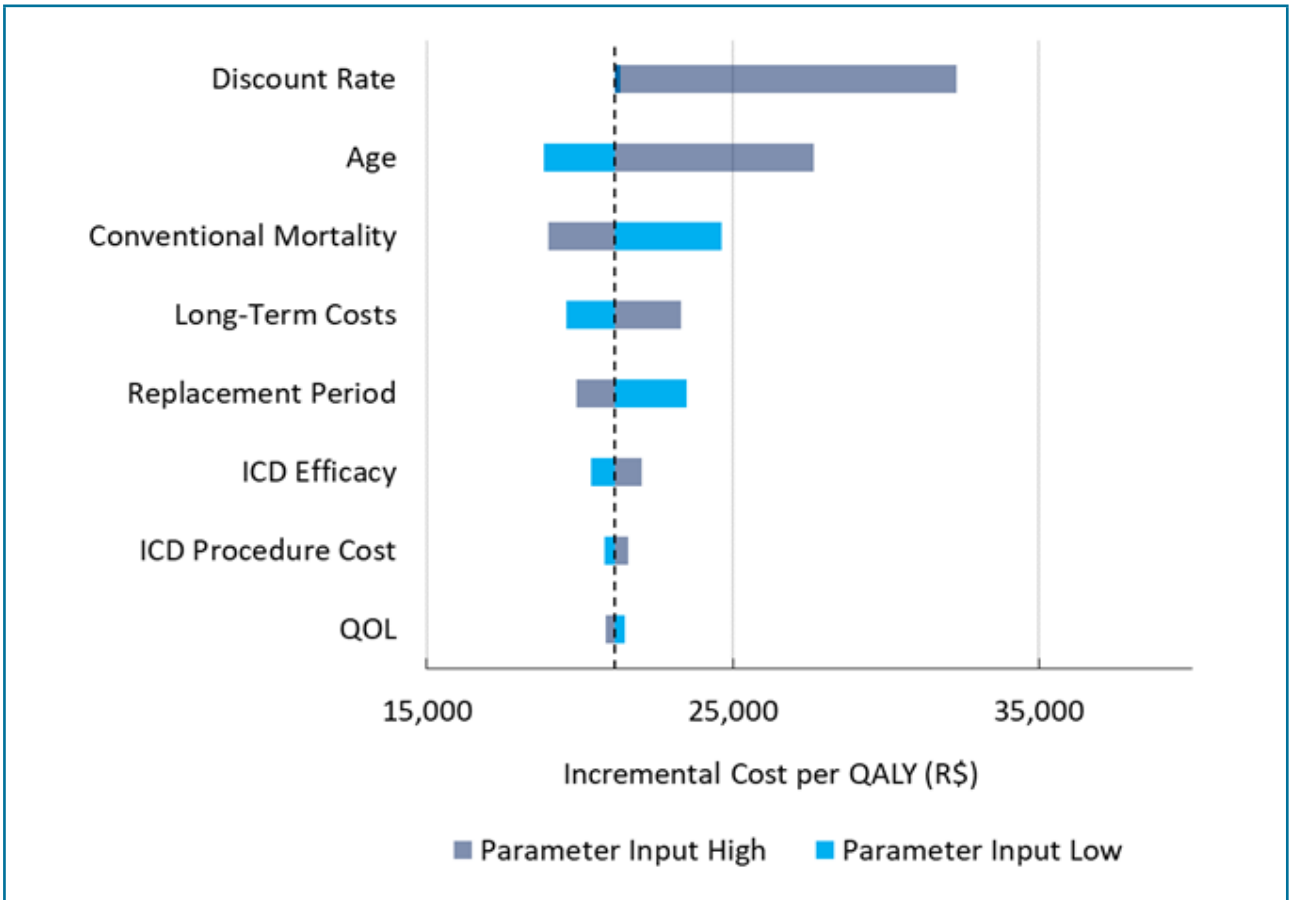

Figure 2 – One-way sensitivity tornado chart. A tornado chart of the range of ICER across high and low parameter input values. Each input was varied, with all others held constant. All ICER values remained below the willingness to pay threshold.

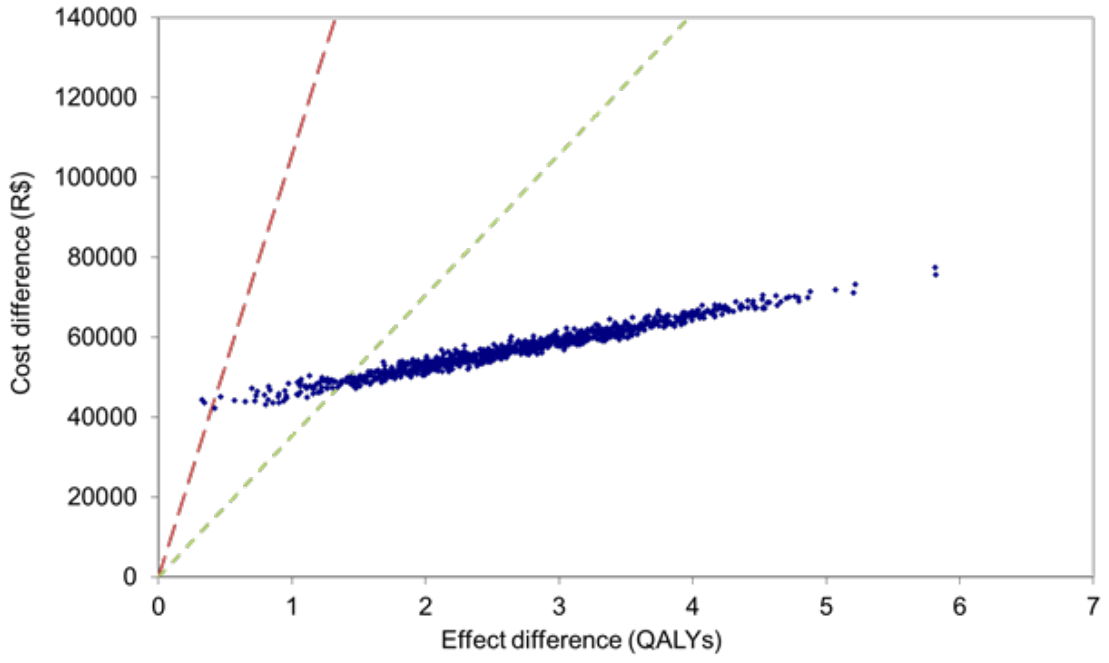

Figure 3 – Probabilistic Sensitivity Analysis scatterplot. The range of ICER given probabilistic variation in model inputs. All ICER values remained below the willingness to pay threshold. Dots represent individual ICER data points, the green dashed line represents WTP at 1x GDP per capita, the red dashed line represents WTP at 3x GDP per capita.

a real world setting outside of clinical trials.[29] However, Ribeiro et al.[30] performed an evaluation specific to the Brazil healthcare system, concluding that the ICER was elevated in both the public (R$68,318/QALY) and private (R$90,942/QALY) perspectives relative to the WTP, based on three times GDP per capita in 2007 (R$40,545).

The cost effectiveness of ICD therapy in Brazil has clearly improved since the 2010 assessment, and this can be explained by several factors. First, the model is highly sensitive to the longevity of ICD therapy, which has improved significantly over time. Ribeiro et al.[30] assumed a replacement interval of five years, based on expectations of devices manufactured in the 1990's, while the current model assumes a median replacement interval of 9.5 years, reflecting advancements in device longevity reported in both the literature and recent product performance reports from device manufacturers.[21,31] Extended longevity results in fewer ICD reimplantation costs in the model. Second, while this report has used the same approach as the WTP (WHO recommendation of three times GDP per capita), the GDP per capita in Brazil indicates a WTP that has more than doubled when compared to 2007 levels (R$105,723 versus R$40,545). Economic growth increases the ability to extend one's life saving benefits of ICD therapy to more people. Third, the model is sensitive to the efficacy of ICD therapy, which has improved relative to the prior report, reducing the number needed to treat in order to save one life from 13 to 10[10,32]. Other factors, such as the cost of devices and related hospitalizations may also have contributed to the observed differences between the current and former reports of cost-effectiveness.

Despite convincing evidence from multiple randomized clinical trials [1,3,33], strong recommendations in international society guidelines,[4], and corroboration of mortality benefits in the Brazilian healthcare system,[11] ICD therapy remains underutilized. In a seven-year period, 3,295 ICD implants were reported within the Brazilian National Health System .[11] placing the annual rate of ICD use at 2-3 implants per million in the Brazilian population. By comparison, the average rate of ICD implantation in Europe is approximately 100 implants per million.[34] To the extent that economic factors play a role, this study provides information for decision makers to direct

scarce resources first toward those who can benefit the most. While it remains cost effective to treat the PP population with ICD therapy, from an economic standpoint, a priority should be placed on treating patients with a 1.5 PP indication.

It is important, however, to acknowledge the limitations of this analysis. The Improve SCA trial was not randomized, but the mortality analysis from the trial adjusted for baseline characteristics are likely to have an impact on mortality, and the effectiveness of ICD therapy has been replicated in non-randomized observational trials. Costs and benefits were modeled beyond the timeline of direct observation in the Improve SCA trial; however, this is a standard approach in economic modeling and necessary for the proper perspective for decision makers. Patients in the Improve SCA trial were not all from Brazil, yet they were from countries of similar economic development. Further, ICD therapy application is well developed and largely standardized around the world. Conclusions from this report are not generalizable beyond the 1.5 PP population in the Brazilian public healthcare system.

Conclusion

Developments over time, including identification of the 1.5 PP population of high-risk patients, improved ICD longevity, and economic growth has led to improved cost effectiveness of ICD therapy. ICD therapy in this context should be considered highly cost effective and represents an economically efficient way to address the underutilization of ICD therapy in indicated patients in Brazil.

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Potential Conflict of Interest

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Author contributions

Conception and design of the research: Wherry K, Holbrook R. Acquisition of data: Fujii F. Analysis and interpretation of the data: Wherry K, Holbrook R, Fujii F. Statistical analysis: Wherry K, Holbrook R, Higuera L. Writing of the manuscript: Wherry K, Holbrook R, Higuera L. Critical revision of the manuscript for intellectual content: Rodriguez D, Fujii F.

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