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ORIGINAL RESEARCH

Comparative Effectiveness of Implantable Defibrillators for Asymptomatic Brugada Syndrome: A Decision-Analytic Model

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BACKGROUND: Optimal management of asymptomatic Brugada syndrome (BrS) with spontaneous type I electrocardiographic pattern is uncertain.

METHODS AND RESULTS: We developed an individual-level simulation comprising 2 000 000 average-risk individuals with asymptomatic BrS and spontaneous type I electrocardiographic pattern. We compared (1) observation, (2) electrophysiologic study (EPS)-guided implantable cardioverter-defibrillator (ICD), and (3) upfront ICD, each using either subcutaneous or transvenous ICD, resulting in 6 strategies tested. The primary outcome was quality-adjusted life years (QALYs), with cardiac deaths (arrest or procedural-related) as a secondary outcome. We varied BrS diagnosis age and underlying arrest rate. We assessed cost-effectiveness at $100 000/QALY. Compared with observation, EPS-guided subcutaneous ICD resulted in 0.35 QALY gain/individual and 4130 cardiac deaths avoided/100 000 individuals, and EPS-guided transvenous ICD resulted in 0.26 QALY gain and 3390 cardiac deaths avoided. Compared with observation, upfront ICD reduced cardiac deaths by a greater margin (subcutaneous ICD, 8950; transvenous ICD, 6050), but only subcutaneous ICD improved QALYs (subcutaneous ICD, 0.25 QALY gain; transvenous ICD, 0.01 QALY loss), and complications were higher. ICD-based strategies were more effective at younger ages and higher arrest rates (eg, using subcutaneous devices, upfront ICD was the most effective strategy at ages 20–39.4 years and arrest rates >1.37%/year; EPS-guided ICD was the most effective strategy at ages 39.5–51.3 years and arrest rates 0.47%–1.37%/year, and observation was the most effective strategy at ages >51.3 years and arrest rates <0.47%/year). EPS-guided subcutaneous ICD was cost-effective ($80 508/QALY).

CONCLUSIONS: Device-based approaches (with or without EPS risk stratification) can be more effective than observation among selected patients with asymptomatic BrS. BrS management should be tailored to patient characteristics.

Key Words: Brugada syndrome ■ cost-effectiveness ■ implantable defibrillator

Brugada syndrome (BrS) is an inherited disorder associated with increased risk of sudden cardiac death (SCD) attributable to ventricular arrhythmias.[1] Yet SCD risk is variable and most patients will not have an event.[2] Implantable cardioverter-defibrillators (ICDs) can avert SCD,[3] but are associated with immediate and long-term risks, require repeated interventions to maintain, are expensive, and may reduce quality-of-life.[4,5] Therefore, proper risk stratification and recommendations for ICD implantation are of critical importance in BrS management.

Some individuals are at sufficiently high SCD risk that ICDs are clearly indicated, such as those with a history of malignant arrhythmias.[6] Conversely, some are at recognizably low risk such that ICDs are not recommended, such as asymptomatic individuals with normal resting ECGs.[6] In contrast, the optimal management of asymptomatic individuals

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CLINICAL PERSPECTIVE

What Is New?

- Using a comprehensive simulation model including 2 million individuals representing an average-risk population of patients with asymptomatic Brugada syndrome (BrS) and spontaneous Type I electrocardiographic pattern, we compared the clinical effectiveness of observation, electrophysiologic study-guided implantable cardioverter-defibrillator placement, and upfront implantable cardioverter-defibrillator placement.
- We systematically assessed the effects of varying clinical factors including age of BrS diagnosis and annual rate of malignant ventricular arrhythmias.
- The most effective strategy varied based upon patient characteristics. For example, implantable cardioverter-defibrillator-based approaches were particularly favorable among individuals diagnosed with BrS at younger ages and having higher rates of malignant ventricular arrhythmias.

What Are the Clinical Implications?

- Implantable cardioverter-defibrillator-based approaches (with or without electrophysiologic study-based risk stratification) can be more effective than observation among selected patients with asymptomatic BrS under modeled scenarios.
- Management of patients with BrS should be tailored to patient characteristics.
- Improved precision regarding event rates in patients with asymptomatic BrS and spontaneous Type I electrocardiogram patterns is needed.

Nonstandard Abbreviations and Acronyms

BrS	Brugada syndrome
EPS	electrophysiologic study
ICD	implantable cardioverter-defibrillator
QALY	quality-adjusted life years
SCD	sudden cardiac death

with spontaneous ST-segment elevation in the right precordial leads (ie, type I Brugada pattern[1]), who have an ≈3-fold SCD risk,[7,8] is unclear and current guidelines do not provide explicit recommendations for or against ICD.[6] Management typically includes observation,[9] though risk stratification with electrophysiologic study (EPS) and ICD implant for high risk findings may be reasonable.[2] At the same time, recent innovations such as the subcutaneous ICD may offer a favorable adverse event profile, thereby potentially altering the risk-benefit equation in favor of ICD-based strategies.[10,11]

Although uncertainty in the optimal management of BrS remains a challenge, the rarity of the condition renders a definitive clinical trial impractical. We therefore developed a decision-analytic model to estimate the comparative effectiveness of contemporary management strategies for individuals with asymptomatic BrS and spontaneous type I electrographic pattern, across a range of plausible clinical scenarios.

METHODS

Data Availability

The code underlying the simulation model described in the current study will be made available upon request to the corresponding author. Given that all data used in this study stem from previously published reports, and no new patient data were generated or used, this study did not require Institutional Review Board approval.

Model Design

We constructed an individual-level simulation model to compare management strategies for patients with asymptomatic BrS and spontaneous type I pattern. An individual-level simulation was chosen to incorporate the effects of relevant patient-level factors (eg, years since last generator replacement) on future outcomes. The base case model included 2 000 000 individuals (71% male[12,13]) diagnosed with BrS at age 41 years[2,9,14] (varied in dedicated age analyses, see below) and followed until death or age 90. We assessed a lifetime horizon since the consequences of a strategy may not be realized until many years later. The time between health state transitions was 1 year. Model structure is summarized in Figure 1.

Management Strategies

We tested 3 strategies: (1) observation; (2) EPS, with ICD implant only if EPS demonstrated high-risk findings (ie, inducible ventricular arrhythmia with single or double extra-stimuli); and (3) upfront ICD. In strategies (1) and (2), an ICD would also be placed after any survived malignant arrhythmia. Strategy (2) is endorsed in current guidelines as a weak recommendation (class IIb), whereas the others are not explicitly mentioned.[6]

Each strategy was modeled assuming use of transvenous ICD versus use of subcutaneous ICD, resulting in 6 strategies. Thus, in the primary model we assumed

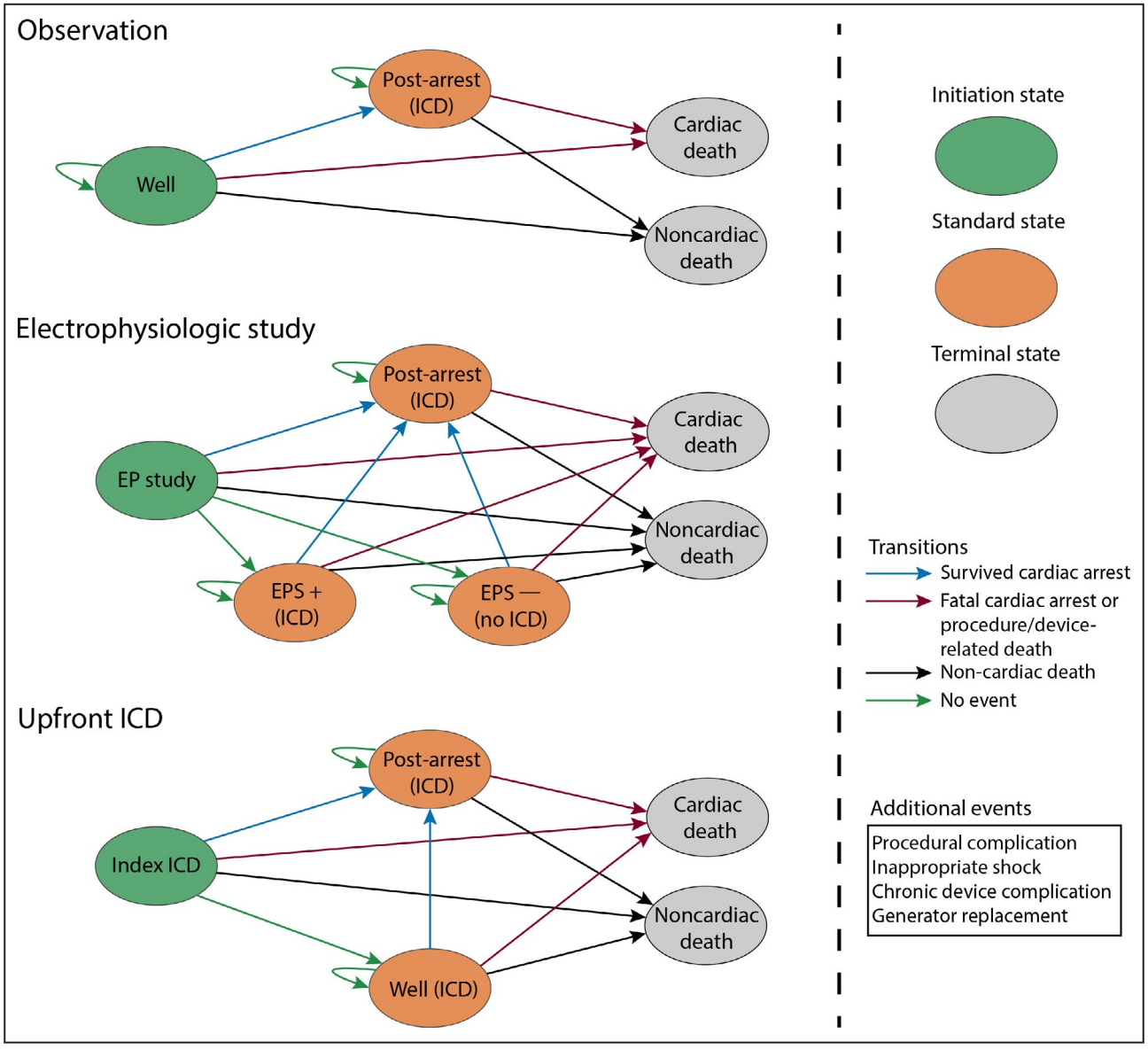

Figure 1. Overview of model structure.
Depicted is an overview of model structure. Health states comprising each of the 3 strategies modeled (observation [with ICD for survived arrest], electrophysiologic study [with ICD for positive findings], and upfront ICD) are depicted from top to bottom. Initiation states (states at which simulation starts) are depicted in green, standard states in orange, and terminal states (states where individuals must remain) in gray. Events mediating transitions between states are depicted with colored arrows. Additional events occurring within health states are depicted in the box. EPS indicates electrophysiologic study; and ICD, implantable cardioverter-defibrillator.

that all individuals are eligible for subcutaneous ICD. However, since subcutaneous ICDs are not uniformly available or may be clinically contraindicated, we developed a secondary model using transvenous ICDs only.

Outcomes

Outcomes were modeled from the healthcare system perspective. The primary effectiveness end point was quality-adjusted life years (QALYs). Secondary end points included cardiac deaths (ie, deaths related to ventricular arrhythmia or procedural/device-related complication), total deaths, acute procedural/device-related complications, chronic device-related complications, inappropriate shocks, and total ICDs placed. Comparisons of clinical end points across strategies are presented as within-device type (eg, EPS-guided subcutaneous ICD versus observation with subcutaneous ICD after survived arrest) unless otherwise specified.

Given the considerable costs associated with ICD,[15] we performed secondary cost-effectiveness analyses

comparing effective strategies. We calculated the incremental cost-effectiveness ratio, defined as the ratio of incremental costs to QALYs gained, and considered a strategy cost-effective if the incremental cost-effectiveness ratio between it and its next less costly comparator was below $100 000/QALY.[16,17]

Input Parameters

We modeled clinical events using published literature.[18–28] Given our model's lifetime horizon, we applied annualized event rates over the life course. Since the rate of cardiac arrest in BrS declines with age and current studies provide only up to a decade of follow-up, we modeled the lifetime incidence of arrest using an exponential function calibrated to published event rates obtained separately within middle-aged[2,29–32] and older individuals[29,30,33] (Data S1). Where possible, all device-related complication rates were estimated using the recent PRAETORIAN trial.[11] The relative risk of arrhythmic events following positive versus negative findings at EPS were derived from a recent multi-center pooled analysis reporting on patients with asymptomatic BrS.[2] Average life expectancy was modeled using population-based age- and sex-stratified mortality rates from the 2017 US National Vital Statistics Reports.[34]

We incorporated device-related disutility.[35–38] We also incorporated short-term disutilities after discrete adverse events (eg, inappropriate shocks), and intermediate-term disutilities to account for the psychological effects of aborted SCD.[5,39] We estimated all quality-of-life parameters using published literature, using patient-reported outcomes where possible. We applied a half-cycle correction to all QALYs. All future QALYs were discounted at 3%/year.

We obtained all costs using published literature.[40–46] Costs were standardized to US dollar value as of November 2019. We applied discrete cost penalties associated with short-term adverse events (eg, procedural complications). We applied a half-cycle correction to all costs. All future costs were discounted at 3%/year. All model input parameters are shown in Table 1.

Sensitivity Analyses

To account for parameter uncertainty, we conducted probabilistic sensitivity analyses including all parameters other than diagnosis age, sex, and initial device cost. The distribution of positive and negative EPS and the rate of arrest according to EPS result were also held constant in probabilistic analyses to ensure equivalent event rates across strategies. For each strategy, we tabulated the number of simulations in which the given strategy was most effective. We also plotted the absolute QALYs and absolute costs associated with each strategy on the cost-effectiveness plane. For each strategy, cost-effectiveness probabilities were then plotted against the willingness-to-pay to generate cost-effectiveness acceptability curves and the cost-effectiveness acceptability frontier.

The influence of uncertainty in individual parameters was assessed using value of information analysis. We calculated the overall expected value of perfect information, which provides an estimate of the monetary value of eliminating uncertainty for all parameters, as well as the expected value of partial perfect information, an estimate of the monetary value of eliminating uncertainty for individual parameters.[47] For interpretability, we scaled expected value of partial perfect information estimates to a yearly estimate for the US population assuming an asymptomatic spontaneous Type I BrS prevalence of 0.01% among individuals aged ≥18 years.[48]

We then performed deterministic sensitivity analyses in which we varied single parameters possessing high relative influence (ie, high expected value of partial perfect information) or particular clinical relevance (eg, cost of ICD). Given the clinical importance of BrS diagnosis age and the yearly rate of arrest in asymptomatic BrS,[29,33] we performed dedicated analyses in which we calculated clinical and cost-effectiveness estimates while varying the initial cardiac arrest rate between 0.25% and 1.5%/year[30,33] and BrS diagnosis age between 20 and 65 years. Since previous estimates of the value of EPS risk stratification have varied,[49,50] we also performed deterministic sensitivity analyses in which we varied the relative risk of arrhythmic events given a positive EPS between 1.1 and 1.9. Since ICD utility was a particularly influential parameter, we also performed 2-way sensitivity analyses in which we simultaneously varied EPS risk stratification performance and ICD utility. In analyses varying EPS risk stratification performance, the relative risk observed with a negative EPS and distribution of positive and negative EPS findings were calibrated to maintain equivalent event rates across all strategies.

Analyses were performed using Amua v0.3.0, an open-source decision-analysis package, R v4.0, and the Sheffield Accelerated Value of Information tool.[51–53]

Model Validation

The observed rate of cardiac arrest in our model was validated against outcomes reported in a contemporary BrS meta-analysis (Data S2).[2]

RESULTS

Base Case Analysis

Depending on the device type used after survived SCD, observation resulted in 19.90 QALYs lived per individual and 10 580 to 10 640 cardiac or device-related

Table 1. Model Inputs

Parameter	Estimate	Lower bound	Upper bound	References	Reference type(s)
Events					
Proportion male	0.71			12,13	O,M,R; Review
Initial diagnosis age	41	26	56	2, 9, 14	O,M,R; Meta-analysis,O,M,R; SR
Incidence of SCD (asymptomatic spontaneous Brugada pattern, no history of arrest)	10.2/1000 person-years	5.0/1000 person-years	16.7/1000 person-years	2, 14, 29–31	O,M,R; Meta-analysis,O,M,R; O,M,R
Incidence of SCD (with history of arrest)	77.0/1000 person-years		142/1000 person-years	14, 32	O,M,R; O,M,R
Proportion of SCD that is fatal (ICD)	0.017	0.002*	0.045*	18, 19	O,S,R
Proportion of SCD that is fatal (no ICD)	0.875	0.6*	0.996*	20	SR
Complications					
Transvenous ICD					
Incidence of chronic complication	25.8/1000 person-years	20.6/1000 person-years†	31.0/1000 person-years†	11	RCT
Incidence of inappropriate shocks	19.0/1000 person-years	15.1/1000 person-years†	22.8/1000 person-years†	11	RCT
Probability of acute complication (initial)	0.038	0.030*	0.046*	11	RCT
Probability of acute complication (revision)	0.0091	0.0085*	0.0097*	21	O,M.R
Probability of death from acute complication (initial)	0.062	0.056*	0.067*	22, 23	O.M.R
Probability of death from acute complication (revision)	0.072	0.066*	0.079*	21	O.M.R
Probability of death from chronic complication	0.044	0.03*	0.06*	24	O.M.R
Generator change interval, y	6	4	8	21	O.M.R
Subcutaneous					
Incidence of chronic complication	15.2/1000 person-years	12.1/1000 person-years†	18.3/1000 person-years†	11	RCT
Incidence of inappropriate shocks	25.5/1000 person-years	20.4/1000 person-years†	30.7/1000 person-years†	11	RCT
Probability of acute complication (initial)	0.047	0.038†	0.056†	11	RCT
Probability of acute complication (revision)	0.015	0.012†	0.018†	Derived from transvenous-ICD ratio	O,M,R
Probability of death from acute complication (initial)	0.021	0.017†	0.025†	11, 25	O,M,R
Probability of death from acute complication (revision)	0.024	0.019†	0.029†	Derived from transvenous-ICD ratio	O,M,R
Probability of death from chronic complication	0.015	0.012†	0.018†	Derived from transvenous-ICD ratio	O,M,R
Generator change interval, y	5	4	6	26	O,M,P
Testing					
Probability of EPS+	0.27			2	Meta-analysis,O,M,R

(*Continued*)

Table 1. Continued

Parameter	Estimate	Lower bound	Upper bound	References	Reference type(s)
Probability of EPS complication	0.043	0.033*	0.054*	27, 28	O,S,R; O,S,P
Probability of death from EPS complication	0.00074	0.00002*	0.0027*	27, 28	O,S,R; O,S,P
Relative risk of SCD (EPS+)	1.67	1.3*	1.9*	2	Meta-analysis,O,M,R
Relative risk of SCD (EPS–)	0.753	0.667*	0.89*	2	Meta-analysis,O,M,R
Costs ($)					
Transvenous ICD					
Initial implant	26 083	26 083	32 313	40	DM,Std
Maintenance	128/y	84	172	41	DM,Std
Generator change/revision	20 538	15 633	25 443	40	DM,Std
Non-fatal complication	1075	941	1208	41	DM,MC
Subcutaneous ICD					
Initial implant	26 702	23 226	26 702	42, 43	O,S,R
Maintenance	128/y	84	172	41	DM,Std
Generator change/revision	21 025	18 136	23 914	Derived from transvenous-ICD ratio	DM,Std
Nonfatal complication	1075	941	1208	41	DM,Std
EPS					
EPS	7809	6247†	9371†	44	DM,Std
Nonfatal EPS complication	2141	481		35, 45	DM,MC; O,S,R
Events					
Cardiac arrest (no ICD)	30 000	18 950	41 050	35, 46	DM,MC; O,M,R
Utilities					
ICD	0.95	0.90	1	35–38	DM,Survey
ICD initial implant/revision	0.5 QALYs×3 d‡			35	DM,MC
Nonfatal ICD complication	0.5 QALYs×10 d‡			35	DM,MC
Nonfatal EPS complication	0.5 QALYs×10 d‡			35	DM,MC
Cardiac arrest (no ICD)	0.5 QALYs×10 d‡			35	DM,MC
Cardiac arrest (psychological effects, with/without ICD)	0.76 QALYs×3 mo‡			5, 39	O,M,P
Inappropriate shock (psychological effects)	0.9 QALYs×1 mo‡			5	O,M,P

DM indicates decision model; EPS, electrophysiologic study; ICD, implantable cardioverter-defibrillator; M, multicenter; MC, micro-cost analysis; O,M,R, observational, multicenter, retrospective; O,M,P, observational, multicenter, prospective; O,S,R, observational, single-center, retrospective; O,S,P, observational, single-center, prospective; QALY, quality-adjusted life year; RCT, randomized-controlled trial; SCD, sudden cardiac death; SR, systematic review; and Std, standard source.

*Denotes that bounds are 95% CIs from a beta distribution modeling probability uncertainty in the base case estimate.

†Denotes that bounds were not estimable from published sources and were therefore defined as ±20% of base case estimate.

‡Applied as discrete penalties.

deaths per 100 000 individuals. When compared with observation, EPS-guided ICD using both subcutaneous (0.35 QALY gain per individual, 4130 cardiac deaths avoided per 100,000 individuals) and transvenous (0.26 gain, 3390 cardiac deaths avoided) devices were effective. Upfront ICD minimized cardiac deaths but was only more effective than observation when subcutaneous ICDs were used (0.25 QALY gain, 8950 cardiac deaths avoided). Upfront ICD strategies resulted in the greatest rates of acute (subcutaneous, 15 220; transvenous, 8900) and chronic (subcutaneous, 44 580; transvenous, 76 750) complications per 100 000 individuals. Detailed clinical outcomes by strategy are shown in Table 2. Survival free of cause-specific death according to management strategy is depicted in Figure S1.

In secondary cost-effectiveness analyses, EPS-guided subcutaneous ICD was the most cost-effective strategy (incremental cost-effectiveness ratio, $80 508/QALY), and dominated each alternative (Table 3). In models including only transvenous devices, EPS-guided transvenous ICD was cost-effective (incremental cost-effectiveness ratio, $88 154/QALY) and dominated upfront ICD (Table 3). Cost-effectiveness results excluding EPS-guided strategies are shown in Table S1.

Deterministic Sensitivity Analyses

Higher arrest rates favored ICD-based strategies. Specifically, among strategies using subcutaneous ICDs, QALYs were maximized by observation at rates 0.25% to 0.46%/year, EPS-guided ICD between 0.47% to 1.37%/year, and upfront ICD at >1.37%/year. Among strategies using transvenous ICDs, QALYs were maximized by observation at rates 0.25% to 0.57%/year, EPS-guided ICD between 0.58% to 1.35%/year, and upfront ICD at >1.35%/year (Figure 2, Tables S2 through S6). From a cost-effectiveness standpoint and comparing across all strategies, observation with transvenous ICD was preferred at rates 0.25% to 0.94%/year, and EPS-guided subcutaneous ICD was preferred at rates 0.95% to 1.50%/year (Tables S3, S5, and S6).

Earlier age of BrS diagnosis also favored ICD-based strategies. Specifically, among strategies using subcutaneous ICDs, QALYs were maximized by upfront ICD between ages 20.0 to 39.4 years, EPS-guided ICD between ages 39.5 to 51.3 years, and observation at ages >51.3 years. Among strategies using transvenous ICDs, QALYs were maximized by upfront ICD between ages 20.0 to 35.1 years, EPS-guided ICD between ages 35.2 to 49.1 years, and observation at ages >49.1 years. (Figure 2, Tables S7 through S11). From a cost-effectiveness standpoint and comparing across all strategies, upfront subcutaneous ICD was preferred

Table 2. Clinical Effectiveness Endpoints Per 100 000 Simulated Individuals

Strategy*	# ICDs placed	Acute procedural or device related complications†	Chronic device complications‡	Inappropriate shocks	Arrest deaths	Procedural or device related deaths	Cardiac deaths§	Total deaths	QALYs per individual	ΔQALYs vs observation
Subcutaneous										
Observation	1510	190	510	850	10 560	10	10 580	82 660	19.901	…
Electrophysiologic study	27 790	8490	12 360	20 610	6170	290	6450	81 820	20.247	0.345
Upfront ICD	99 780‖	15 220	44 580	74 540	600	1030	1630	80 830	20.154	0.252
Transvenous										
Observation	1480	110	850	580	10 600	40	10 640	82 570	19.900	…
Electrophysiologic study	27 790	6740	21 270	15 660	6160	1090	7250	81 970	20.164	0.264
Upfront ICD	99 770‖	8900	76 750	56 650	580	4000	4590	81 490	19.891	−0.009

ICD indicates implantable cardioverter-defibrillator; and QALY, quality-adjusted life year.
*Outcomes represent results of individual-level simulation until death or age 90 years.
†Inclusive of access site complication, pneumothorax, skin infection, pocket hematoma, lead malfunction, or any other device defect requiring immediate revision.
‡Inclusive of device infection, pocket hematoma, lead failure, or any other device defect requiring revision.
§Defined as sum of arrest-related deaths and procedural or device-related deaths.
‖Values slightly <100 000 because of age- and sex-related cycle death before ICD implant.

Table 3. Summary Clinical and Cost-Effectiveness Results

Strategy	QALYs*	Costs*	ΔQALYs	ΔCosts	ICER (ΔCosts/ΔQALYs)	Notes
All strategies						
Electrophysiologic study (subcutaneous ICD if positive)	20.247	$31 324.61	0.34642	$27 889.54	$80 508.25	Cost effective at WTP of $100 000/QALY
Electrophysiologic study (transvenous ICD if positive)	20.164	$26 693.45	…	…	…	Weakly dominated
Upfront subcutaneous ICD	20.154	$94 366.88	…			Dominated
Observation (subcutaneous ICD if arrest)	19.902	$3615.57	…	…	…	Weakly dominated
Observation (transvenous ICD if arrest)	19.900	$3435.07	…	…	…	Baseline
Upfront transvenous ICD	19.891	$77 597.65	…	…	…	Dominated
Subcutaneous ICD only						
Electrophysiologic study (ICD if positive)	20.247	$31 324.61	0.34503	$27 709.04	$80 308.25	Cost effective at WTP of $100 000/QALY
Upfront ICD	20.154	$94 366.88	…			Dominated
Observation (ICD if arrest)	19.902	$3615.57	…	…	…	Baseline
Transvenous ICD only						
Electrophysiologic study (ICD if positive)	20.179	$26 693.45	0.26384	$23 258.38	$88 153.80	Cost effective at WTP of $100 000/QALY
Observation (ICD if arrest)	19.901	$3435.07	…	…	…	Baseline
Upfront ICD	19.890	$77 597.65	…	…	…	Dominated

Preferred strategy for each model is highlighted in gray. ICD indicates implantable cardioverter-defibrillator; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; and WTP, willingness-to-pay.

*Costs and life years presented per individual.

at ages 20 to 21.4 years, EPS-guided subcutaneous ICD was preferred at ages 21.5 to 41.6 years, and observation with transvenous ICD was preferred at ages >41.6 (Tables S8, S10, and S11).

Analyses varying the efficacy of EPS for risk stratification demonstrated that EPS-guided subcutaneous ICD was more effective than upfront subcutaneous ICD as long as the relative risk of arrest following a positive EPS was >1.4. EPS-guided subcutaneous ICD remained cost-effective as long as the relative risk was >1.5. In models including only transvenous ICDs, EPS-guided transvenous ICD remained more effective than either observation or upfront ICD even as the relative risk of arrest following a positive EPS fell to 1.1, but was only cost-effective at a relative risk >1.6 (Tables S12 through S14). Results of 2-way sensitivity analyses varying both EPS risk stratification efficacy and ICD utility simultaneously demonstrated that the optimal management strategy varies on the basis of both parameters, with greater ICD utility generally favoring device-based approaches, and greater EPS risk stratification efficacy increasing the range of utilities over which EPS should be considered (Figure 3).

Additional 1-way sensitivity analyses demonstrated that the death rate following arrest without ICD and the ICD generator change interval were also influential on clinical and cost-effectiveness estimates. Variation in the cost of initial ICD implant and EPS had relatively little influence (Table S15 and Figures S2, S3).

Probabilistic Sensitivity Analyses

Probabilistic sensitivity analyses demonstrated considerable model uncertainty, although most clinical and cost-effectiveness estimates were broadly in agreement with the base case analysis (Tables S16 and S17). EPS-guided ICD was more effective than observation in the vast majority of simulations (99.1% for subcutaneous; 96.7% for transvenous). Upfront ICD was more effective than observation in 69.0% of simulations using subcutaneous ICD, and 50.6% of simulations using transvenous ICD. Across all strategies, upfront subcutaneous ICD maximized QALYs in 38.7% of simulations, followed by EPS-guided subcutaneous ICD in 25.7% (Figure 4). EPS-guided subcutaneous ICD had the highest probability of cost-effectiveness at the willingness-to-pay threshold of $100 000/QALY (43%, Figure 4). Probabilistic analysis results for the overall model are shown in Figure 4 and results for the device type-specific models are shown in Figure S4. Cost-effectiveness planes for the overall model and the device type-specific models are shown in Figure S5.

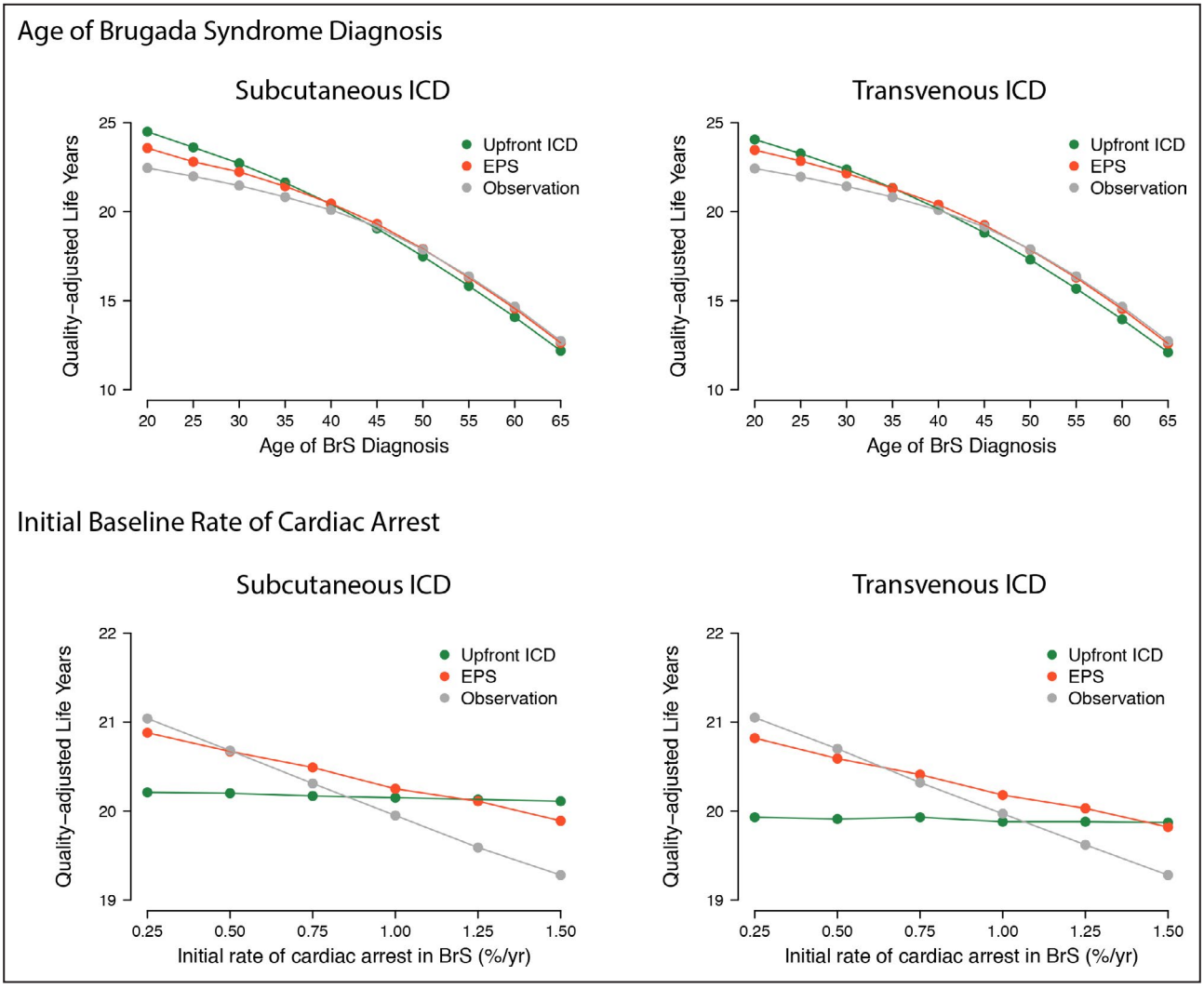

Figure 2. Effects of diagnosis age and initial rate of cardiac arrest on clinical effectiveness.
Depicted is the effect of varying Brugada syndrome diagnosis age (top panels) and initial yearly arrest rate (bottom panels) on the clinical effectiveness of: observation (gray), electrophysiologic study (orange), and upfront implantable cardioverter-defibrillator (green) strategies, using either subcutaneous (left panels) or transvenous (right panels) devices. The *y*-axis depicts total quality-adjusted life years lived. For the initial rate of arrest, the *x*-axis depicts the baseline rate at the start of simulation before applying exponential decay (see text). BrS indicates Brugada syndrome; EPS, electrophysiologic study; and ICD, implantable cardioverter-defibrillator.

Value of information analyses suggested that reducing parameter uncertainty would be highly valuable. The expected value of perfect information for the overall model was $8150 per individual. Assuming an asymptomatic spontaneous Type I BrS prevalence of 0.01%,[48] the expected value of a perfect estimate of ICD utility is ≈$97 million/year in the United States for subcutaneous devices and ≈$95 million/year for transvenous devices. A perfect estimate of the probability of death from arrest without an ICD is valued at ≈$41 million/year, and a perfect estimate of the yearly rate of arrest in asymptomatic BrS is valued at ≈$26 million/year. Other parameters for which reduced uncertainty is estimated to have substantial value are shown in Tables S18 and S19.

DISCUSSION

In a decision-analytic model simulating 2 million individuals with asymptomatic BrS and spontaneous type I electrocardiographic pattern, we found that optimal management varies based on patient characteristics. Specifically, ICD-based approaches maximized QALYs among individuals age <35 years (upfront ICD) up to approximately age 50 years (ICD after EPS-based risk stratification), whereas observation was most appropriate among individuals older than age 50. Similar patterns were observed with variation in the rate of arrest. The clinical and cost-effectiveness of ICD-based strategies also depended importantly on EPS risk stratification efficacy and the effects of living with

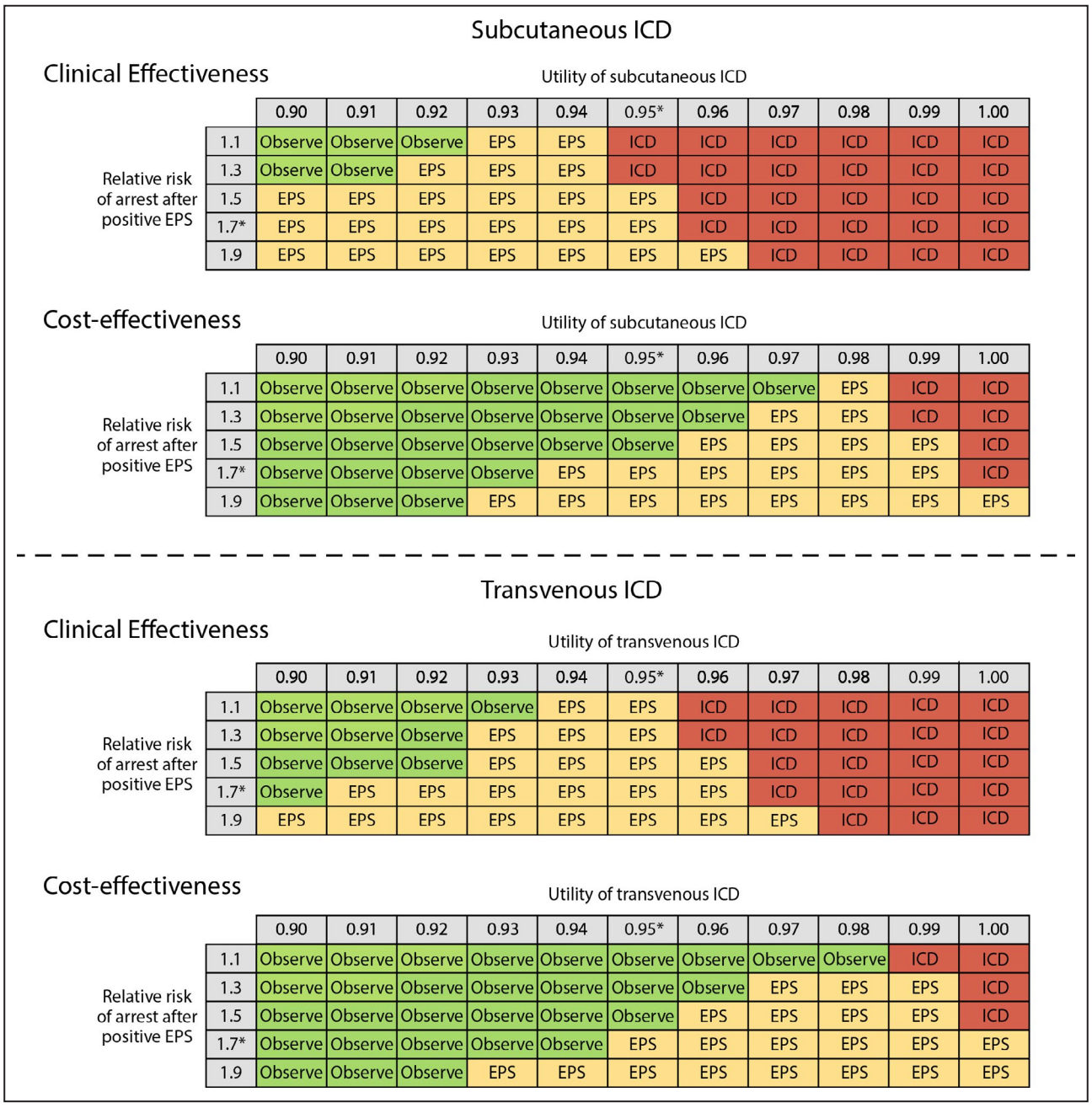

Figure 3. Optimal strategy as a function of electrophysiologic study risk stratification efficacy and implantable cardioverter-defibrillator utility.

Depicted are the results of 2-way sensitivity analyses across varying efficacy of electrophysiologic study for risk stratification (rows) vs utility of implantable cardioverter-defibrillator (columns), for models including subcutaneous devices (upper panels) and transvenous devices (lower panels). In each plot, the optimal strategy for each set of conditions (green: observe, yellow: EPS, red: upfront implantable cardioverter-defibrillator) is depicted in each box, where optimal is defined as the strategy maximizing quality-adjusted life years (effectiveness tables), or the most effective strategy having an incremental cost-effectiveness ratio under the willingness-to-pay threshold of $100 000 per quality-adjusted life years (cost-effectiveness tables). Parameters representing the base case scenario (implantable cardioverter-defibrillator utility 0.95 and relative risk of arrest after positive electrophysiologic study 1.7) are starred. EPS indicates electrophysiologic study; and ICD, implantable cardioverter-defibrillator.

an ICD on quality-of-life. Notably, subcutaneous ICDs were more effective than transvenous ICDs, owing primarily to lower device-related morbidity and mortality. Overall, in a condition sufficiently rare that a definitive outcomes trial is likely impractical, and in which optimal management is currently uncertain, our model provides important evidence the management of individuals with asymptomatic BrS and spontaneous Type

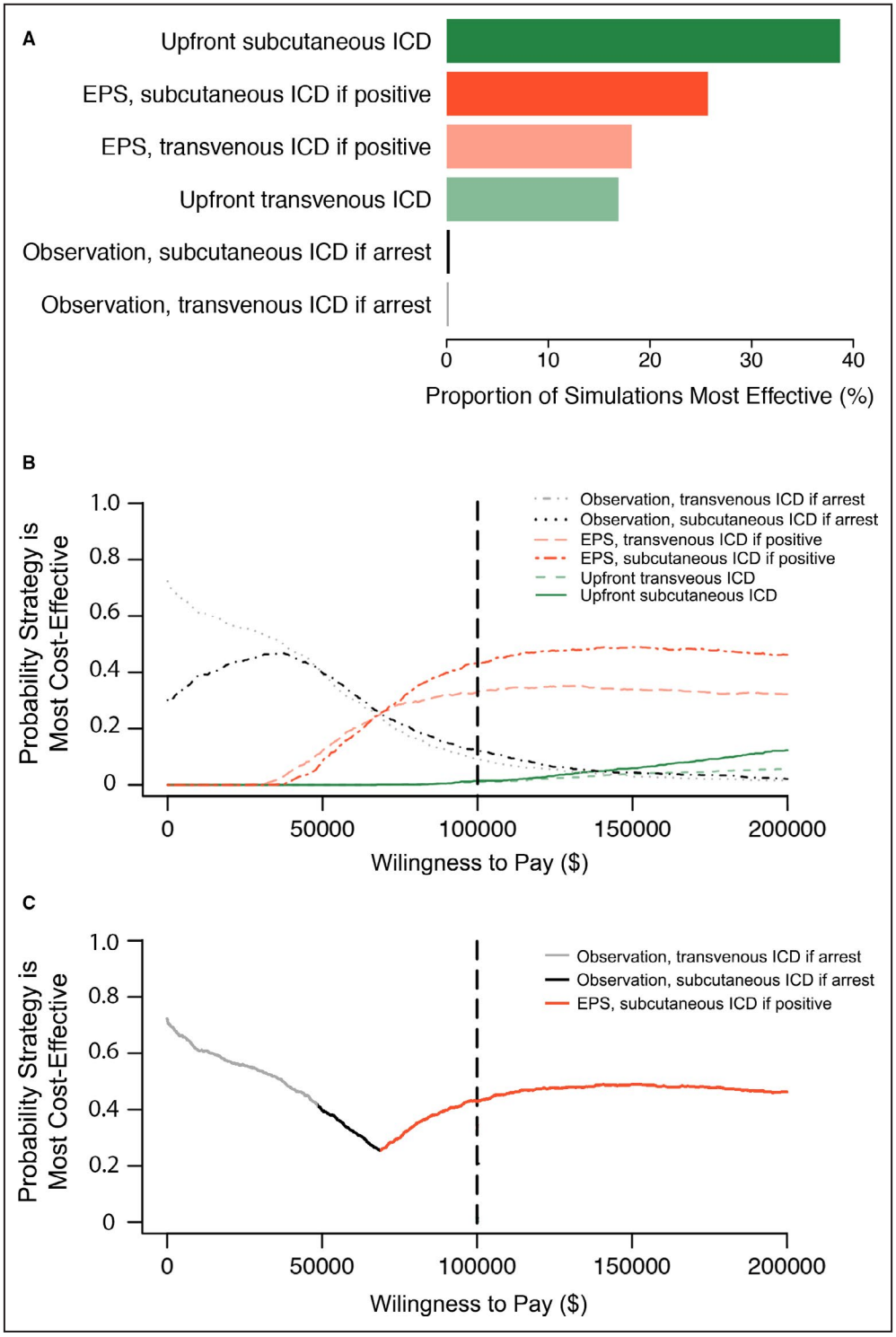

Figure 4. Clinical and cost-effectiveness in probabilistic sensitivity analyses.
Depicted are the results of 1000 runs of probabilistic sensitivity analysis, which estimates the effects of parameter uncertainty on clinical and cost-effectiveness estimates. **A**, The proportion of times each strategy resulted in the greatest overall clinical effectiveness (ie, highest quality-adjusted life years). **B**, A cost-effectiveness acceptability curve, which depicts the probability that each strategy is the most cost-effective option across increasing willingness-to-pay (*x*-axis). **C**, A cost-effectiveness acceptability frontier, which depicts the preferred strategy (by color) and its probability of cost-effectiveness across increasing willingness-to-pay (*x*-axis). For (**B** and **C**), the willingness-to-pay threshold of $100 000/quality-adjusted life year used to define cost-effectiveness in this study is depicted by the vertical hashed line. EPS indicates electrophysiologic study; and ICD, implantable cardioverter-defibrillator.

I pattern should be tailored based on patient characteristics, and highlight the need for more precise estimates within this population.

Our results support and extend previous work by quantifying the comparative effectiveness of both EPS-guided and upfront ICD-based approaches in asymptomatic BrS. In a decision-analytic model including individuals with BrS and high-risk features (eg, aborted SCD), Wang et al[54] found that transvenous ICDs were effective compared with observation with 20 QALYs gained/individual at $9591/QALY. Our model found that device-based strategies are specifically effective for patients with asymptomatic BrS with a spontaneous type I pattern—the population for whom ideal management is most uncertain. Since asymptomatic individuals are lower risk, our effectiveness estimates are more modest and exhibit important variation according to patient characteristics.

On balance, our results support a tailored approach to management of asymptomatic BrS. Although ICD-based strategies were effective under conditions representative of an average-risk asymptomatic BrS population, observation was preferable within important subgroups, such as patients over age 50. It is likely that younger patients with BrS derive greater benefit from ICD given longer average life expectancy leading to greater cumulative risk of an arrest, whereas event rates appear to decline with age.[29,30,33] ICD-based strategies were also favored as the cardiac arrest rate increased. Therefore, in the absence of specific recommendations for or against device-based therapy within the overall asymptomatic BrS population,[6] our results provide important evidence that ICD-based strategies should be considered for certain patients such as those diagnosed at a younger age or who possess a higher anticipated event rate.

Our results suggest that the benefit of ICD-based strategies in appropriately selected patients may be considerable, particularly using subcutaneous ICDs. When compared with observation, EPS-guided ICD implant resulted in a net gain of ≈0.3 to 0.4 QALY, or about 3 adjusted months of life per individual. Although modest, such QALY gains are comparable with those observed with primary prevention ICD in elderly individuals,[55] and may be substantial across a population. When a prophylactic ICD strategy is pursued, our results generally support a preference for subcutaneous devices. When compared directly, EPS-guided and upfront subcutaneous ICD strategies resulted in gains of roughly 0.1 to 0.3 QALY per individual when compared with their transvenous counterparts. Across all strategies, EPS-guided subcutaneous ICD offered favorable cost-effectiveness. Of note, in probabilistic analyses upfront subcutaneous ICD maximized outcomes in over one third of simulations, yet was only cost-effective in a small fraction. Since cost of ICD revision and maintenance were influential parameters, our results suggest that efforts to improve subcutaneous ICD technology and reduce the costs associated with revision and maintenance may substantially improve cost-effectiveness. Notably, long-term outcomes for subcutaneous ICDs are less well-understood,[10,11] and future work is needed to confirm that patterns of safety and efficacy observed with subcutaneous devices continue to hold after decades of follow-up.

Our findings highlight a critical need for improved quantification of clinical outcomes among individuals with asymptomatic BrS. We observed that key parameters such as BrS diagnosis age and rate of arrest have substantial impact on the optimal management strategy for individuals with asymptomatic BrS. For example, we found that the expected value of a perfect estimate of the population-based arrest rate in BrS is ≈$26 million per year in the United States, justifying substantial resource use aimed at obtaining more accurate estimates. Nevertheless, prospectively collected outcomes data reporting on such events beyond a handful of years remain limited. Although we calibrated our model to arrest rates estimated in multiple studies among middle-aged[2,29,30] and older individuals,[29,30,33] and varied the initial arrest rate systematically in detailed sensitivity analyses, it is likely that more robust long-term event data would improve the precision of our effectiveness estimates. We also observed that ICD-related utility was consistently influential. Since the quality-of-life impact of an ICD may vary across individuals, incorporation of patient-reported outcomes and values may facilitate more personalized BrS management.[56] Likewise, EPS risk stratification efficacy was an important determinant of effectiveness for EPS-guided strategies. Although we used a contemporary multicenter pooled analysis to estimate EPS risk stratification performance in asymptomatic BrS,[2] past studies have been inconsistent.[50,57] Our sensitivity analyses support EPS-guided approaches over upfront strategies as long as the relative risk of arrest is >1.1 for transvenous ICD or >1.4 for subcutaneous ICD. Ultimately, we submit that future work is critical to better quantify critical parameters such as arrest rates, ICD utility, and EPS risk stratification performance. Nevertheless, we note that current clinical guidelines use the same limited evidence base used in our simulations, which may underlie the current absence of explicit recommendations for or against device-based therapy.[6]

The current study should be considered in the context of design. First, we did not model medical therapy for SCD prevention in BrS (eg, quinidine), since guidelines emphasize device-based therapy.[58] Second, limited evidence suggests that subcutaneous ICDs may be less efficacious in BrS because of T-wave oversensing.[59] We did not incorporate this possibility since improved algorithms have likely overcome previous limitations.[60] Third, some studies

suggest that the frequency of time spent in spontaneous type I Brugada pattern is a risk factor for adverse outcomes.[61] We did not explicitly incorporate time spent with a manifest Brugada pattern in our models. Fourth, although our models suggest that a patient's anticipated event rate is an important determinant of optimal management, it is currently difficult to estimate. Our findings therefore identify the ability to accurately quantify risk of SCD among individuals with asymptomatic BrS as a critical unmet need. Fifth, although we used previously published sources to estimate costs, we acknowledge that that imperfect cost estimates are a limitation of our analysis. We submit that contemporary studies reporting on costs of BrS-related events and interventions would enable more precise cost-effectiveness estimates. Sixth, clinical decisions about indwelling devices should always be made with consideration of the individual circumstances at hand, and our simulation results cannot substitute for good clinical judgment.

CONCLUSIONS

Our decision-analytic model found that ICD-based strategies are likely to be effective in subsets of average-risk individuals with asymptomatic BrS and spontaneous type I Brugada pattern, particularly those diagnosed at younger ages. Nevertheless, observation appears appropriate in certain subgroups, such as individuals aged >50 years, or those in whom the expected malignant arrhythmia rate is <0.5%/year upon initial diagnosis. Therefore, ICD-based management of asymptomatic BrS should be tailored based on patient characteristics. Future studies of the epidemiology of BrS would enable more precise clinical and cost-effectiveness estimates and clarify the potential roles of emerging therapies (eg, quinidine, catheter ablation) and improved forms of risk stratification.

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Supplementary Material

Datas S1–S2
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Supplemental Material

Data S1. Supplemental Methods.

Arrest rate modeling

The yearly rate of cardiac arrest in the base case was assumed to be 1.02% per year based on multiple estimates of the arrest rate among middle-aged individuals with asymptomatic BrS (see **Table 1** in main text). However, since such studies provide only several years of follow-up, and separate studies suggest a lower incidence of arrest among individuals at older ages, we modeled an exponential decline in the rate of arrest using the equation $0.0102 \times e^{-t \times 0.0742}$, where t = years lived. This equation models an initial rate of 0.0102 at age 41 (start of simulation) calibrated to a target rate of 0.0025 at age 60. The rate of arrest continues to decline following the same decay rate until death or end of simulation.

In analyses assessing the effect of varying BrS diagnosis age, the same equation and rates were used, with the exception that individuals aged <41 were assumed to have a yearly rate of arrest of 1.02% until reaching age 41, at which point the decay began. Although some data suggest an even higher rate of arrest (up to 2%/year) among younger individuals with BrS,[30] we chose to maintain a constant rate of 1.02% per year as a conservative assumption given potential for biased estimates of event rates, especially within studies assessing younger individuals with BrS (**Table**).

Table. Rate of arrest according to age in the base case analysis.

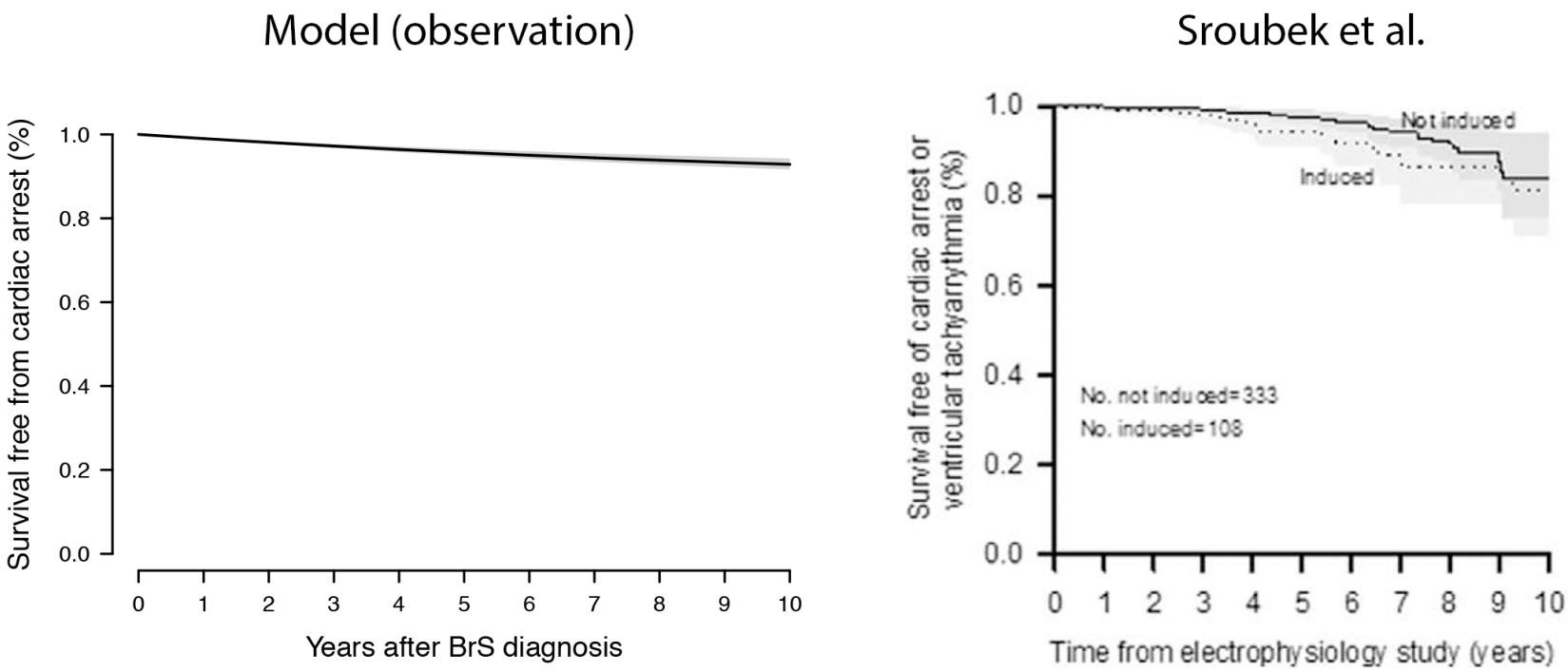
Age	Yearly rate of arrest
20-41	0.0102
45	0.0076
50	0.0052
55	0.0036
60	0.0025
70	0.0012
80	0.00056

Electrophysiologic study modeling

Based on published data, the relative risk of arrest after EPS was assumed to be 1.67 after positive findings (i.e., inducible ventricular arrhythmia with single or double extra stimuli) and 0.753 after negative findings. Similarly, the probability of a positive EPS was set to 0.27 and the probability of a negative EPS was set to 0.73 (see **Table 1** in the main text). These values are similar, but not identical, to the original source since they were calibrated in order to maintain an arrest rate equal to the comparable population not undergoing EPS (i.e., such that simply undergoing EPS does not change the population level arrest rate). We maintained the respective rate ratios when performing sensitivity analyses varying the arrest rate, so as to maintain a comparable event rate across strategies.

Data S2. Model validation

Survival free of cardiac arrest



To assess validity of the baseline rate of cardiac arrest in asymptomatic BrS (a key input parameter), we compared the cumulative incidence of cardiac arrest at 10 years with the 10-year survival free of cardiac arrest or ventricular tachyarrhythmia reported by Sroubek et al[2] (which was not included as an explicit input or calibration target in our model). We found the rates to be comparable with consideration to uncertainty in our model (left panel) and uncertainty in the published result (right panel, figure from Sroubek et al reproduced with permission[2]). BrS=Brugada syndrome

Table S1. Cost effectiveness analysis (electrophysiologic study strategy excluded)

Strategy	QALYs	Costs	ΔQALYs	ΔCosts	ICER (ΔCosts/ΔQALYs)	Notes*
All strategies						
Upfront subcutaneous ICD	20.154	$94,366.88	0.25328	$90,931.81	$359,016.14	Not cost-effective
Observation (subcutaneous ICD if arrest)	19.902	$3,615.57	0.00138	$180.50	$130,339.21	Not cost-effective
Observation (transvenous ICD if arrest)	19.900	$3,435.07	-	-	-	Baseline
Upfront transvenous ICD	19.891	$77,597.65	-	-	-	Dominated
Subcutaneous ICD only						
Upfront ICD	20.164	$94,422.19	0.20824	$90,770.95	$435,908.32	Not cost-effective
Observation (ICD if arrest)	19.955	$3,651.24	-	-	-	Baseline
Transvenous ICD only						
Upfront ICD	19.879	$77,547.81	-	-	-	Dominated
Observation (ICD if arrest)	19.928	$3,458.44	-	-	-	Baseline

*All results presented per individual at willingness-to-pay threshold of $100,000 per QALY gained
Preferred strategy for each scenario is highlighted in green
ICD=implantable cardioverter-defibrillator; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life-year

Table S2. Clinical effectiveness endpoints for subcutaneous ICD strategies stratified by initial rate of arrest in asymptomatic BrS (per 100,000 individuals)

Strategy*	# ICDs placed	Acute procedural or device-related complications†	Chronic device complications‡	Inappropriate shocks	Arrest deaths	Procedural or device-related deaths	Cardiac deaths§	Total deaths
Arrest rate 0.25%/yr								
Observation	390	50	130	220	2720	0	2730	80990
Electrophysiologic study	27150	8380	12170	20290	1580	280	1870	80780
Upfront ICD	99780‖	15280	44790	72770	160	1010	1170	80650
Arrest rate 0.5%/yr								
Observation	750	90	250	420	5350	10	5350	81590
Electrophysiologic study	27350	8400	12190	20380	3110	280	3400	81140
Upfront ICD	99780	15300	44830	74700	300	1020	1320	80670
Arrest rate 0.75%/yr								
Observation	1110	140	370	620	7910	10	7910	82060
Electrophysiologic study	27560	8420	12260	20490	4590	290	4880	81470
Upfront ICD	99780	15260	44780	74540	450	1020	1470	80720
Arrest rate 1%/yr								
Observation	1470	180	490	820	10380	10	10390	82610
Electrophysiologic study	27760	8470	12310	20610	6040	290	6330	81810
Upfront ICD	99780	15240	44730	74630	600	1020	1620	80800
Arrest rate 1.25%/yr								
Observation	1810	220	620	1020	12780	10	12800	83080
Electrophysiologic study	27940	8460	12340	20670	7500	280	7780	82170
Upfront ICD	99780	15210	44580	74450	710	1020	1730	80800
Arrest rate 1.5%/yr								
Observation	2120	260	720	1190	15090	20	15100	83530
Electrophysiologic study	28130	8500	12430	20740	8860	280	9140	82430
Upfront ICD	99780	15250	44660	74520	850	1010	1860	80810

*All outcomes represent results of individual-level simulation until death or age 90 as rates per 100,000 individuals
†Procedural or device-related complications include access site complication, pneumothorax, skin infection, pocket hematoma, lead malfunction, or any other device defect requiring immediate revision
‡Chronic complications include device infection, pocket hematoma, lead failure, or any other device defect requiring revision
§Cardiac deaths represent sum of arrest-related deaths and procedural or device-related deaths
‖Values slightly less than 100000 due to age and sex-related cycle death prior to ICD placement
ICD=implantable cardioverter-defibrillator

Table S3. Clinical and cost-effectiveness of subcutaneous ICD strategies stratified by annual rate of arrest in asymptomatic BrS

Subcutaneous ICD Strategy	QALYs	Costs	ΔQALYs	ΔCosts	ICER (ΔCosts/ΔQALYs)	Notes*
Arrest rate 0.25%/yr						
Observation (ICD if arrest)	21.020	$929.88	-	-	-	Baseline
Electrophysiologic study	20.880	$29,865.72	-	-	-	Dominated
Upfront ICD	20.206	$94,572.69	-	-	-	Dominated
Arrest rate 0.50%/yr						
Electrophysiologic study	20.670	$30,347.74	0.02030	$28,530.91	$1,405,121.15	Not cost-effective
Observation (ICD if arrest)	20.650	$1,816.83	-	-	-	Baseline
Upfront ICD	20.188	$94,508.14	-	-	-	Dominated
Arrest rate 0.75%/yr						
Electrophysiologic study	20.461	$30,823.79	0.17189	$28,131.12	$163,654.84	Not cost-effective
Observation (ICD if arrest)	20.290	$2,692.66	-	-	-	Baseline
Upfront ICD	20.176	$94,457.41	-	-	-	Dominated
Arrest rate 1.00%/yr						
Electrophysiologic study	20.261	$31,294.80	0.33145	$27,741.36	$83,696.61	Cost-effective
Upfront ICD	20.153	$94,362.77	-	-		Dominated
Observation (ICD if arrest)	19.930	$3,553.43				Baseline
Arrest rate 1.25%/yr						
Upfront ICD	20.145	$94,333.38	0.09331	$62,594.23	$670,854.23	Not cost-effective
Electrophysiologic study	20.051	$31,739.15	0.46503	$27,350.96	$58,815.33	Cost-effective
Observation (ICD if arrest)	19.586	$4,388.19	-	-	-	Baseline
Arrest rate 1.50%/yr						
Upfront ICD	20.132	$94,290.55	0.27273	$62,093.75	$227,674.08	Not cost-effective
Electrophysiologic study	19.859	$32,196.81	0.60935	$27,022.18	$44,346.03	Cost-effective
Observation (ICD if arrest)	19.249	$5,174.62	-	-	-	Baseline

*All results presented per individual at willingness-to-pay threshold of $100,000 per QALY gained
Preferred strategy for each scenario is highlighted in green
ICD=implantable cardioverter-defibrillator; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life-year

Table S4. Clinical effectiveness endpoints for transvenous ICD strategies stratified by annual rate of arrest in asymptomatic BrS (per 100,000 individuals)

Strategy*	# ICDs placed	Acute procedural or device-related complications†	Chronic device complications‡	Inappropriate shocks	Arrest deaths	Procedural or device-related deaths	Cardiac deaths§	Total deaths
Arrest rate 0.25%/yr								
Observation	380	30	230	150	2720	10	2730	80950
Electrophysiologic study	27140	6650	20940	15420	1570	1090	2660	81040
Upfront ICD	99780‖	8890	77140	56810	150	4030	4180	81410
Arrest rate 0.5%/yr								
Observation	750	60	450	300	5350	20	5370	81530
Electrophysiologic study	27340	6660	20980	15470	3060	1090	4160	81350
Upfront ICD	99780	8900	77050	56670	300	4000	4300	81480
Arrest rate 0.75%/yr								
Observation	1120	80	650	440	7910	30	7940	82070
Electrophysiologic study	27560	6670	21160	15580	4570	1090	5660	81650
Upfront ICD	99780	8870	76990	56680	430	3990	4420	81500
Arrest rate 1%/yr								
Observation	1470	110	860	590	10370	50	10410	82610
Electrophysiologic study	27740	6690	21230	15530	6040	1100	7140	81980
Upfront ICD	99780	8890	76850	56630	570	4010	4580	81550
Arrest rate 1.25%/yr								
Observation	1800	130	1060	730	12740	50	12790	83130
Electrophysiologic study	27940	6720	21310	15610	7440	1110	8560	82300
Upfront ICD	99770	8880	76860	56620	710	3970	4680	81590
Arrest rate 1.5%/yr								
Observation	2110	150	1240	860	15070	70	15130	83560
Electrophysiologic study	28110	6730	21420	15650	8840	1120	9660	82670
Upfront ICD	99770	8880	76760	56570	840	3980	4820	81630

*All outcomes represent results of individual-level simulation until death or age 90 as rates per 100,000 individuals
†Procedural or device-related complications include access site complication, pneumothorax, skin infection, pocket hematoma, lead malfunction, or any other device defect requiring immediate revision
‡Chronic complications include device infection, pocket hematoma, lead failure, or any other device defect requiring revision
§Cardiac deaths represent sum of arrest-related deaths and procedural or device-related deaths
‖Values slightly less than 100000 due to age and sex-related cycle death prior to ICD placement
ICD=implantable cardioverter-defibrillator

Table S5. Clinical and cost-effectiveness of transvenous ICD strategies stratified by annual rate of arrest in asymptomatic BrS

Transvenous ICD Strategy	QALYs	Costs	ΔQALYs	ΔCosts	ICER (ΔCosts/ΔQALYs)	Notes*
Arrest rate 0.25%/yr						
Observation (ICD if arrest)	21.029	$878.06	-	-	-	Baseline
Electrophysiologic study	20.809	$25,289.98	-	-	-	Dominated
Upfront ICD	19.936	$77,738.30	-	-	-	Dominated
Arrest rate 0.50%/yr						
Observation (ICD if arrest)	20.651	$1,734.87	-	-	-	Baseline
Electrophysiologic study	20.599	$25,745.21	-	-	-	Dominated
Upfront ICD	19.918	$77,678.64	-	-	-	Dominated
Arrest rate 0.75%/yr						
Electrophysiologic study	20.396	$26,223.51	0.10727	$23,653.78	$220,496.90	Not cost-effective
Observation (ICD if arrest)	20.289	$2,569.73	-	-	-	Baseline
Upfront ICD	19.905	$77,640.72	-	-	-	Dominated
Arrest rate 1.00%/yr						
Electrophysiologic study	20.185	$26,641.67	0.25564	$23,266.05	$91,012.04	Cost-effective
Observation (ICD if arrest)	19.929	$3,375.62	-	-	-	Baseline
Upfront ICD	19.888	$77,586.22	-	-	-	Dominated
Arrest rate 1.25%/yr						
Electrophysiologic study	19.985	$27,090.27	0.40121	$22,929.01	$57,149.40	Cost-effective
Upfront ICD	19.875	$77,544.74	-	-	-	Dominated
Observation (ICD if arrest)	19.584	$4,161.26	-	-	-	Baseline
Arrest rate 1.50%/yr						
Upfront ICD	19.858	$77,491.20	0.06971	$49,992.93	$717,172.97	Not cost-effective
Electrophysiologic study	19.788	$27,498.27	0.54132	$22,581.16	$41,714.89	Cost-effective
Observation (ICD if arrest)	19.247	$4,917.12	-	-	-	Baseline

*All results presented per individual at willingness-to-pay threshold of $100,000 per QALY gained
Preferred strategy for each scenario is highlighted in green
ICD=implantable cardioverter-defibrillator; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life-year

Table S6. Clinical and cost-effectiveness of all strategies stratified by annual rate of arrest in asymptomatic BrS

Strategy	QALYs	Costs	ΔQALYs	ΔCosts	ICER	Notes*
Arrest rate 0.25%/yr						
Observation (transvenous ICD if arrest)	21.029	$878.06	-	-	-	Baseline
Observation (subcutaneous ICD if arrest)	21.020	$929.88	-	-	-	Dominated
Electrophysiologic study (subcutaneous ICD if positive)	20.880	$29,865.72	-	-	-	Dominated
Electrophysiologic study (transvenous ICD if positive)	20.809	$25,289.98	-	-	-	Dominated
Upfront subcutaneous ICD	20.206	$94,572.69	-	-	-	Dominated
Upfront transvenous ICD	19.936	$77,738.30	-	-	-	Dominated
Arrest rate 0.50%/yr						
Electrophysiologic study (subcutaneous ICD if positive)	20.670	$30,347.74	0.01958	$28,612.87	$1,461,520.52	Not cost-effective
Observation (transvenous ICD if arrest)	20.651	$1,734.87	-	-	-	Baseline
Observation (subcutaneous ICD if arrest)	20.650	$1,816.83	-	-	-	Dominated
Electrophysiologic study (transvenous ICD if positive)	20.599	$25,745.21	-	-	-	Dominated
Upfront subcutaneous ICD	20.188	$94,508.14	-	-	-	Dominated
Upfront transvenous ICD	19.918	$77,678.64	-	-	-	Dominated
Arrest rate 0.75%/yr						
Electrophysiologic study (subcutaneous ICD if positive)	20.461	$30,823.79	0.17189	$28,131.12	$163,654.84	Not cost-effective
Electrophysiologic study (transvenous ICD if positive)	20.396	$26,223.51	-	-	-	Dominated
Observation (subcutaneous ICD if arrest)	20.290	$2,692.66	0.00090	$122.93	$137,110.19	Not cost-effective
Observation (transvenous ICD if arrest)	20.289	$2,569.73	-	-	-	Baseline
Upfront subcutaneous ICD	20.176	$94,457.41	-	-	-	Dominated
Upfront transvenous ICD	19.905	$77,640.72	-	-	-	Dominated
Arrest rate 1.00%/yr						
Electrophysiologic study (subcutaneous ICD if positive)	20.261	$31,294.80	0.33167	$27,919.18	$84,177.10	Cost-effective
Electrophysiologic study (transvenous ICD if positive)	20.185	$26,641.67	-	-	-	Dominated
Upfront subcutaneous ICD	20.153	$94,362.77	-	-	-	Dominated
Observation (subcutaneous ICD if arrest)	19.930	$3,553.43	-	-	-	Dominated
Observation (transvenous ICD if arrest)	19.929	$3,375.62	-	-	-	Baseline

Upfront ICD	19.888	$77,586.22	-	-	-	Dominated
Arrest rate 1.25%/yr						
Upfront subcutaneous ICD	20.145	$94,333.38	0.09331	$62,594.23	$670,854.23	Not cost-effective
Electrophysiologic study (subcutaneous ICD if positive)	20.051	$31,739.15	0.06636	$4,648.88	$70,052.01	Cost-effective
Electrophysiologic study (transvenous ICD if positive)	19.985	$27,090.27	0.40121	$22,929.01	$57,149.40	Cost-effective
Upfront transvenous ICD	19.875	$77,544.74	-	-	-	Dominated
Observation (subcutaneous ICD if arrest)	19.586	$4,388.19	-	-	-	Dominated
Observation (transvenous ICD if arrest)	19.584	$4,161.26	-	-	-	Baseline
Arrest rate 1.50%/yr						
Upfront subcutaneous ICD	20.132	$94,290.55	0.27273	$62,093.75	$227,674.08	Not cost-effective
Electrophysiologic study (subcutaneous ICD if positive)	19.859	$32,196.81	0.07052	$4,698.53	$66,630.37	Cost-effective
Upfront transvenous ICD	19.858	$77,491.20	-	-	-	Dominated
Electrophysiologic study (transvenous ICD if positive)	19.788	$27,498.27	0.54132	$22,581.16	$41,714.89	Cost-effective
Observation (subcutaneous ICD if arrest)	19.249	$5,174.62	-	-	-	Dominated
Observation (transvenous ICD if arrest)	19.247	$4,917.12	-	-	-	Baseline

*All results presented per individual at willingness-to-pay threshold of $100,000 per QALY gained
Preferred strategy for each scenario is highlighted in green
ICD=implantable cardioverter-defibrillator; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life-year

Table S7. Clinical effectiveness endpoints for subcutaneous ICD strategies stratified by age of BrS diagnosis

Strategy*	# ICDs placed	Acute procedural or device-related complications†	Chronic device complications‡	Inappropriate shocks	Arrest deaths	Procedural or device-related deaths	Cardiac deaths§	Total deaths
Age 20								
Observation	3520	570	1700	2850	24980	40	25020	86010
Electrophysiologic study	28990	10290	19110	31820	15040	430	15470	84250
Upfront ICD	99910‖	21290	67220	112090	1810	1520	3330	81740
Age 25								
Observation	3470	530	1510	2520	24640	30	24680	85930
Electrophysiologic study	28940	9900	17540	29240	14740	400	15140	84170
Upfront ICD	99870	19870	61760	102990	1660	1400	3060	81570
Age 30								
Observation	2600	370	1100	1810	18500	30	18530	84550
Electrophysiologic study	29500	9700	16440	27360	10860	380	11240	83170
Upfront ICD	99850	18470	56310	94090	1210	1270	2480	81380
Age 35								
Observation	2140	290	820	1370	15040	20	15060	83700
Electrophysiologic study	28130	9020	14180	23710	8840	330	9170	82620
Upfront ICD	99820	17150	50990	84980	930	1160	2090	81110
Age 40								
Observation	1610	200	560	940	11340	10	11360	82830
Electrophysiologic study	27840	8590	12570	21050	6640	290	6930	82000
Upfront ICD	99790	15730	45550	76010	650	1050	1700	80860
Age 45								
Observation	1100	120	330	560	7790	10	7800	81910
Electrophysiologic study	27530	8200	11020	18450	4490	260	4750	81210
Upfront ICD	99710	14310	40100	67120	410	920	1330	80570
Age 50								
Observation	740	80	190	310	5200	0	5200	81090
Electrophysiologic study	27280	7770	9490	15880	3010	230	3240	80660
Upfront ICD	99570	13010	34840	58270	250	830	1080	80230

Age 55								
Observation	490	50	110	180	3440	0	3450	80210
Electrophysiologic study	27080	7370	8110	13520	1970	200	2160	79890
Upfront ICD	99320	11690	29780	49710	150	720	870	79640
Age 60								
Observation	320	30	60	100	2210	0	2210	79170
Electrophysiologic study	26910	7020	6780	11310	1270	170	1440	78960
Upfront ICD	99010	10440	25010	41700	90	600	690	78700
Age 65								
Observation	200	20	30	50	1420	0	1420	77770
Electrophysiologic study	26760	6670	5510	9210	790	140	940	77560
Upfront ICD	98610	9230	20390	33910	50	520	570	77480

*All outcomes represent results of individual-level simulation until death or age 90 as rates per 100,000 individuals
†Procedural or device-related complications include access site complication, pneumothorax, skin infection, pocket hematoma, lead malfunction, or any other device defect requiring immediate revision
‡Chronic complications include device infection, pocket hematoma, lead failure, or any other device defect requiring revision
§Cardiac deaths represent sum of arrest-related deaths and procedural or device-related deaths
||Values slightly less than 100000 due to age and sex-related cycle death prior to ICD placement
ICD=implantable cardioverter-defibrillator

Table S8. Clinical and cost-effectiveness of subcutaneous ICD strategies stratified by age of BrS diagnosis

Subcutaneous ICD Strategy	QALYs	Costs ($)	ΔQALYs	ΔCosts ($)	ICER	Notes*
Age 20						
Upfront ICD	24.477	$115,070.20	0.87921	$75,750.72	$86,157.97	Cost-effective
Electrophysiologic study (ICD if positive)	23.598	$39,319.48	1.18003	$31,531.32	$26,720.77	Cost-effective
Observation (ICD if arrest)	22.418	$7,788.16	-	-	-	Baseline
Age 25						
Upfront ICD	23.647	$111,130.54	0.69060	$73,325.18	$106,176.22	Not cost-effective
Electrophysiologic study (ICD if positive)	22.956	$37,805.36	1.01196	$30,759.62	$30,396.21	Cost-effective
Observation (ICD if arrest)	21.944	$7,045.74	-	-	-	Baseline
Age 30						
Upfront ICD	22.711	$106,689.60	0.46388	$69,477.19	$149,774.73	Not cost-effective
Electrophysiologic study (ICD if positive)	22.247	$37,212.40	0.84150	$31,054.79	$36,903.88	Cost-effective
Observation (ICD if arrest)	21.405	$6,157.61	-	-	-	Baseline
Age 35						
Upfront ICD	21.642	$101,619.73	0.23286	$67,489.15	$289,823.35	Not cost-effective
Electrophysiologic study (ICD if positive)	21.409	$34,130.57	0.62718	$28,975.94	$46,200.69	Cost-effective
Observation (ICD if arrest)	20.782	$5,154.64	-	-	-	Baseline
Age 40						
Electrophysiologic study (ICD if positive)	20.449	$31,885.92	0.38447	$27,982.88	$72,782.85	Cost-effective
Upfront ICD	20.421	$95,828.81	-	-	-	Dominated
Observation (ICD if arrest)	20.065	$3,903.05	-	-	-	Baseline
Age 45						
Electrophysiologic study (ICD if positive)	19.321	$29,372.50	0.17003	$26,738.68	$157,263.19	Not cost-effective
Observation (ICD if arrest)	19.151	$2,633.82	-	-	-	Baseline
Upfront ICD	19.033	$89,253.60	-	-	-	Dominated
Age 50						
Electrophysiologic study (ICD if positive)	17.909	$26,905.79	0.01996	$25,164.52	$1,260,883.57	Not cost-effective
Observation (ICD if arrest)	17.889	$1,741.27	-	-	-	Baseline
Upfront ICD	17.487	$81,941.91	-	-	-	Dominated
Age 55						
Observation (ICD if arrest)	16.360	$1,138.48	-	-	-	Baseline
Electrophysiologic study (ICD if positive)	16.304	$24,445.98	-	-	-	Dominated

Upfront ICD	15.826	$74,111.48	-	-	-	Dominated
Age 60						
Observation (ICD if arrest)	14.643	$727.97	-	-	-	Baseline
Electrophysiologic study (ICD if positive)	14.541	$21,973.39	-	-	-	Dominated
Upfront ICD	14.066	$65,824.68	-	-	-	Dominated
Age 65						
Observation (ICD if arrest)	12.730	$459.81	-	-	-	Baseline
Electrophysiologic study (ICD if positive)	12.629	$19,422.31	-	-	-	Dominated
Upfront ICD	12.183	$56,974.69	-	-	-	Dominated

*All results presented per individual at willingness-to-pay threshold of $100,000 per QALY gained
Preferred strategy for each scenario is highlighted in green
ICD=implantable cardioverter-defibrillator; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life-year

Table S9. Clinical effectiveness endpoints for transvenous ICD strategies stratified by age of BrS diagnosis

Strategy*	# ICDs placed‖	Acute procedural or device-related complications†	Chronic device complications‡	Inappropriate shocks	Arrest deaths	Procedural or device-related deaths	Cardiac deaths§	Total deaths
Age 20								
Observation	3540	330	2960	2020	24960	160	25110	86020
Electrophysiologic study	28990	7540	32780	23990	15040	1670	16710	84510
Upfront ICD	99900	11570	115370	85130	1770	5890	7660	82830
Age 25								
Observation	3100	280	2420	1660	21810	130	21940	85360
Electrophysiologic study	28710	7370	30060	22040	13040	1540	14580	84000
Upfront ICD	99870	10910	106410	78340	1480	5450	6930	82550
Age 30								
Observation	2620	220	1880	1290	18520	100	18610	84570
Electrophysiologic study	28440	7180	27240	19930	10980	1410	12390	83500
Upfront ICD	99840	10300	97030	71400	1180	4990	6170	82260
Age 35								
Observation	2110	170	1410	950	15020	70	15090	83750
Electrophysiologic study	28130	6950	24430	17930	8820	1260	10080	82860
Upfront ICD	99820	9700	87880	64690	910	4530	5440	81940
Age 40								
Observation	1600	120	950	650	11320	50	11370	82870
Electrophysiologic study	27840	6740	21750	15980	6610	1130	7740	82150
Upfront ICD	99790	9000	78760	57980	640	4080	4720	81620
Age 45								
Observation	1100	80	570	390	7800	30	7830	81930
Electrophysiologic study	27520	6520	19130	14060	4490	1000	5490	81500
Upfront ICD	99710	8330	69710	51390	400	3620	4010	81240
Age 50								
Observation	740	50	330	230	520	20	5220	81100
Electrophysiologic study	27280	6320	16590	12200	2990	860	3850	80790
Upfront ICD	99570	7650	60580	44730	240	3180	3420	80890

Age 55								
Observation	480	30	190	130	3440	10	3450	80160
Electrophysiologic study	27080	6110	14180	10410	1970	750	2720	79990
Upfront ICD	99320	6950	52110	38380	150	2740	2890	80220
Age 60								
Observation	320	20	100	70	2230	10	2240	79190
Electrophysiologic study	26900	5960	11830	8650	1280	650	1930	79090
Upfront ICD	99000	6490	43410	31990	90	2330	2420	79260
Age 65								
Observation	200	10	50	30	1420	0	1420	77800
Electrophysiologic study	26750	5780	9630	7090	800	540	1340	77710
Upfront ICD	98600	5930	35490	26150	50	1940	1990	77920

*All outcomes represent results of individual-level simulation until death or age 90 as rates per 100,000 individuals
†Procedural or device-related complications include access site complication, pneumothorax, skin infection, pocket hematoma, lead malfunction, or any other device defect requiring immediate revision
‡Chronic complications include device infection, pocket hematoma, lead failure, or any other device defect requiring revision
§Cardiac deaths represent sum of arrest-related deaths and procedural or device-related deaths
||Values slightly less than 100000 due to age and sex-related cycle death prior to ICD placement
ICD=implantable cardioverter-defibrillator

Table S10. Clinical and cost-effectiveness of transvenous ICD strategies stratified by age of BrS diagnosis

Transvenous ICD Strategy	QALYs	Costs	ΔQALYs	ΔCosts	ICER (ΔCosts/ΔQALYs)	Notes*
Age 20						
Upfront ICD	24.056	$93,479.76	0.58034	$60,227.57	$103,779.94	Not cost-effective
Electrophysiologic study (ICD if positive)	23.476	$33,252.19	1.06298	$25,875.42	$24,342.37	Cost-effective
Observation (ICD if arrest)	22.413	$7,376.77	-	-	-	Baseline
Age 25						
Upfront ICD	23.258	$90,251.42	0.40474	$58,278.41	$143,991.51	Not cost-effective
Electrophysiologic study (ICD if positive)	22.853	$31,973.02	0.91794	$25,286.90	$27,547.40	Cost-effective
Observation (ICD if arrest)	21.935	$6,686.12	-	-	-	Baseline
Age 30						
Upfront ICD	22.362	$86,875.49	0.22276	$56,289.91	$252,687.83	Not cost-effective
Electrophysiologic study (ICD if positive)	22.139	$30,585.58	0.73678	$24,734.64	$33,571.29	Cost-effective
Observation (ICD if arrest)	21.402	$5,850.94	-	-	-	Baseline
Age 35						
Upfront ICD	21.328	$83,136.53	0.00704	$54,147.55	$7,691,367.18	Not cost-effective
Electrophysiologic study (ICD if positive)	21.321	$28,988.98	0.54265	$24,124.10	$44,456.24	Cost-effective
Observation (ICD if arrest)	20.778	$4,864.88	-	-	-	Baseline
Age 40						
Electrophysiologic study (ICD if positive)	20.379	$27,087.02	0.32162	$23,385.87	$72,711.74	Cost-effective
Upfront ICD	20.143	$78,475.02	-	-	-	Dominated
Observation (ICD if arrest)	20.057	$3,701.15	-	-	-	Baseline
Age 45						
Electrophysiologic study (ICD if positive)	19.255	$24,959.62	0.10309	$22,443.08	$217,693.59	Not cost-effective
Observation (ICD if arrest)	19.151	$2,516.53	-	-	-	Baseline
Upfront ICD	18.797	$73,131.91	-	-	-	Dominated
Age 50						
Observation (ICD if arrest)	17.886	$1,669.77	-	-	-	Baseline
Electrophysiologic study (ICD if positive)	17.863	$22,861.18	-	-	-	Dominated
Upfront ICD	17.256	$67,070.69	-	-	-	Dominated
Age 55						
Observation (ICD if arrest)	16.363	$1,090.67	-	-	-	Baseline

Electrophysiologic study (ICD if positive)	16.268	$20,737.96	-	-	-	Dominated
Upfront ICD	15.662	$60,462.15	-	-	-	Dominated
Age 60						
Observation (ICD if arrest)	14.640	$706.08	-	-	-	Baseline
Electrophysiologic study (ICD if positive)	14.505	$18,771.85	-	-	-	Dominated
Upfront ICD	13.933	$54,106.17	-	-	-	Dominated
Age 65						
Observation (ICD if arrest)	12.733	$444.97	-	-	-	Baseline
Electrophysiologic study (ICD if positive)	12.602	$16,960.64	-	-	-	Dominated
Upfront ICD	12.086	$47,804.15	-	-	-	Dominated

*All results presented per individual at willingness-to-pay threshold of $100,000 per QALY gained
Preferred strategy for each scenario is highlighted in green
ICD=implantable cardioverter-defibrillator; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life-year

Table S11. Clinical and cost-effectiveness of all strategies stratified by age of BrS diagnosis

Strategy	QALYs	Costs	ΔQALYs	ΔCosts	ICER	Notes*
Age 20						
Upfront subcutaneous ICD	24.477	$115,070.20	0.87921	$75,750.72	$86,157.97	Cost-effective
Upfront transvenous ICD	24.056	$93,479.76	-	-	-	Dominated
Electrophysiologic study (subcutaneous ICD if positive)	23.598	$39,319.48	0.12213	$6,067.29	$49,679.43	Cost-effective
Electrophysiologic study (transvenous ICD if positive)	23.476	$33,252.19	1.06298	$25,875.42	$24,342.37	Cost-effective
Observation (subcutaneous ICD if arrest)	22.418	$7,788.16	-	-	-	Dominated
Observation (transvenous ICD if arrest)	22.413	$7,376.77	-	-	-	Baseline
Age 25						
Upfront subcutaneous ICD	23.647	$111,130.54	0.69060	$73,325.18	$106,176.22	Not cost-effective
Upfront transvenous ICD	23.258	$90,251.42	-	-	-	Dominated
Electrophysiologic study (subcutaneous ICD if positive)	22.956	$37,805.36	0.10299	$5,832.34	$56,629.92	Cost-effective
Electrophysiologic study (transvenous ICD if positive)	22.853	$31,973.02	0.91794	$25,286.90	$27,547.40	Cost-effective
Observation (subcutaneous ICD if arrest)	21.944	$7,045.74	-	-	-	Dominated
Observation (transvenous ICD if arrest)	21.935	$6,686.12	-	-	-	Baseline
Age 30						
Upfront subcutaneous ICD	22.711	$106,689.60	0.46388	$69,477.19	$149,774.73	Not cost-effective
Upfront transvenous ICD	22.362	$86,875.49	-	-	-	Dominated
Electrophysiologic study (subcutaneous ICD if positive)	22.247	$37,212.40	0.10821	$6,626.82	$61,237.72	Cost-effective
Electrophysiologic study (transvenous ICD if positive)	22.139	$30,585.58	0.73678	$24,734.64	$33,571.29	Cost-effective
Observation (subcutaneous ICD if arrest)	21.405	$6,157.61	-	-	-	Dominated
Observation (transvenous ICD if arrest)	21.402	$5,850.94	-	-	-	Baseline
Age 35						
Upfront subcutaneous ICD	21.642	$101,619.73	0.23286	$67,489.15	$289,823.35	Not cost-effective
Electrophysiologic study (subcutaneous ICD if positive)	21.409	$34,130.57	0.08834	$5,141.59	$58,201.60	Cost-effective
Upfront transvenous ICD	21.328	$83,136.53	-	-	-	Dominated
Electrophysiologic study (transvenous ICD if positive)	21.321	$28,988.98	0.54265	$24,124.10	$44,456.24	Cost-effective
Observation (subcutaneous ICD if arrest)	20.782	$5,154.64	-	-	-	Dominated
Observation (transvenous ICD if arrest)	20.778	$4,864.88	-	-	-	Baseline
Age 40						
Electrophysiologic study (subcutaneous ICD if positive)	20.449	$31,885.92	0.38447	$27,982.88	$72,782.85	Cost-effective
Upfront subcutaneous ICD	20.421	$95,828.81	-	-	-	Dominated
Electrophysiologic study (transvenous ICD if positive)	20.379	$27,087.02	-	-	-	Dominated

Upfront transvenous ICD	20.143	$78,475.02	-	-	-	Dominated
Observation (subcutaneous ICD if arrest)	20.065	$3,903.05	0.00772	$201.90	$26,153.48	Cost-effective
Observation (transvenous ICD if arrest)	20.057	$3,701.15	-	-	-	Baseline
Age 45						
Electrophysiologic study (subcutaneous ICD if positive)	19.321	$29,372.50	0.16949	$26,855.97	$158,450.07	Not cost-effective
Electrophysiologic study (transvenous ICD if positive)	19.255	$24,959.62	-	-	-	Dominated
Observation (transvenous ICD if arrest)	19.151	$2,516.53	-	-	-	Baseline
Observation (subcutaneous ICD if arrest)	19.151	$2,633.82	-	-	-	Dominated
Upfront subcutaneous ICD	19.033	$89,253.60	-	-	-	Dominated
Upfront transvenous ICD	18.797	$73,131.91	-	-	-	Dominated
Age 50						
Electrophysiologic study (subcutaneous ICD if positive)	17.909	$26,905.79	0.02309	$25,236.02	$1,092,833.89	Not cost-effective
Observation (subcutaneous ICD if arrest)	17.889	$1,741.27	0.00313	$71.49	$22,809.25	Cost-effective
Observation (transvenous ICD if arrest)	17.886	$1,669.77	-	-	-	Baseline
Electrophysiologic study (transvenous ICD if positive)	17.863	$22,861.18	-	-	-	Dominated
Upfront subcutaneous ICD	17.487	$81,941.91	-	-	-	Dominated
Upfront transvenous ICD	17.256	$67,070.69	-	-	-	Baseline
Age 55						
Observation (transvenous ICD if arrest)	16.363	$1,090.67	-	-	-	Baseline
Observation (subcutaneous ICD if arrest)	16.360	$1,138.48	-	-	-	Dominated
Electrophysiologic study (subcutaneous ICD if positive)	16.304	$24,445.98	-	-	-	Dominated
Electrophysiologic study (transvenous ICD if positive)	16.268	$20,737.96	-	-	-	Dominated
Upfront subcutaneous ICD	15.826	$74,111.48	-	-	-	Dominated
Upfront transvenous ICD	15.662	$60,462.15	-	-	-	Dominated
Age 60						
Observation (subcutaneous ICD if arrest)	14.643	$727.97	0.00312	$21.88	$7,023.15	Cost-effective
Observation (transvenous ICD if arrest)	14.640	$706.08	-	-	-	Baseline
Electrophysiologic study (subcutaneous ICD if positive)	14.541	$21,973.39	-	-	-	Dominated
Electrophysiologic study (transvenous ICD if positive)	14.505	$18,771.85	-	-	-	Dominated
Upfront subcutaneous ICD	14.066	$65,824.68	-	-	-	Dominated
Upfront transvenous ICD	13.933	$54,106.17	-	-	-	Dominated
Age 65						
Observation (transvenous ICD if arrest)	12.733	$444.97	-	-	-	Baseline
Observation (subcutaneous ICD if arrest)	12.730	$459.81	-	-	-	Dominated
Electrophysiologic study (subcutaneous ICD if positive)	12.629	$19,422.31	-	-	-	Dominated

Electrophysiologic study (transvenous ICD if positive)	12.602	$16,960.64	-	-	-	Dominated
Upfront subcutaneous ICD	12.183	$56,974.69	-	-	-	Dominated
Upfront transvenous ICD	12.086	$47,804.15	-	-	-	Dominated

*All results presented per individual at willingness-to-pay threshold of $100,000 per QALY gained
Preferred strategy for each scenario is highlighted in green
ICD=implantable cardioverter-defibrillator; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life-year

Table S12. Clinical and cost-effectiveness of subcutaneous ICD strategies according to risk stratification efficacy of electrophysiologic study

Subcutaneous ICD Strategy	QALYs	Costs	ΔQALYs	ΔCosts	ICER	Notes*
Relative risk of ventricular arrhythmia/sudden cardiac death given positive EPS: 1.3						
Upfront ICD	20.154	$94,366.88	0.25190	$90,751.31	$360,273.33	Not cost-effective
Electrophysiologic study (ICD if positive)	20.101	$31,688.84	0.19933	$28,073.27	$140,838.37	Not cost-effective
Observation (ICD if arrest)	19.902	$3,615.57	-	-	-	Baseline
Relative risk of ventricular arrhythmia/sudden cardiac death given positive EPS: 1.5						
Electrophysiologic study (ICD if positive)	20.179	$31,486.34	0.27724	$27,870.77	$100,530.36	Not cost-effective
Upfront ICD	20.154	$94,366.88	-	-	-	Dominated
Observation (ICD if arrest)	19.902	$3,615.57	-	-	-	Baseline
Relative risk of ventricular arrhythmia/sudden cardiac death given positive EPS: 1.7 (base case)						
Electrophysiologic study (ICD if positive)	20.247	$31,324.61	0.34503	$27,709.04	$80,308.25	Cost-effective
Upfront ICD	20.154	$94,366.88	-	-	-	Dominated
Observation (ICD if arrest)	19.902	$3,615.57	-	-	-	Baseline
Relative risk of ventricular arrhythmia/sudden cardiac death given positive EPS: 1.9						
Electrophysiologic study (ICD if positive)	20.334	$31,098.61	0.43185	$27,483.04	$63,640.75	Cost-effective
Upfront ICD	20.154	$94,366.88	-	-	-	Dominated
Observation (ICD if arrest)	19.902	$3,615.57	-	-	-	Baseline

*All results presented per individual at willingness-to-pay threshold of $100,000 per QALY gained
Preferred strategy for each scenario is highlighted in green
ICD=implantable cardioverter-defibrillator; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life-year

Table S13. Clinical and cost-effectiveness of transvenous ICD strategies according to risk stratification efficacy of electrophysiologic study

Strategy	QALYs	Costs	ΔQALYs	ΔCosts	ICER	Notes*
Relative risk of ventricular arrhythmia/sudden cardiac death given positive EPS: 1.3						
Electrophysiologic study (ICD if positive)	20.029	$27,053.28	0.12821	$23,618.21	$184,210.48	Not cost-effective
Observation (ICD if arrest)	19.900	$3,435.07	-	-	-	Baseline
Upfront ICD	19.891	$77,597.65	-	-	-	Dominated
Relative risk of ventricular arrhythmia/sudden cardiac death given positive EPS: 1.5						
Electrophysiologic study (ICD if positive)	20.099	$26,836.64	0.19872	$23,401.57	$117,761.62	Not cost-effective
Observation (ICD if arrest)	19.900	$3,435.07	-	-	-	Baseline
Upfront ICD	19.891	$77,597.65	-	-	-	Dominated
Relative risk of ventricular arrhythmia/sudden cardiac death given positive EPS: 1.7 (base case)						
Electrophysiologic study (ICD if positive)	20.164	$26,693.45	0.26384	$23,258.38	$88,153.80	Cost-effective
Observation (ICD if arrest)	19.900	$3,435.07	-	-	-	Baseline
Upfront ICD	19.891	$77,597.65	-	-	-	Dominated
Relative risk of ventricular arrhythmia/sudden cardiac death given positive EPS: 1.9						
Electrophysiologic study (ICD if positive)	20.259	$26,479.35	0.35901	$23,044.28	$64,188.41	Cost-effective
Observation (ICD if arrest)	19.900	$3,435.07	-	-	-	Baseline
Upfront ICD	19.891	$77,597.65	-	-	-	Dominated

*All results presented per individual at willingness-to-pay threshold of $100,000 per QALY gained
Preferred strategy for each scenario is highlighted in green
ICD=implantable cardioverter-defibrillator; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life-year

Table S14. Clinical and cost-effectiveness of all strategies according to risk stratification efficacy of electrophysiologic study

Strategy	QALYs	Costs	ΔQALYs	ΔCosts	ICER	Notes*
Relative risk of ventricular arrhythmia/sudden cardiac death given positive EPS: 1.3						
Upfront subcutaneous ICD	20.154	$94,366.88	0.25328	$90,931.81	$1,192,367.69	Not cost-effective
Electrophysiologic study (subcutaneous ICD if positive)	20.101	$31,688.84	0.19933	$28,073.27	$140,838.37	Not cost-effective
Electrophysiologic study (transvenous ICD if positive)	20.029	$27,053.28	-	-	-	Dominated
Observation (subcutaneous ICD if arrest)	19.902	$3,615.57	0.00138	$180.50	$130,339.21	Not cost-effective
Observation (transvenous ICD if arrest)	19.900	$3,435.07	-	-	-	Baseline
Upfront transvenous ICD	19.891	$77,597.65	-	-	-	Dominated
Relative risk of ventricular arrhythmia/sudden cardiac death given positive EPS: 1.5						
Electrophysiologic study (subcutaneous ICD if positive)	20.179	$31,486.34	0.27862	$28,051.27	$100,678.52	Not cost-effective
Upfront subcutaneous ICD	20.154	$94,366.88	-	-	-	Dominated
Electrophysiologic study (transvenous ICD if positive)	20.099	$26,836.64	-	-	-	Dominated
Observation (subcutaneous ICD if arrest)	19.902	$3,615.57	-	-	-	Dominated
Observation (transvenous ICD if arrest)	19.900	$3,435.07	-	-	-	Baseline
Upfront transvenous ICD	19.891	$77,597.65	-	-	-	Dominated
Relative risk of ventricular arrhythmia/sudden cardiac death given positive EPS: 1.7 (base case)						
Electrophysiologic study (subcutaneous ICD if positive)	20.247	$31,324.61	0.34642	$27,889.54	$80,508.25	Cost-effective
Electrophysiologic study (transvenous ICD if positive)	20.164	$26,693.45	-	-	-	Dominated
Upfront subcutaneous ICD	20.154	$94,366.88	-	-	-	Dominated
Observation (subcutaneous ICD if arrest)	19.902	$3,615.57	-	-	-	Dominated
Observation (transvenous ICD if arrest)	19.900	$3,435.07	-	-	-	Baseline
Upfront transvenous ICD	19.891	$77,597.65	-	-	-	Dominated
Relative risk of ventricular arrhythmia/sudden cardiac death given positive EPS: 1.9						
Electrophysiologic study (subcutaneous ICD if positive)	20.247	$31,324.61	0.43323	$27,663.54	$63,853.95	Cost-effective
Electrophysiologic study (transvenous ICD if positive)	20.164	$26,693.45	-	-	-	Dominated
Upfront subcutaneous ICD	20.154	$94,366.88	-	-	-	Dominated
Observation (subcutaneous ICD if arrest)	19.902	$3,615.57	-	-	-	Dominated
Observation (transvenous ICD if arrest)	19.900	$3,435.07	-	-	-	Baseline
Upfront transvenous ICD	19.891	$77,597.65	-	-	-	Dominated

*All results presented per individual at willingness-to-pay threshold of $100,000 per QALY gained
Preferred strategy for each scenario is highlighted in green
ICD=implantable cardioverter-defibrillator; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life-year

Table S15. One-way sensitivity analysis

Strategy	Parameter	Base value	Lower bound	Upper bound	QALY at lower bound	QALY at upper bound	ICER at lower bound	ICER at upper bound	QALY Threshold*	ICER Threshold†
Subcutaneous										
Electrophysiologic study	Initial rate of arrest (%/year)	1.02	0.25	1.50	-0.14	0.61	Dominated below 0.5	44346	0.47	0.95
	Utility of ICD	0.95	0.9	1	0.069	0.62	401048	44622	Effective throughout	0.938
	Probability of death from arrest (no ICD)	0.875	0.6	1	0.15	0.42	179702	66556	Effective throughout	0.781
	Generator change interval	5	4	6	0.34	0.34	99422	70251	Effective throughout	Cost-effective throughout
	Cost of EPS ($)	7809	5000	10000	0.35	0.35	76581	83571	-	Cost-effective throughout
	Cost of ICD ($)	26702	20000	30000	0.35	0.35	77866	81809	-	Cost-effective throughout
Upfront ICD	Initial rate of arrest (%/year)	1.02	0.25	1.50	-0.14	0.61	Dominated below 1.25	227674	1.13	Never cost-effective
	Utility of ICD	0.95	0.9	1	-0.87	0.68	Dominated below 0.96	92257	0.956	0.997
	Probability of death from arrest (no ICD)	0.875	0.6	1	-0.17	0.02	Dominated below 1	2709443	0.973	Never cost-effective
	Generator change interval	5	4	6	0.25	0.26	Dominated	Dominated	Ineffective throughout	Never cost-effective
	Cost of EPS ($)	7809	5000	10000	-0.093	-0.093	Dominated	Dominated	-	Never cost-effective
	Cost of ICD ($)	26702	20000	30000	-0.093	-0.093	Dominated	Dominated	-	Never cost-effective
Transvenous										
Electrophysiologic study	Initial rate of arrest (%/year)	1.02	0.25	1.50	-0.22	0.54	Dominated below 0.75	41715	0.58	0.98

	Utility of ICD	0.95	0.9	1	-0.0083	0.54	Dominated below 0.91	43396	0.902	0.945
	Probability of death from arrest (no ICD)	0.875	0.6	1	0.083	0.36	268360	66707	0.82	0.84
	Generator change interval	6	4	8	0.27	0.26	121074	70037	Effective throughout	5.01
	Cost of EPS ($)	7809	5000	10000	0.26	0.26	82997	92716	Effective throughout	Cost-effective throughout
	Cost of ICD ($)	26083	20000	30000	0.26	0.26	85247	90025	Effective throughout	Cost-effective throughout
Upfront ICD	Initial rate of arrest (%/year)	1.02	0.25	1.50	-0.87	0.07	Dominated below 1.5	717173	1.40	Never cost-effective
	Utility of ICD	0.95	0.9	1	-1.04	0.49	Dominated below 0.97	103138	0.968	Never cost-effective
	Probability of death from arrest (no ICD)	0.875	0.6	1	-0.51	-0.17	Dominated	Dominated	Ineffective throughout	Never cost-effective
	Generator change interval	6	4	8	-0.27	-0.28	Dominated	Dominated	Ineffective throughout	Never cost-effective
	Cost of EPS ($)	7809	5000	10000	-0.29	-0.29	Dominated	Dominated	Ineffective throughout	Never cost-effective
	Cost of ICD ($)	26083	20000	30000	-0.29	-0.29	Dominated	Dominated	Ineffective throughout	Never cost-effective

*Threshold denotes parameter value at which strategy is equally effective to observation for EPS strategies, and equally effective to EPS for upfront ICD strategies
†Threshold denotes parameter value at which strategy ICER intersects the $100,000/QALY willingness-to-pay-threshold (if such a value exists)
ICD=implantable cardioverter-defibrillator; EPS=electrophysiologic study; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life-year

Table S16. Probabilistic sensitivity analysis (clinical effectiveness endpoints)

Strategy*	# ICDs placed	Acute procedural or device-related complications†	Chronic device complications‡	Inappropriate shocks	Arrest deaths	Procedural or device-related deaths	Cardiac deaths§	Total deaths
Subcutaneous								
Observation (ICD if arrest)	1760 (90-5130)	230 (10-710)	590 (20-1620)	1000 (50-2940)	10370 (6230-13630)	10 (0-40)	10380 (6260-13640)	82580 (81620-83280)
Electrophysiologic study	27860 (26930-29740)	8700 (7140-10730)	12170 (8430-17580)	20390 (16320-27650)	6080 (3620-8000)	290 (220-360)	6370 (3620-8000)	81790 (81300-82330)
Upfront ICD	99780 (99780-99790)	15690 (11750-21640)	43910 (30440-59970)	73620 (59920-96110)	560 (50-1670)	1040 (830-1260)	1600 (1000-2750)	80790 (80540-81160)
Transvenous								
Observation (ICD if arrest)	1570 (60-5510)	120 (0-390)	910 (30-3390)	620 (20-2220)	10560 (6760-13240)	120 (0-390)	10610 (6860-13260)	82620 (81790-83240)
Electrophysiologic study	27780 (26920-29930)	6920 (5570-8160)	20610 (16600-25860)	15310 (11830-19060)	6180 (4030-7880)	1100 (760-1520)	7280 (5180-9000)	82020 (81490-82540)
Upfront ICD	99780 (99780-99790)	9260 (7090-11920)	74430 (61310-93220)	55570 (43070-71270)	560 (50-1560)	4000 (2890-5460)	4550 (3240-6240)	81560 (81140-82050)

*All outcomes presented as mean (95% credible interval) rate per 100,000 individuals obtained using probabilistic simulation (n=200,000 for 100 iterations)
†Procedural or device-related complications include access site complication, pneumothorax, skin infection, pocket hematoma, lead malfunction, or any other device defect requiring immediate revision
‡Chronic complications include device infection, pocket hematoma, lead failure, or any other device defect requiring revision
§Cardiac deaths represent sum of arrest-related deaths and procedural or device-related deaths
ICD=implantable cardioverter-defibrillator

Table S17. Probabilistic sensitivity analysis (summary clinical and cost-effectiveness endpoints)

Strategy	**Costs ($)**	**Quality-adjusted life expectancy**
Observation (transvenous ICD if arrest)	3,457* (1880-6000)	19.91 (19.49-20.41)
Observation (subcutaneous ICD if arrest)	3,622 (1900-6600)	19.91 (19.49-20.41)
Electrophysiologic study (transvenous ICD if positive)	27,938 (19799-40556)	20.19 (19.83-20.56)
Electrophysiologic study (subcutaneous ICD if positive)	32,193 (25700-40551)	20.25 (19.89-20.62)
Upfront transvenous ICD	82,015 (53500-127013)	19.92 (19.09-20.72)
Upfront subcutaneous ICD	97,397 (74000-127500)	20.17 (19.34-20.94)

*All outcomes presented as per-individual mean (95% credible interval) obtained using probabilistic simulation (n=200,000 for 1,000 iterations)
ICD=implantable cardioverter-defibrillator

Table S18. Value of information analyses

Parameter*	Per person EVPPI, $ (standard error)†	Yearly EVPPI for United States, $ in millions‡	Indexed to overall EVPI
Utility of subcutaneous ICD	3,818.77 (570.10)	97	0.47
Utility of transvenous ICD	3,703.40 (1037.72)	95	0.45
Probability of death from arrest (no ICD)	1,615.43 (804.03)	41	0.20
Generator change interval for transvenous ICD§	1,419.55 (921.32)	36	0.17
Yearly incidence of arrest given asymptomatic Brugada syndrome	1,007.87 (770.97)	26	0.12
Cost of subcutaneous ICD revision	656.38 (617.99)	17	0.08
Cost of arrest (no ICD)	169.41 (557.33)	4	0.02
Cost of subcutaneous ICD maintenance	117.00 (582.72)	3	0.01
Probability of death from complication related to transvenous ICD revision	42.18 (526.33)	1	0.01

*Parameters with top ten highest Expected Value of Partial Perfect Information (EVPPI) values displayed
†Overall expected value of perfect information (EVPI): $8,150 per person
‡Estimated yearly EVPPI for the 2019 United States population (assuming age ≥18 years and 0.01% prevalence of asymptomatic BrS with Type I pattern[48])
§Generator change interval for subcutaneous ICD not included in EVPPI calculation given insufficient number of unique values in probabilistic sensitivity analysis
ICD=implantable cardioverter defibrillator; EVPPI=expected value of partial perfect information; EVPI=expected value of perfect information

Table S19. Summary of most influential parameters

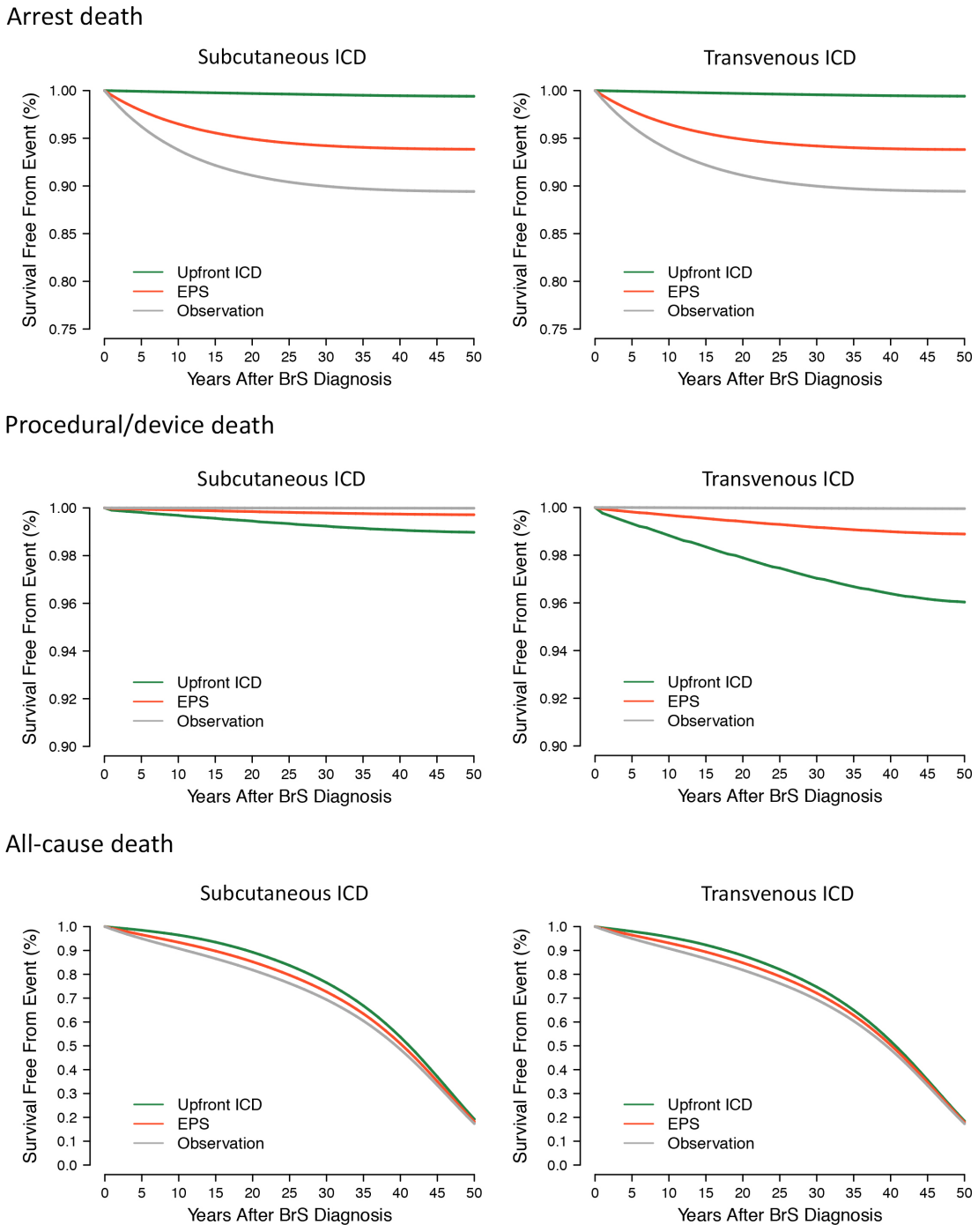
Parameter*	Estimate	Lower bound	Upper bound	Highest quality of evidence
Events				
Age of BrS diagnosis	41	26	56	Meta,O,M,R
Relative risk of arrest given positive EPS	1.67	1.3	1.9	Meta,O,M,R
Relative risk of arrest given negative EPS	0.753	0.667	0.89	Meta,O,M,R
Yearly incidence of arrest given asymptomatic Brugada syndrome	10.2 / 1000 person-years	5.0 / 1000 person-years	16.7 / 1000 person-years	Meta,O,M,R
Probability of death from arrest (no ICD)	0.875	0.6	0.996	SR
Generator change interval for transvenous ICD	6	4	8	O,M,R
Probability of death from complication related to transvenous ICD revision	0.072	0.066†	0.079†	O,M,R
Costs				
Cost of arrest (no ICD)	30000	18950	41050	DM,MC; O,M,R
Cost of subcutaneous ICD revision/replacement	21025	18136	23914	Derived from transvenous ICD ratio
Cost of subcutaneous ICD maintenance	128	84	172	DM,Std
Utilities				
Utility of ICD	0.95	0.90	1	DM,Su

*Influential parameters defined as having influence of clinical and cost-effectiveness estimates in deterministic sensitivity analysis, or top ten expected value of partial perfect information (see **Table S18**)

†Denotes that bounds are 95% confidence intervals from a beta distribution modeling probability uncertainty in the base case estimate

DM=decision model; EPS=electrophysiologic study; ICD=implantable cardioverter-defibrillator; M=multicenter; MC=micro-cost analysis; Meta=meta-analysis; O=observational, R=retrospective; Std=standard source; SR=systematic review; Su=survey

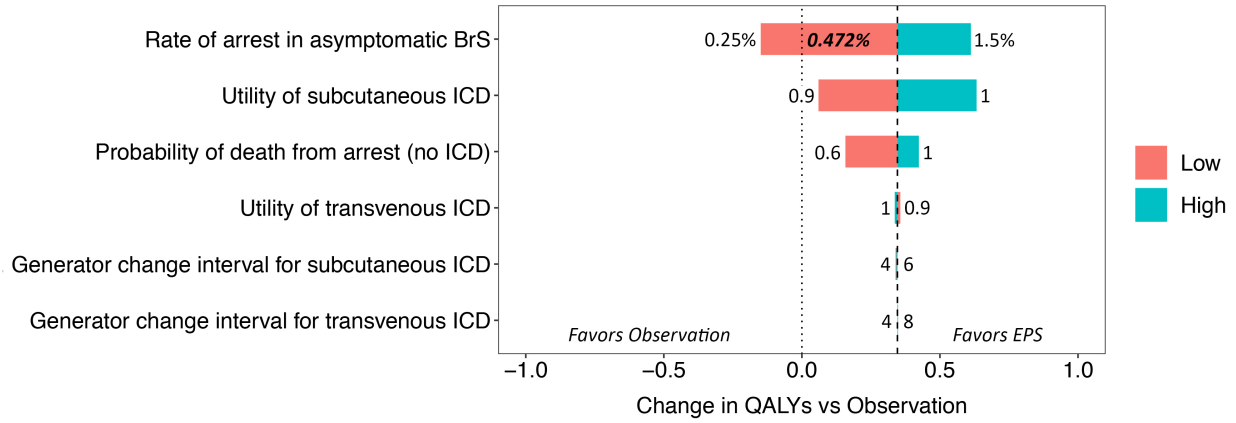
Figure S1. Clinical endpoints according to BrS management strategy



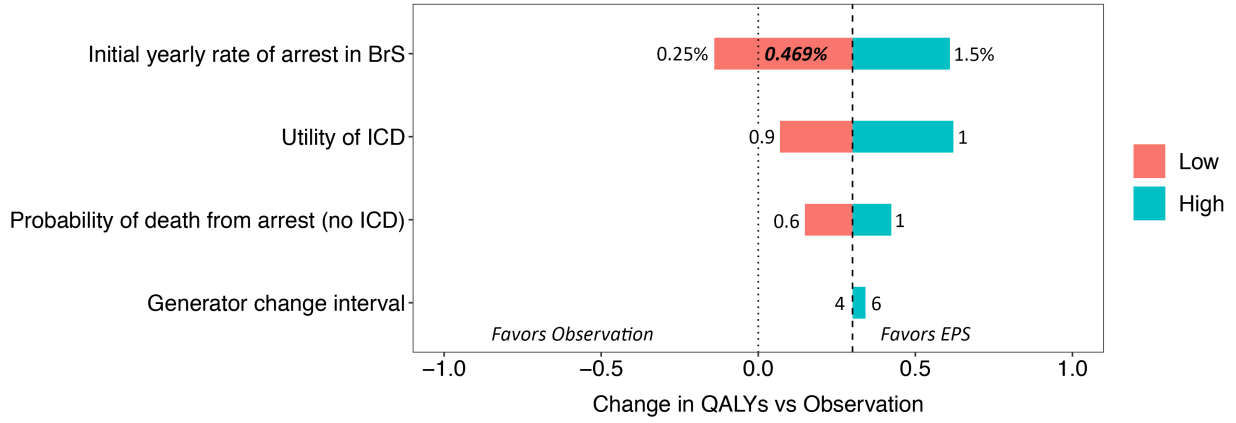
Depicted is survival free of arrest-related death (upper panels), procedural or device complication-related death (middle panels), and all-cause death (lower panels). Within each plot, survival is depicted for observation (gray), electrophysiologic study (orange), and upfront ICD (green), using either subcutaneous (left panels) or transvenous (right panels) devices. EPS=electrophysiologic study; ICD=implantable cardioverter-defibrillator

Figure S2. Tornado diagram of EPS-guided ICD strategies (clinical effectiveness)

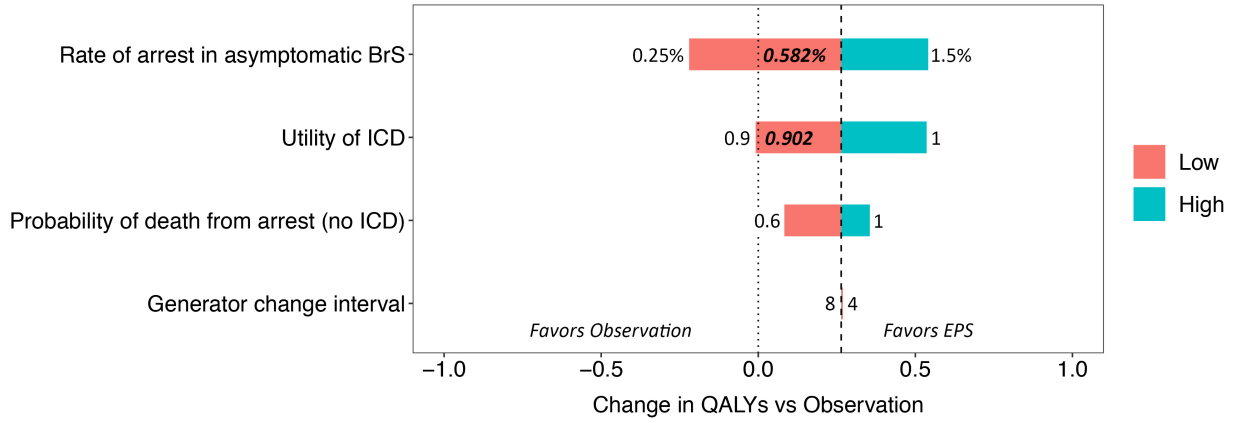
Electrophysiologic study-guided subcutaneous ICD vs observation with transvenous ICD (all strategies)



Electrophysiologic study-guided ICD vs observation (subcutaneous ICD strategies only)



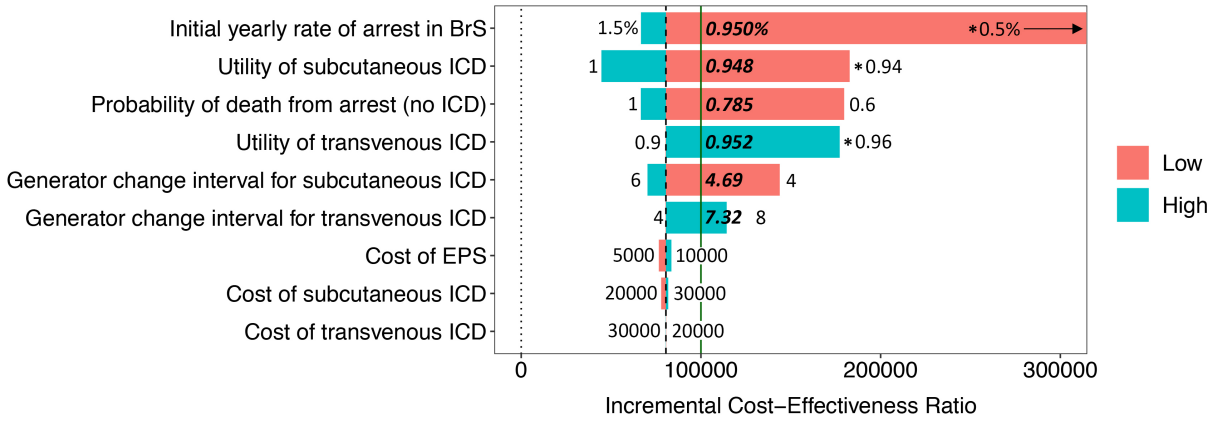
Electrophysiologic study-guided ICD vs observation (transvenous ICD strategies only)



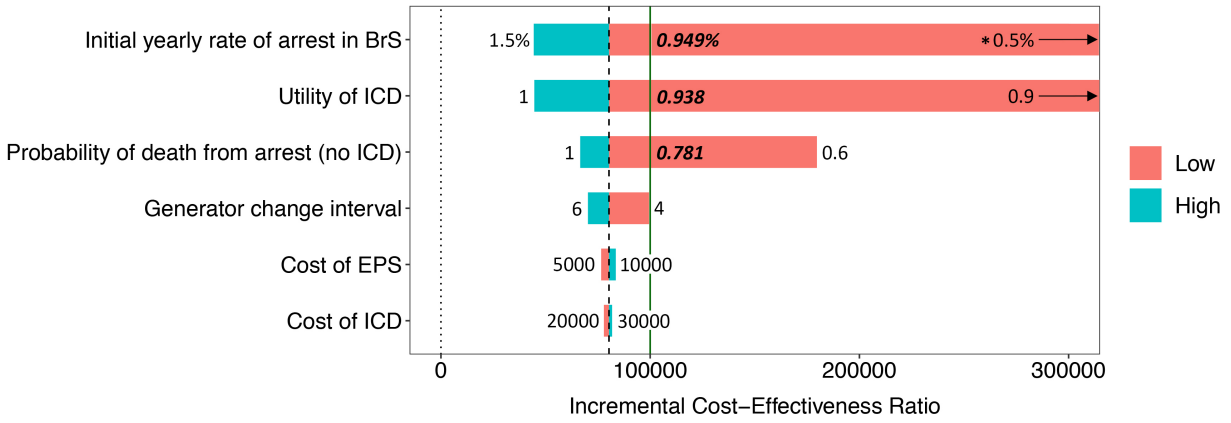
Depicted are tornado diagrams depicting results of one-way sensitivity analyses assessing the comparative clinical effectiveness of electrophysiologic study-guided ICD versus observation (overall and within-device type). The specific comparison shown is listed above each plot. In each plot, the relevant parameter is listed on the left, with the corresponding bar demonstrating the range of effectiveness (defined as change in QALYs as compared to baseline) observed as the parameter is varied from its lowest bound (red) to its highest bound (teal). The values corresponding to the upper and lower bounds are shown on the sides of each bar. The hashed vertical line from which the bars emanate depicts the base case effectiveness. Where variation in the parameter results in crossing the effectiveness threshold, the relevant threshold is depicted in bolded, italicized text next to the dotted vertical line representing equal effectiveness. BrS=Brugada syndrome; EPS=electrophysiologic study; ICD=implantable cardioverter-defibrillator; QALY=quality-adjusted life-year

Figure S3. Tornado diagram of EPS-guided ICD strategies (cost-effectiveness)

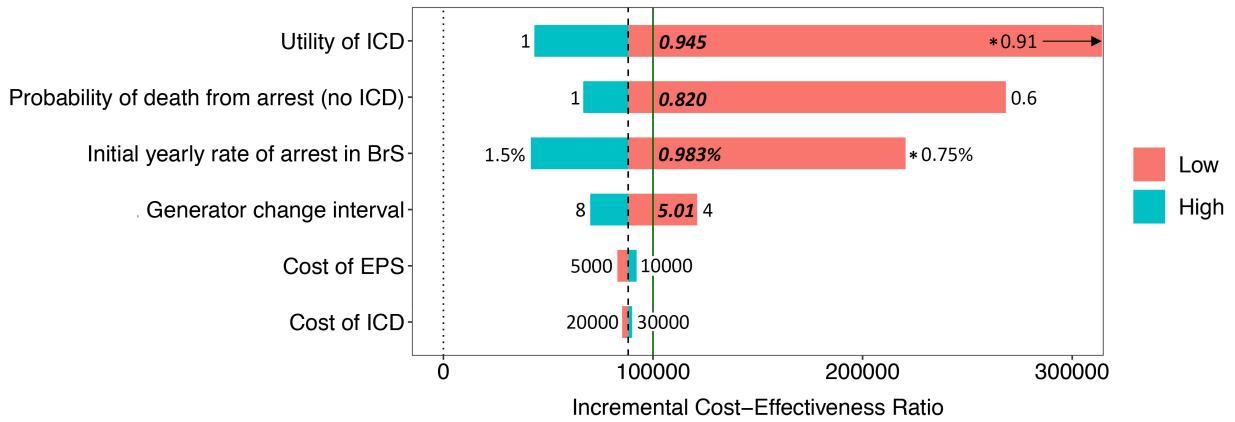
Electrophysiologic study-guided subcutaneous ICD vs observation with transvenous ICD (all strategies)



Electrophysiologic study-guided ICD vs observation (subcutaneous ICD strategies only)

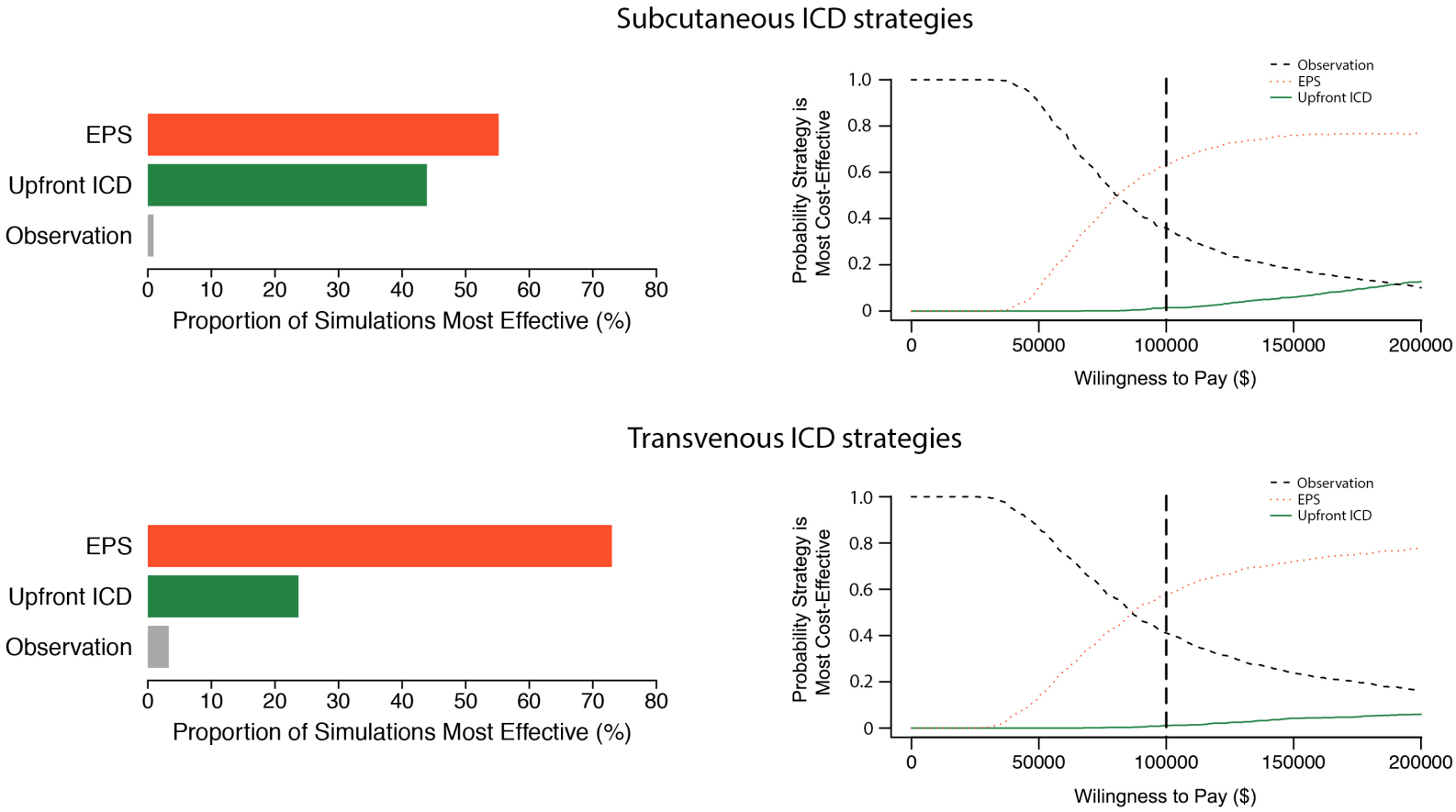


Electrophysiologic study-guided ICD vs observation (transvenous ICD strategies only)



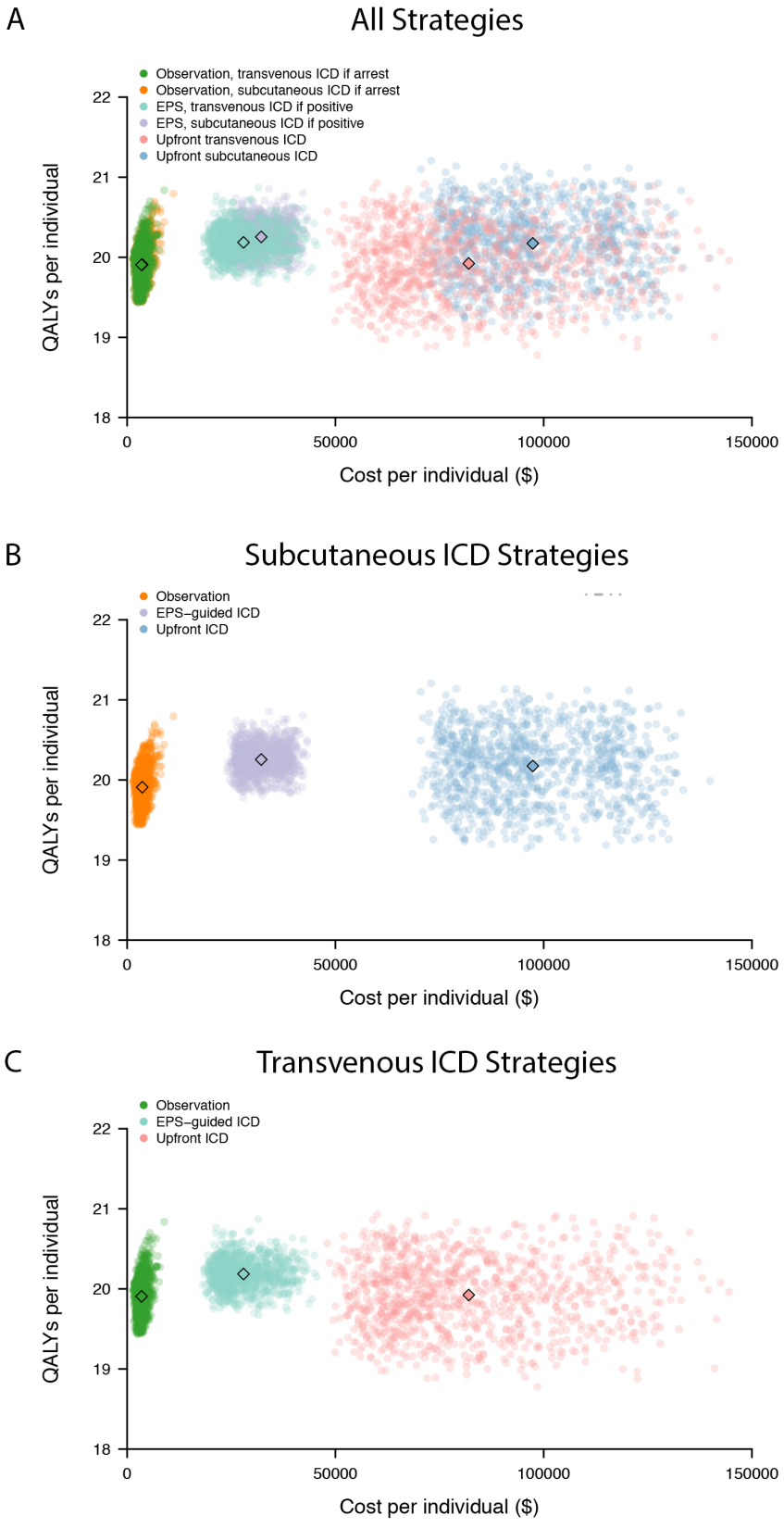
Depicted are tornado diagrams depicting results of one-way sensitivity analyses assessing the cost-effectiveness of electrophysiologic study-guided ICD versus observation (overall and within-device type). The specific comparison shown is listed above each plot. In each plot, the relevant parameter is listed on the left, with the corresponding bar demonstrating the range of cost-effectiveness (defined as the incremental cost-effectiveness ratio [ICER] compared to baseline) observed as the parameter is varied from its lowest bound (red) to its highest bound (teal). The values corresponding to the upper and lower bounds are shown on the sides of each bar. The hashed vertical line from which the bars emanate depicts the base case cost-effectiveness. Where variation in the parameter results in crossing the willingness-to-pay threshold, the relevant threshold is depicted in bolded, italicized text next to the green vertical line representing $100,000 per QALY. Asterisks denote that the strategy is dominated at values more extreme than those listed. Arrows denote that the indicated bar extends beyond $300,000 but is not depicted for graphical purposes. BrS=Brugada syndrome; EPS=electrophysiologic study; ICD=implantable cardioverter-defibrillator; QALY=quality-adjusted life-year

Figure S4. Clinical and cost-effectiveness in probabilistic analyses stratified by device type



Depicted are the results of 1,000 runs of probabilistic sensitivity analysis, which estimates the effects of parameter uncertainty on clinical and cost-effectiveness estimates. Panel A shows the proportion of times each strategy resulted in the greatest overall effectiveness (i.e., highest quality-adjusted life-years [QALYs]). Panel B shows the probability that a given strategy is the most cost-effective option across increasing willingness-to-pay (x-axis). The willingness-to-pay threshold of $100,000/QALY used to define cost-effectiveness in this study is depicted by the vertical hashed line. EPS=electrophysiologic study; ICD=implantable cardioverter defibrillator

Figure S5. Cost-effectiveness planes



Depicted are cost-effectiveness planes demonstrating the results of 1,000 runs of probabilistic sensitivity analysis. In each plot, every point depicts the absolute cost and absolute quality-adjusted life expectancy observed in each run. Points are colored based on the strategy pursued (see legend). The filled diamond within each cluster of points represents the mean value for that strategy. The top plot depicts all strategies, the middle plot depicts only subcutaneous ICD-based strategies, and the bottom plot depicts only transvenous ICD-based strategies. EPS=electrophysiologic study; ICD=implantable cardioverter-defibrillator; QALY=quality-adjusted life-year