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To cite this article: Lucas Higuera, Reece Holbrook, Kael Wherry, Diego A. Rodriguez, Alejandro Cuesta, Juan Valencia, Julián Arcos & Agustín López Gómez (2021) Comparison of cost-effectiveness of implantable cardioverter defibrillator therapy in patients for primary prevention in Latin America: an analysis using the Improve SCA study, Journal of Medical Economics, 24:1, 173-180, DOI: [10.1080/13696998.2021.1877451](https://doi.org/10.1080/13696998.2021.1877451)

To link to this article: <https://doi.org/10.1080/13696998.2021.1877451>



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Published online: 04 Feb 2021.



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ORIGINAL RESEARCH



# Comparison of cost-effectiveness of implantable cardioverter defibrillator therapy in patients for primary prevention in Latin America: an analysis using the Improve SCA study

Lucas Higuera<sup>a</sup>, Reece Holbrook<sup>a</sup>, Kael Wherry<sup>b</sup>, Diego A. Rodriguez<sup>c</sup>, Alejandro Cuesta<sup>d</sup> , Juan Valencia<sup>e</sup>, Julián Arcos<sup>f</sup> and Agustín López Gómez<sup>g</sup>

<sup>a</sup>Health Economics and Outcomes Research, CRHF, Medtronic plc, Mounds View, MN, USA; <sup>b</sup>Health Economics and Outcomes Research, Diabetes, Medtronic plc, Northridge, CA, USA; <sup>c</sup>Cardiology - Electrophysiology, Fundación Cardioinfantil, Bogotá DC, Colombia; <sup>d</sup>Centro Cardiovascular Universitario, Hospital de Clínicas, Universidad de la República, Montevideo, Uruguay; <sup>e</sup>Reimbursement and Health Economics, Latin America, Medtronic plc, Miami, FL, USA; <sup>f</sup>Clinical Affairs, Latin America, Medtronic plc, Bogotá DC, Colombia; <sup>g</sup>Reimbursement, Andean Region, Medtronic plc, Bogotá DC, Colombia

## ABSTRACT

**Objective:** The mortality benefit of implantable cardioverter defibrillators (ICDs) for primary prevention (PP) of sudden cardiac arrest (SCA) has been well-established, but ICD therapy remains globally underutilized. The results of the Improve SCA study showed a 49% relative risk reduction in all-cause mortality among ICD patients with 1.5 primary prevention (1.5PP) characteristics (patients with one or more risk factors,  $p < 0.0001$ ). We evaluated the cost-effectiveness of ICD compared to no ICD therapy among patients with 1.5PP characteristics in three Latin American countries and analyzed the factors involved in cost-effectiveness.

**Methods:** We used a published Markov model that compares costs and outcomes of ICD to no ICD therapy from local payers' perspective and included country-specific and disease-specific inputs from the Improve SCA study and current literature. We used WHO-recommended willingness-to-pay (WTP) thresholds to assess cost-effectiveness and compared model outcomes between countries.

**Results:** Incremental costs per QALY (quality-adjusted life year) saved by ICD compared to no ICD therapy are Colombian Pesos COP\$46,729,026 in Colombia, Mexican Pesos MXN\$246,016 in Mexico, and Uruguayan Pesos UYU\$1,213,614 in Uruguay in the base case scenario; all three figures are between 1–3-times GDP per capita for each country. One-way and probabilistic sensitivity analyses confirm the base case scenario results. Non-cardiac accumulated deaths are lower in Mexico, resulting in a comparatively increased cost-effective ICD therapy.

**Limitations:** The Improve SCA study was not randomized, so clinical results could be biased; however, measures were taken to reduce this bias. Costs and benefits were modelled beyond the timeline of direct observation in the Improve SCA study.

**Conclusions:** ICD therapy is cost-effective in Mexico and Uruguay and potentially cost-effective in Colombia for a 1.5PP population. Variability in ICER estimates by country can be explained by differences in non-cardiac deaths and cost inputs.

## ARTICLE HISTORY

Received 19 October 2020  
Revised 10 December 2020  
Accepted 11 January 2021

## KEYWORDS

Implantable cardioverter defibrillator; primary prevention; cost-effectiveness analysis; Latin America; comparison of cost-effectiveness

## JEL CLASSIFICATION CODES

I110 Analysis of Health Care Markets; D610 Allocative Efficiency; Cost-Benefit Analysis

## Introduction

Implantable cardioverter defibrillators (ICD) therapy has been well-established as the gold standard for prevention of sudden cardiac death (SCD) in a primary and secondary prevention population with a high risk of ventricular tachyarrhythmias (VT/VF)<sup>1–3</sup>. Primary prevention ICD therapy efficacy in patients with moderately symptomatic heart failure and reduced systolic function is well-established through multiple randomized clinical trials<sup>4,5</sup> and confirmed in real-world observational evidence<sup>1</sup>. This evidence has been used to establish strong recommendations for ICD use in society guidelines internationally<sup>2,3</sup> and has been leveraged to

establish the cost-effectiveness of ICD therapy in multiple healthcare systems<sup>6,7</sup>. However, ICD therapy for SCD prevention remains underutilized globally, due in part to a lack of reimbursement and cost considerations.

The Improve SCA study<sup>8</sup> was a prospective, non-randomized, non-blinded, multi-center, global study which enrolled ( $n = 3,889$ ) patients from Asia, Latin America, Eastern Europe, the Middle East, and Africa, and categorized patients by their prevention level (primary and secondary) and by ICD implantation condition (with and without an ICD). This study identified a high-risk subset of patients in primary prevention called 1.5 primary prevention (1.5PP) based on the presence of at least one of the following documented risk factors:

**CONTACT** Lucas Higuera  [lucas.figuera@medtronic.com](mailto:lucas.figuera@medtronic.com)  Medtronic plc, 8200 Coral Sea St NE, Mounds View, MN, 55112, USA

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non-sustained ventricular tachycardia (NSVT), frequent premature ventricular contractions (PVCs) >10/h, left ventricular ejection fraction (LVEF) <25%, pre-syncope, or syncope<sup>9</sup>. The objectives of this study were to compare the time to first therapy between patients with 1.5PP characteristics and patients with primary (risk of sustained ventricular arrhythmias) and secondary prevention characteristics (history of sustained ventricular arrhythmias), and to compare the mortality rates between patients with 1.5PP characteristics with an ICD and those without an ICD. Improve SCA patients with 1.5PP characteristics were found to have a higher rate of appropriate therapy than patients with primary prevention characteristics. Moreover, patients with 1.5PP characteristics with an ICD experienced a 49% relative risk reduction in all-cause mortality compared to patients without an ICD (HR = 0.51; 95% CI = 0.40–0.66,  $p < 0.001$ )<sup>8</sup>.

Countries in Latin America allocate sizeable public resources towards the financing of defined health benefit plans (of public health expenditures, more than 70% in Colombia, 72% in Uruguay, and 28.1% in Mexico are allocated towards this goal), which have become instruments of equity in health spending<sup>10</sup>. The healthcare systems of Colombia, Mexico, and Uruguay, despite having different levels of segmentation, centrally define benefits and reimbursement levels within their health benefit plans<sup>10</sup>. Health technology assessments and cost-effective analysis are policy mechanisms that improve the efficiency of these plans. Previous analyses have found ICD therapy to be cost-effective for the primary prevention population in developed countries, but it is not clear how measures of cost-effectiveness of ICD therapy differ by country, or which factors explain these differences. This study calculates and compares the cost-effectiveness of ICD therapy in the 1.5PP population in Colombia, Mexico, and Uruguay using a combination of global clinical inputs and local costs and competing mortality inputs, following local guidelines for health technology assessments.

## Methods

In this analysis, we used an existing Markov decision model<sup>6</sup> to estimate the lifetime cost, quality-of-life, survival, and incremental cost-effectiveness of ICD therapy versus no ICD therapy for a population at risk for SCA (1.5PP) for each country. A previous study (SCD-HeFT) found no significant difference in the risk of death between treatment with amiodarone and treatment with a placebo<sup>4</sup>; hence, no ICD therapy was selected as the control instead of pharmacologic based therapy, as the latter only increases costs compared to the former. Model inputs are shown in Table 1 and described in detail below. The model analysis was performed in Microsoft Excel.

### Model structure and model inputs

A standard indication for primary prevention ICD therapy and at least one 1.5PP risk factor in a simulated cohort of 1,000 patients is used in this model. The starting age for this cohort is 60.2 years old, and it is 77.6% male; these

characteristics follow the cohort of patients with 1.5PP characteristics in the Improve SCA study. The model is structured as a Markov model with two treatment arms, ICD therapy or no ICD therapy (Figure 1); patients in the ICD therapy arm can face ICD complications and decide to continue or discontinue ICD therapy. A more detailed account of the model paths is described in the literature<sup>6</sup>. We assumed that ICD patients who discontinue ICD therapy have the same overall mortality risk as patients in the no ICD arm. Patients incur costs and outcomes by progressing through the model in monthly increments over a lifetime (420 months), which allows the model to account for all costs incurred by patients that survive without a sudden cardiac arrest event.

Inputs to the model that are shared in all country analyses were based on the Improve SCA clinical study<sup>8</sup> results, current literature, and administrative claims-based analyses. The probability of implant-related operative death (0.0002) was based on the US National ICD Registry and applied only to the ICD treatment arm<sup>11</sup>, and the probabilities of other forms of death during the study follow-up duration (sudden cardiac death, non-sudden cardiac death, non-cardiac death, and unknown death) were based on results from the Improve SCA study<sup>8</sup>; it is assumed that these probabilities are the same in all three countries in the analysis. Inappropriate shock probability was derived from a weighted average based on results from existing clinical trials (MADIT RIT, ADVANCE III, PROVIDE, and PainFree SST) that showed reductions in inappropriate shock rates due to device programming<sup>12–14</sup>. Probabilities of lead failure or dislodgement after initial implant were based on studies of the annual incidence of lead failure and ICD lead dislodgement at 1 year after implant<sup>15,16</sup>. The probability of lead dislodgement or replacement after ICD replacement was based on data from the REPLACE registry<sup>17</sup>. Given the lack of information about the specific probabilities of lead failure and lead dislodgement, in order to not prioritize one complication over the other it was assumed that half of the combined rate reported in the REPLACE registry could be attributed to lead failure and half could be attributed to lead dislodgement. The probabilities of lead infection after initial implant and after replacement were estimated with administrative healthcare claims from a large US insurer<sup>18</sup>. After the first year of an initial or replacement implant, the lifetime risk of lead infection was double the value of the 1-year claims-based probability<sup>19</sup>. Lifetime mortality rates were obtained from local actuarial life tables and are used to adjust the non-cardiac mortality rates. All model inputs are listed in Table 1.

### Economic data

Device-related and the long-term healthcare utilization costs associated with heart disease were modelled over a patient's lifetime. Cost inputs are country-specific and reflect the healthcare prices and productivity of each country (Table 2). In Colombia, procedural costs of initial ICD implant, subsequent revision or replacement, and ICD-related complications (infection and dislodgement) which include: cost of devices, admission fee, drug fee, examination etc., were derived from

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	8
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	8
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	11
Continue ICD therapy after shock	0.0034	0.0002	Beta	5,12,13,17,25,33
Discontinue ICD therapy after shock	0.0001	0.00007	Beta	
Lead replacement (initial implant)	0.0004	0.0005	Beta	15,16
Lead replacement (replacement implant)	0.0008	0.0009	Beta	21
Lead dislodgement (initial implant)	0.018	0.0012	Beta	15,16
Lead dislodgement (replacement implant)	0.005	0.0009	Beta	21
ICD infection (initial implant)	0.0244	0.0049	Beta	18,19
ICD infection (replacement implant)	0.0432	0.0064	Beta	
Utility				
Annual utility of heart failure patient	0.837	0.007	Beta	8
ICD complication state	0.7408	0.0112	Beta	
Model input parameters, country-specific				
Model parameters				
Costs, LCU				
Initial ICD implant procedure	\$2,157,233 <sup>a</sup>	\$161,205 <sup>a</sup>		Uruguay
Replacement ICD implant procedure	\$2,157,233 <sup>a</sup>	\$161,205 <sup>a</sup>		\$456,482 <sup>a</sup>
Lead replacement	\$4,524,463 <sup>b</sup>	\$68,583 <sup>b</sup>		\$331,689 <sup>b</sup>
ICD generator removal	\$1,473,095 <sup>a</sup>	\$68,583 <sup>c</sup>		\$232,781 <sup>a</sup>
ICD lead dislodgement	\$1,473,095 <sup>a</sup>	\$68,583 <sup>c</sup>		\$173,644 <sup>b</sup>
ICD inappropriate shock	\$2,487,381 <sup>c</sup>	\$45,131 <sup>d</sup>		\$107,987 <sup>a</sup>
ICD infection	\$25,896,485 <sup>a</sup>	\$76,313 <sup>a</sup>		\$56,164 <sup>c</sup>
Monthly inpatient cost	\$703,148 <sup>e</sup>	\$2,954 <sup>e</sup>		\$130,233 <sup>a</sup>
Monthly outpatient cost	\$399,473 <sup>d</sup>	\$2,449 <sup>e</sup>		\$11,521 <sup>b</sup>
Discount factor (%)	5.0 <sup>e</sup>	5.0 <sup>f</sup>		\$2,989 <sup>b</sup>
Costs	5.0 <sup>e</sup>	5.0 <sup>f</sup>		5.0 <sup>d</sup>
Outcomes				5.0 <sup>d</sup>
Colombia				
Initial ICD implant procedure	\$2,157,233 <sup>a</sup>	\$161,205 <sup>a</sup>		
Replacement ICD implant procedure	\$2,157,233 <sup>a</sup>	\$161,205 <sup>a</sup>		
Lead replacement	\$4,524,463 <sup>b</sup>	\$68,583 <sup>b</sup>		
ICD generator removal	\$1,473,095 <sup>a</sup>	\$68,583 <sup>c</sup>		
ICD lead dislodgement	\$1,473,095 <sup>a</sup>	\$68,583 <sup>c</sup>		
ICD inappropriate shock	\$2,487,381 <sup>c</sup>	\$45,131 <sup>d</sup>		
ICD infection	\$25,896,485 <sup>a</sup>	\$76,313 <sup>a</sup>		
Monthly inpatient cost	\$703,148 <sup>e</sup>	\$2,954 <sup>e</sup>		
Monthly outpatient cost	\$399,473 <sup>d</sup>	\$2,449 <sup>e</sup>		
Discount factor (%)	5.0 <sup>e</sup>	5.0 <sup>f</sup>		
Costs	5.0 <sup>e</sup>	5.0 <sup>f</sup>		
Uruguay				
Initial ICD implant procedure	\$2,157,233 <sup>a</sup>	\$161,205 <sup>a</sup>		
Replacement ICD implant procedure	\$2,157,233 <sup>a</sup>	\$161,205 <sup>a</sup>		
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Monthly inpatient cost	\$703,148 <sup>e</sup>	\$2,954 <sup>e</sup>		
Monthly outpatient cost	\$399,473 <sup>d</sup>	\$2,449 <sup>e</sup>		
Discount factor (%)	5.0 <sup>e</sup>	5.0 <sup>f</sup>		
Costs	5.0 <sup>e</sup>	5.0 <sup>f</sup>		
Mexico				
Initial ICD implant procedure	\$2,157,233 <sup>a</sup>	\$161,205 <sup>a</sup>		
Replacement ICD implant procedure	\$2,157,233 <sup>a</sup>	\$161,205 <sup>a</sup>		
Lead replacement	\$4,524,463 <sup>b</sup>	\$68,583 <sup>b</sup>		
ICD generator removal	\$1,473,095 <sup>a</sup>	\$68,583 <sup>c</sup>		
ICD lead dislodgement	\$1,473,095 <sup>a</sup>	\$68,583 <sup>c</sup>		
ICD inappropriate shock	\$2,487,381 <sup>c</sup>	\$45,131 <sup>d</sup>		
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Discount factor (%)	5.0 <sup>e</sup>	5.0 <sup>f</sup>		
Costs	5.0 <sup>e</sup>	5.0 <sup>f</sup>		
IMSS				
Initial ICD implant procedure	\$2,157,233 <sup>a</sup>	\$161,205 <sup>a</sup>		
Replacement ICD implant procedure	\$2,157,233 <sup>a</sup>	\$161,205 <sup>a</sup>		
Lead replacement	\$4,524,463 <sup>b</sup>	\$68,583 <sup>b</sup>		
ICD generator removal	\$1,473,095 <sup>a</sup>	\$68,583 <sup>c</sup>		
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ICD inappropriate shock	\$2,487,381 <sup>c</sup>	\$45,131 <sup>d</sup>		
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Discount factor (%)	5.0 <sup>e</sup>	5.0 <sup>f</sup>		
Costs	5.0 <sup>e</sup>	5.0 <sup>f</sup>		
Uruguay				
Initial ICD implant procedure	\$2,157,233 <sup>a</sup>	\$161,205 <sup>a</sup>		
Replacement ICD implant procedure	\$2,157,233 <sup>a</sup>	\$161,205 <sup>a</sup>		
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ICD generator removal	\$1,473,095 <sup>a</sup>	\$68,583 <sup>c</sup>		
ICD lead dislodgement	\$1,473,095 <sup>a</sup>	\$68,583 <sup>c</sup>		
ICD inappropriate shock	\$2,487,381 <sup>c</sup>	\$45,131 <sup>d</sup>		
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Monthly outpatient cost	\$399,473 <sup>d</sup>	\$2,449 <sup>e</sup>		
Discount factor (%)	5.0 <sup>e</sup>	5.0 <sup>f</sup>		
Costs	5.0 <sup>e</sup>	5.0 <sup>f</sup>		

Local currency units: Colombian pesos COP\$, Mexican pesos MXN\$, Uruguayan pesos UYU\$. Abbreviations: ICD, Implantable Cardioverter-Defibrillator; LCU, Local Currency Unit.

<sup>a</sup>National Resource Fund (FNR). <sup>b</sup>Observatorio del Sistema de Salud del Uruguay. <sup>c</sup>Procedures from Turakhia et al (2017)<sup>34</sup>, priced according to FNR fees. <sup>d</sup>Local HTA guidelines.<sup>24</sup>

<sup>a</sup>Mexican Social Security Institute (IMSS) DRG November 2018 <sup>b</sup>IMSS unit costs 2018 and weighted lead replacement price. <sup>c</sup>IMSS unit costs 2018. <sup>d</sup>Procedures from Turakhia et al (2017)<sup>34</sup> to IMSS fees. <sup>e</sup>Tamayo et al (2013)<sup>20</sup>, priced according to IMSS fees. <sup>f</sup>Local HTA guidelines.<sup>22</sup>

<sup>a</sup>Social Security Institute (ISS) 2001 fee schedule, increased by 30%. <sup>b</sup>ISS 2001 fee schedule, increased by 30% plus Medtronic's list price of cardiac lead. <sup>c</sup>Procedures from Turakhia et al (2017)<sup>34</sup>, priced according to ISS 2001 fee schedule, increased by 30%. <sup>d</sup>Tamayo et al (2013)<sup>20</sup>. <sup>e</sup>Local HTA guidelines.<sup>23</sup>

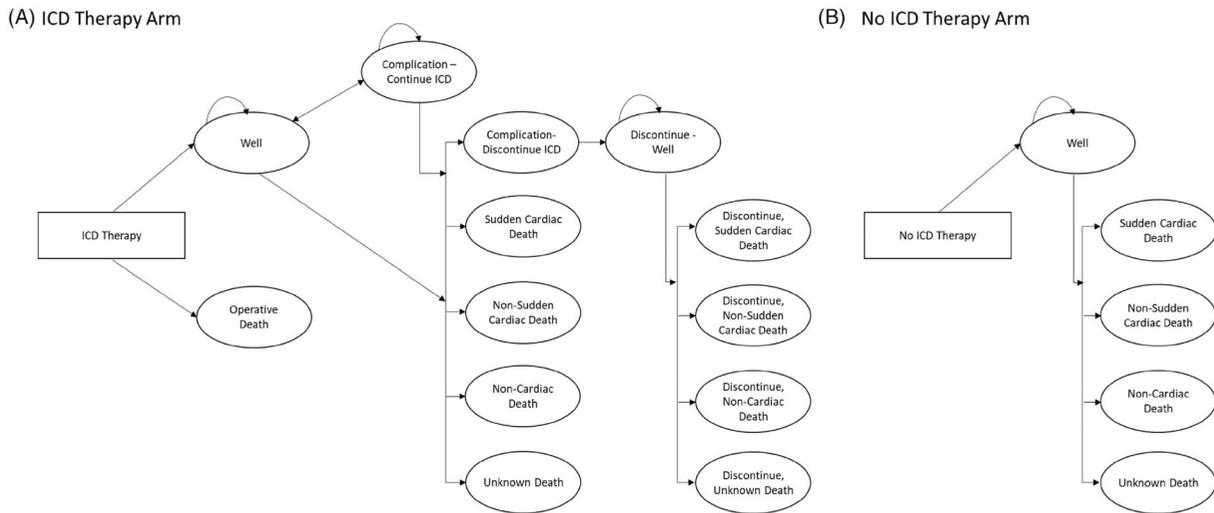


Figure 1. Model schematic.

Table 2. Base case scenario results.

Base case scenario results			Colombia	Mexico	Uruguay
Undiscounted	ICD Therapy	Aggregated costs (LCU <sup>a</sup> )	\$170,751,553	\$1,318,578	\$3,025,052
		Aggregated costs (PPP Adjusted <sup>b</sup> )	\$123,994	\$133,634	\$109,351
		Effectiveness (life-years)	9.72	13.91	9.52
		Effectiveness (QALY)	8.19	11.71	8.02
		Operative Death			
	No ICD Therapy	Aggregated costs (LCU <sup>a</sup> )	\$100,032,746	\$629,155	\$1,294,250
		Aggregated costs (PPP Adjusted <sup>b</sup> )	\$72,641	\$63,763	\$46,785
		Effectiveness (life-years)	7.56	9.70	7.43
		Effectiveness (QALY)	6.38	8.19	6.28
		Differential	Cost (LCU <sup>a</sup> )	\$70,718,807	\$689,423
	Effectiveness (QALY saved)	1.80	3.52	1.74	
	<b>ICER (Costs per QALY saved, LCU<sup>a</sup>)</b>	<b>\$39,200,164</b>	<b>\$195,751</b>	<b>\$994,538</b>	
Discounted	ICD Therapy	Aggregated costs (LCU <sup>a</sup> )	\$132,937,755	\$911,631	\$2,383,754
		Aggregated costs (PPP Adjusted <sup>b</sup> )	\$96,535	\$92,391	\$86,169
		Effectiveness (life-years)	7.36	9.25	7.23
		Effectiveness (QALY)	6.20	7.79	6.09
		No ICD Therapy	Aggregated costs (LCU <sup>a</sup> )	\$79,017,109	\$456,244
	Aggregated costs (PPP Adjusted <sup>b</sup> )		\$57,380	\$46,239	\$37,075
	Effectiveness (life-years)		5.97	7.04	5.89
	Effectiveness (QALY)		5.04	5.94	4.97
	Differential		Cost (LCU <sup>a</sup> )	\$38,957,646	\$455,387
		Effectiveness (QALY saved)	1.15	1.85	1.12
	ICER (Costs per QALY saved, LCU <sup>a</sup> )	\$46,729,026	\$246,016	\$1,214,937	

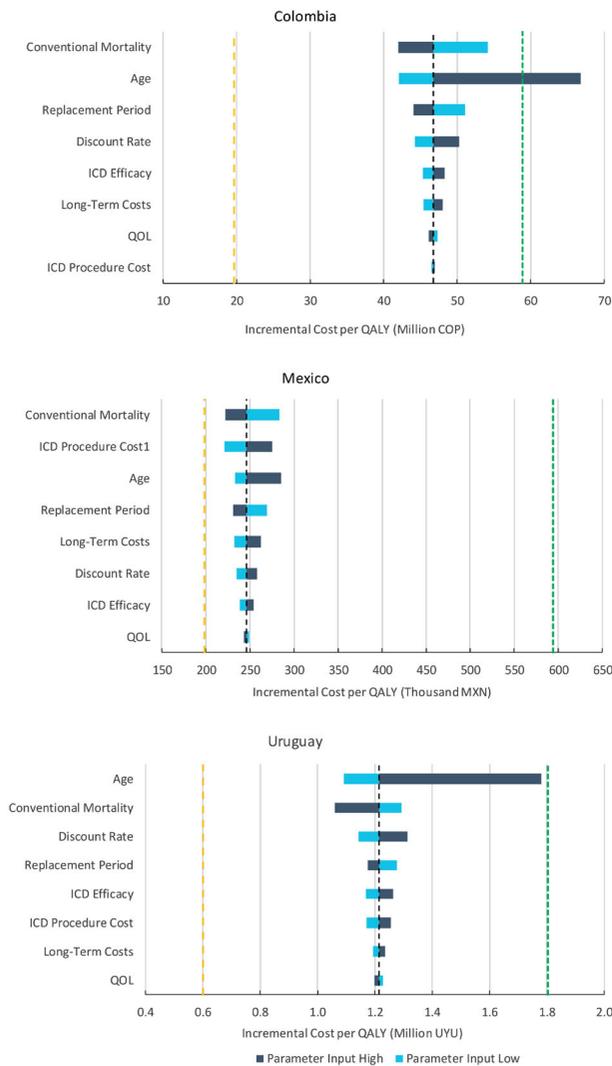
<sup>a</sup>Local currency units: Colombian pesos COP\$, Mexican pesos MXN\$, Uruguayan pesos UYU\$.

<sup>b</sup>Local currency adjusted to international dollars using PPP Conversion Factor for private consumption from the World Bank - World Development Indicators, accessed online 11 June 2020.

Abbreviations. ICD, Implantable Cardioverter-Defibrillator; LCU, Local Currency Unit; QALY, quality-adjusted life year; ICER incremental cost-effectiveness ratio.

the 2001 fee schedule from the Social Security Institute (Instituto de Seguro Sociales – ISS) and increased by 30% according to the local HTA guidelines. Ongoing inpatient and outpatient costs were estimated from a local publication and adjusted by inflation<sup>20</sup>. For Mexico, costs were derived from fee schedules available from the Mexican Social Security Institute (Instituto Mexicano del Seguro Social – IMSS). Uruguayan costs come from the National Resource Fund (Fondo Nacional de Recursos – FNR) fee schedules. Costs of inappropriate shock were derived from an analysis of procedures commonly performed at encounters for shocks<sup>21</sup>, and priced following local fee schedules. Long-term inpatient and outpatient costs were estimated from a publication on the costs of heart failure in Colombia<sup>20</sup>; costs for Mexico were adjusted using local fee schedules, while these costs for

Uruguay were obtained from the National Health Observatory (Observatorio del Sistema de Salud del Uruguay). To obtain long-term care costs, the long-term inpatient costs were multiplied by the average number of hospitalizations per year for patients indicated for ICD therapy based on the SCD-HeFT trial<sup>7</sup>. These costs reflect the perspective of a public payer of high complexity services in Uruguay, and the payer of an employee-based plan in Colombia and Mexico. Costs and outcomes discount rates follow local guidelines for health technology assessments<sup>22–24</sup>. All costs are expressed in local currency units (Colombian Pesos COP\$, Mexican Pesos MXN\$, and Uruguayan Pesos UYU\$), and were adjusted to constant 2017 prices (in Colombia and Mexico) or 2019 prices (in Uruguay) using local general price indices; for the international comparison, costs in local currency units were



**Figure 2.** One-way sensitivity tornado charts. <sup>1</sup>Includes device cost. Abbreviations. ICD, Implantable Cardioverter-Defibrillator; QoL, Quality-of-Life; COP, Colombian Pesos; MXN, Mexican Pesos.

converted to purchasing power parity (PPP) adjusted 2019 dollars using the World Bank’s PPP conversion factor.

**Health-related quality-of-life**

An analysis of EQ-5D data collected in the PainFree SST clinical trial<sup>25</sup> was used for the quality-of-life basis. Preference weights for EQ-5D health states were obtained from the quality-of-life literature for Latin America<sup>6,26</sup>. We assumed the baseline utility for ICD patients and no ICD patients to be the same. The patients who experienced an ICD-related complication, which usually affect patients in the short-term and don’t have permanent effects on the patient, received a utility decrement of 0.096 that is equivalent to a decrement of 3.5 days of quality-adjusted life years<sup>27</sup>.

**Construction of the ICER (w/WTP) and sensitivity analysis**

The 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). The 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. Willingness-to-pay (WTP) threshold values of one- and three-times the Gross Domestic Product (GDP) per capita in Colombia and Mexico for 2017 and in Uruguay for 2019 were used, as recommended by the World Health Organization (WHO) for countries without an established WTP for healthcare technology adoption<sup>28</sup>.

**Results**

**Base case scenario**

Table 2 shows the results of the base-case scenario for each country. In Colombia, ICD therapy for 1.5PP resulted in a benefit of 7.36 (discounted) and 9.72 (undiscounted) life-years, while no ICD therapy resulted in a benefit of 5.97 and 7.56 life-years, respectively. Measured in QALYs, the discounted benefit from ICD therapy is 6.20 and 5.04 from no ICD therapy, resulting in an incremental effectiveness of 1.15 QALYs. Discounted costs from ICD therapy and no ICD therapy account for COP \$132,937,755 and COP \$79,017,109, respectively. The ICER for ICD therapy is COP \$46,729,026 per QALY. Following Colombian guidelines for health technology assessments<sup>23</sup>, we find that ICD therapy for 1.5PP is potentially cost-effective at COP \$58,903,902, 3-times the Colombian GDP per capita WTP threshold in the base case scenario. Undiscounted results for Mexico show a differential cost between ICD therapy and no ICD therapy of MXN \$689,423, and a difference of 3.52 QALYs saved with ICD therapy. Discounted results show differential costs of MXN \$455,387, and a difference of 1.85 QALYs saved, which leads to an ICER for ICD therapy of MXN \$246,016. At a WTP threshold of 3-times the Mexican GDP per capita of MXN \$594,383, we find ICD therapy cost-effective in Mexico in the base case scenario. Undiscounted results for Uruguay show a differential cost between ICD therapy and no ICD therapy of UYU \$1,730,802, and a difference of 1.74 QALYs saved with ICD therapy. Discounted results show differential costs of UYU \$1,358,114 and a difference of 1.12 QALYs saved, which leads to an ICER for ICD therapy of UYU \$1,214,937. At a WTP threshold of 3-times the Uruguayan GDP per capita of UYU \$1,802,860, we find ICD therapy cost-effective in Uruguay in the base case scenario.

**Sensitivity analyses**

Figure 2 shows Tornado charts resulting from one-way sensitivity analysis per country. Each bar represents the resulting ICER of changing the parameter of the Markov model on the y-axis, while the remaining parameters are constant and the short-dashed and the long-dashed lines represent the 3-times and 1-time GDP per capita WTP thresholds, respectively. Most results confirm the base case scenario in all three countries; only the high value for age in Colombia results in

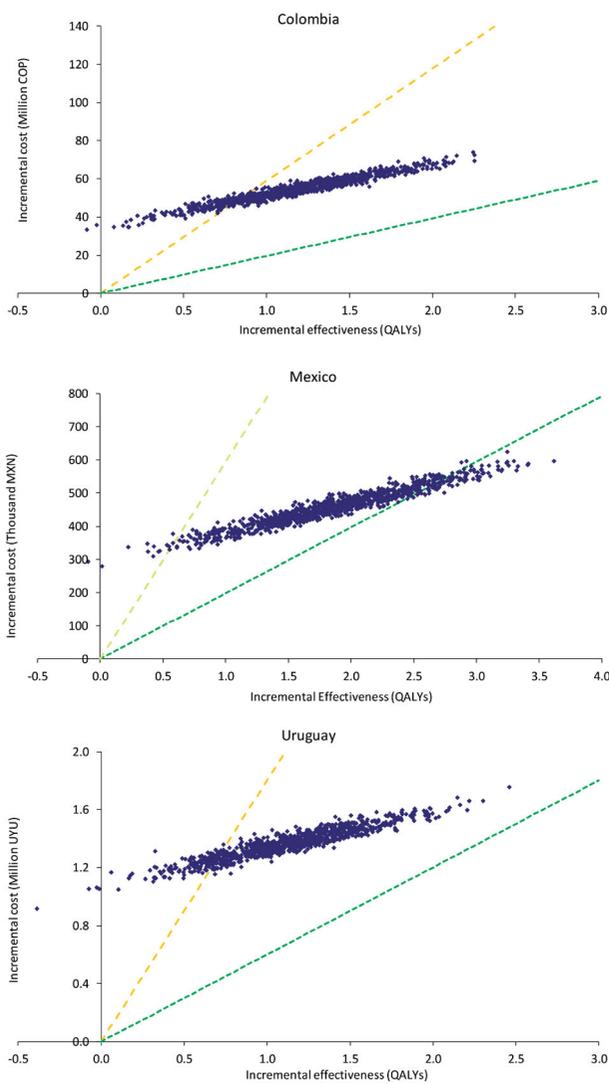


Figure 3. Probabilistic sensitivity analysis scatterplot.

an ICER above the 3-times WTP threshold. In Colombia and Mexico, the results are most sensitive to changes in conventional mortality, while in Uruguay it is most sensitive to age. In addition, in Mexico the results are particularly sensitive to ICD procedure costs.

Figure 3 shows the simulated costs per QALY of the probabilistic sensitivity analysis for each country, where each dot corresponds to the resulting cost per QALY of a model iteration, and the dashed lines show the WTP thresholds of 1- and 3-times the GDP per capita of the corresponding country. Results for Colombia show a mean cost per QALY of COP \$46,389,154 (median cost per QALY COP \$46,483,046, 95% Credible Interval [COP \$33,780,726–\$95,957,807] per QALY) after 1,000 iterations. A total of 81.4% of simulations result in costs per QALY below the 3-times GDP per capita WTP threshold; no iteration resulted in costs per QALY below the 1-time GDP per capita WTP threshold. Results from the Mexico PSA indicate that after 1,000 simulations, the mean cost per QALY was MXN \$245,482, with a median cost per QALY of MXN \$244,843, and a 95% Credible Interval of [MXN \$183,382–\$490,506]. Also, 98.7% of simulations result in costs per QALY below the 3-times GDP per capita WTP threshold, and 9% of iterations resulted in costs per QALY

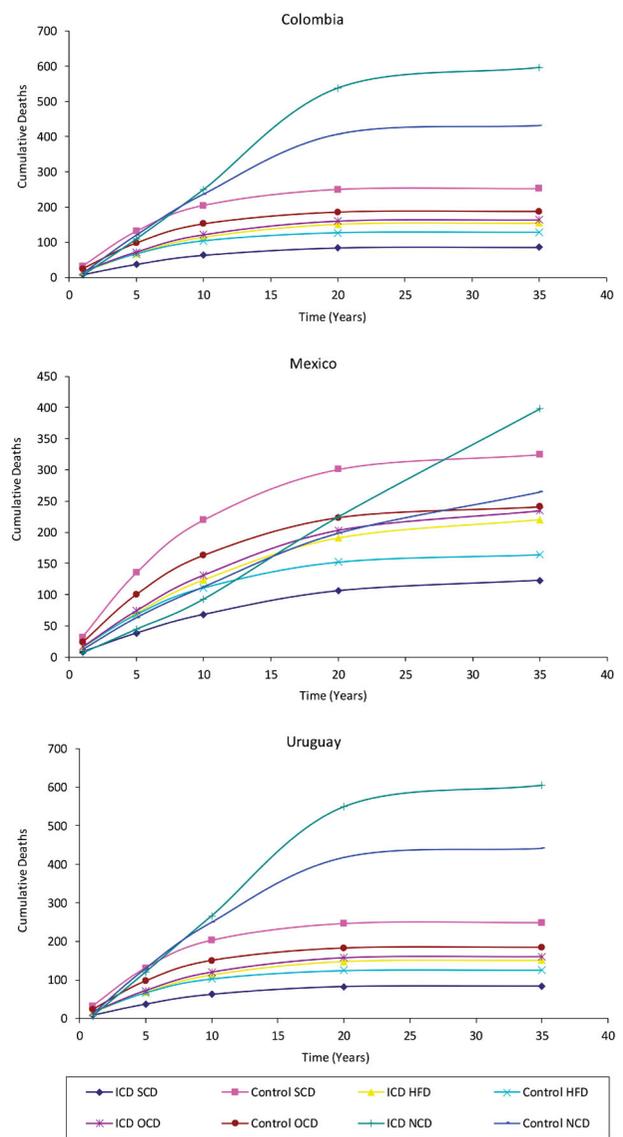


Figure 4. Cumulative deaths by country. Abbreviations. ICD, Implantable Cardioverter-Defibrillator; SCD, Sudden Cardiac Death; HFD, Heart Failure Cardiac Death; OCD, Other Cardiac Death; NCD, Non-Cardiac Death.

below the 1-time GDP per capita WTP threshold. Results from the Uruguay PSA indicate that after 1,000 simulations, the mean cost per QALY was UYU \$1,215,895, with a median cost per QALY of UYU \$1,214,379 and a 95% Credible Interval of [UYU \$809,047–\$2,795,561]. Also, 86.4% of simulations result in costs per QALY below the 3-times GDP per capita WTP threshold, but no iterations resulted in costs per QALY below the 1-time GDP per capita WTP threshold.

### Discussion

Results show that costs per QALY of ICD therapy in a 1.5PP population are between 1- and 3-times GDP per capita WTP threshold in Colombia, Mexico, and Uruguay; sensitivity analyses confirm these results. However, Colombian guidelines for health technology assessment consider costs per QALY between 1- and 3-times GDP per capita as *potentially* cost-effective. These results are in line with the literature on the cost-effectiveness of ICD therapy. There is established

evidence of the cost-effectiveness of ICD therapy in the primary prevention population. An analysis of the randomized SCD-HeFT trial by Mark et al.<sup>7</sup> found ICD therapy to be economically attractive at \$41,530/QALY (at a WTP of \$100,000) in the US healthcare system. Similar results were shown within the healthcare system of a European country, using the same model in this study and a meta-analysis of six randomized primary prevention trials<sup>6</sup>. In addition, ICD therapy for the 1.5 prevention population has been found to be cost-effective in Brazil<sup>29</sup>. This cost-effectiveness evidence has been validated in a real world setting outside of clinical trials<sup>30</sup>.

Even though the results coincide in the cost-effectiveness of ICD therapy in all three countries, there are differences in costs and effectiveness between these countries. **Table 2** shows that, despite using the same mortality risks in the Markov model, results for Mexico have a higher effectiveness in both ICD Therapy and No ICD Therapy arms of the model. Discounted effectiveness results in Mexico are 0.90 and 1.59 QALYs more than in Colombia, and 0.97 and 1.70 more than in Uruguay in the No ICD Therapy and ICD Therapy arms, respectively. These differences can be explained by differences in population health among countries (the model used country-specific data for this input), particularly differences in non-cardiac death rates; results from the model show non-cardiac cumulative deaths in both arms overtake any cardiac deaths at the end of the model time in the Mexican case (**Figure 4**). In Colombia and Uruguay, non-cardiac deaths overtake any cardiac deaths early in the model timeline and are the most prevalent cause of death. These results are in line with the Tornado charts, where the high value for age at implant leads to high ICERs in Colombia and Uruguay, but not in Mexico: all else equal, as older patients are more susceptible to non-cardiac death in Colombia and Uruguay than in Mexico, an older cohort in Colombia or Uruguay receives less utility from ICD therapy than in Mexico, hence the resulting ICER for an older cohort is higher in Colombia or Uruguay than in Mexico. Discounted costs of ICD therapy are similar between countries (within \$10,000 purchase-parity adjusted dollars), but No ICD therapy costs in Colombia are 24.1% and 54.8% higher than in Mexico and Uruguay, respectively (**Table 2**). These differences in costs and effectiveness highlight the importance of using local inputs in cost-effectiveness analyses.

Despite convincing evidence from multiple randomized clinical trials<sup>1,4,14</sup> and strong recommendations in international society guidelines<sup>2</sup>, ICD utilization is relatively low in Latin America, ranging from one implant per million in Perú to 56 implants per million in Argentina<sup>31</sup>. These numbers are starkly low relative to other areas. The average rate of ICD implantation in Europe is approximately 100 implants per million<sup>32</sup>. Regarding economic factors, it remains cost-effective to treat the primary prevention population with ICD therapy; a budget impact model could provide additional information on the effect of treating a primary prevention population. This study provides information from an economic standpoint for decision-makers to first direct scarce resources toward those who can benefit the most. Priority

should be placed on treating patients with a 1.5PP indication.

It is important to acknowledge the limitations of this analysis. The Improve SCA study was a non-randomized trial and may produce biased results; however, the mortality analysis from the trial was adjusted for baseline characteristics that are associated with mortality, reducing the potential bias. Moreover, the effectiveness of ICD therapy is replicated in non-randomized observational trials. Additionally, mortality rates from the study could be misclassified, as deaths in the Improve SCA study were not adjudicated by a central committee. Costs and benefits were modelled beyond the timeline of direct observation in the Improve SCA study, however this is a standard approach in economic modelling and necessary for the proper perspective for decision-makers.

## Conclusions

ICD therapy is cost-effective in Mexico and Uruguay and potentially cost-effective in Colombia for the 1.5 primary prevention population identified in the Improve SCA trial. There is variability in the ICER estimates with respect to the willingness-to-pay thresholds that can be explained by differences in local health technology assessment guidelines, population health, and healthcare costs.

## Transparency

### Declaration of funding

Medtronic, Inc funded this study.

### Declaration of financial/other interests

Medtronic; DAR: proctor/lecture fees: Boston Scientific, proctorship: Biosense Webster, St. Jude Medical/Abbott, steering committee fees: Medtronic. AC: registration and transfer to medical congresses: St. Jude Medical/Abbott, Medtronic.

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

## Acknowledgements

We are grateful to Brian Van Dorn of Medtronic for providing the utility estimates based on the Improve SCA<sup>8</sup> study of life data, and Janet E O'Brien, of Medtronic for medical writing assistance.

## Previous presentations

Results for Mexico were presented at the 2018 ISPOR Annual Conference, and results for Colombia were presented at the 2019 ISPOR Latin America Conference.

## ORCID

Alejandro Cuesta  <http://orcid.org/0000-0003-1315-5581>

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