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. Yet SCD risk is variable and most patients will not have an event. Implantable cardioverter-defibrillators (ICDs) can avert SCD, but are associated with immediate and long-term risks, require repeated interventions to maintain, are expensive, and may reduce quality-of-life. 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. Conversely, some are at recognizably low risk such that ICDs are not recommended, such as asymptomatic individuals with normal resting ECGs. In contrast, the optimal management of asymptomatic individuals...
with spontaneous ST-segment elevation in the right precordial leads (ie, type I Brugada pattern), who have an ≈3-fold SCD risk, is unclear and current guidelines do not provide explicit recommendations for or against ICD. Management typically includes observation, though risk stratification with electrophysiologic study (EPS) and ICD implant for high risk findings may be reasonable. 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.

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) diagnosed with BrS at age 41 years 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.

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

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

| Abbreviation | Definition |
|--------------|------------|
| BrS          | Brugada syndrome |
| EPS          | electrophysiologic study |
| ICD          | implantable cardioverter-defibrillator |
| QALY         | quality-adjusted life years |
| SCD          | sudden cardiac death |
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, 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.\(^{[31]}\) 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 1 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\(^{[30,32]}\) 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...
| 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 |                      |                      | Subcutaneous ICD |                      |
|----------------------|-----------------|----------------------|----------------------|------------------|----------------------|
|                      | Initial implant | 26,083               | 26,083               | 26,702           | 23,226               |
|                      | Maintenance     | 128/y                | 84                   | 128/y            | 84                   |
|                      | Generator change/revision | 20,538          | 15,633               | 21,025           | 18,136               |
|                      | Non-fatal complication | 1075              | 941                  | 1075             | 941                  |

|                      | EPS             |                      |                      | Nonfatal EPS complication | 2,141               |
|----------------------|-----------------|----------------------|----------------------|-------------------------|---------------------|
|                      | EPS             | 7,809                | 6,247                | 9,071†                  | 44                  |
|                      | Nonfatal EPS complication | 2,141          | 481                  | 35, 45                 | DM, MC; O,S,R       |

|                      | Events          |                      |                      |                      |                     |
|----------------------|-----------------|----------------------|----------------------|----------------------|---------------------|
|                      | Cardiac arrest (no ICD) | 30,000           | 18,950               | 41,050               | 35, 46              |

|                      | Utilities       |                      |                      |                      |                     |
|----------------------|-----------------|----------------------|----------------------|----------------------|---------------------|
|                      | ICD             | 0.95                 | 0.90                 | 1                    | 35–38               |
|                      | ICD initial implant/revision | 0.5 QALYs×3 d‡ | 0.5 QALYs×10 d‡ | 0.5 QALYs×10 d‡ | 0.5 QALYs×10 d‡ | 0.76 QALYs×3 mo‡ | 0.9 QALYs×1 mo‡ | 5, 39 | O,M,P |
|                      | 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                    | O,M,P               |
|                      | Inappropriate shock (psychological effects) | 0.9 QALYs×1 mo‡ | 5                    | O,M,P               |

DM indicates decision model; EPS, electrophysiology 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.
Deterministic Sensitivity Analyses

Higher arrest rates favored ICD-based strategies. Specifically, among strategies using subcutaneous ICDs, QALYs were maximized by observation at arrest rates of 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 arrest rates of 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 in secondary cost-effectiveness analyses. EPS-guided transvenous ICD was the most cost-effective strategy (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.

## Table 2. Clinical Effectiveness Endpoints Per 100 000 Simulated Individuals

| Strategy* | # ICDs | 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 | 860 | 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-related cycle death before ICD implant.
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.

### 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**                    |         |              |         |        |                      |                                            |
| Electrocardiogram and 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**                     |         |              |         |        |                      |                                            |
| Electrocardiogram and 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.
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%, 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.

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| Clinical Effectiveness | Utility of subcutaneous ICD |
|------------------------|-----------------------------|
| Relative risk of arrest after positive EPS | 0.90 | 0.91 | 0.92 | 0.93 | 0.94 | 0.95* | 0.96 | 0.97 | 0.98 | 0.99 | 1.00 |
| 1.1 Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe |
| 1.3 Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe |
| 1.5 EPS | EPS | EPS | EPS | EPS | EPS | EPS | EPS | EPS | EPS | EPS | EPS |
| 1.7* EPS | EPS | EPS | EPS | EPS | EPS | EPS | EPS | EPS | EPS | EPS | EPS |
| 1.9 EPS | EPS | EPS | EPS | EPS | EPS | EPS | EPS | EPS | EPS | EPS | EPS |

| Cost-effectiveness | Utility of subcutaneous ICD |
|---------------------|-----------------------------|
| Relative risk of arrest after positive EPS | 0.90 | 0.91 | 0.92 | 0.93 | 0.94 | 0.95* | 0.96 | 0.97 | 0.98 | 0.99 | 1.00 |
| 1.1 Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe |
| 1.3 Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe |
| 1.5 Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe |
| 1.7* Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe |
| 1.9 Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe |

| Clinical Effectiveness | Utility of transvenous ICD |
|------------------------|-----------------------------|
| Relative risk of arrest after positive EPS | 0.90 | 0.91 | 0.92 | 0.93 | 0.94 | 0.95* | 0.96 | 0.97 | 0.98 | 0.99 | 1.00 |
| 1.1 Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe |
| 1.3 Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe |
| 1.5 Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe |
| 1.7* Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe |
| 1.9 Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe |

| Cost-effectiveness | Utility of transvenous ICD |
|---------------------|-----------------------------|
| Relative risk of arrest after positive EPS | 0.90 | 0.91 | 0.92 | 0.93 | 0.94 | 0.95* | 0.96 | 0.97 | 0.98 | 0.99 | 1.00 |
| 1.1 Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe |
| 1.3 Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe |
| 1.5 Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe |
| 1.7* Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe |
| 1.9 Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe | Observe |

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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{5} 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,\textsuperscript{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,\textsuperscript{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\textsuperscript{2,29,30} and older individuals,\textsuperscript{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.\textsuperscript{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,\textsuperscript{2} past studies have been inconsistent.\textsuperscript{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.\textsuperscript{5}

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.\textsuperscript{58} Second, limited evidence suggests that subcutaneous ICDs may be less efficacious in BrS because of T-wave oversensing.\textsuperscript{59} We did not incorporate this possibility since improved algorithms have likely overcome previous limitations.\textsuperscript{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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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, 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         | 99780Ⅰ        | 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         | 99780Ⅰ        | 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         | 99780Ⅰ        | 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         | 99780Ⅰ        | 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         | 99780Ⅰ        | 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         | 99780Ⅰ        | 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
ⅠValues 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**  |       |         |        |        |                      | Baseline       |
| 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**  |       |         |        |        |                      | Not cost-effective |
| 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**  |       |         |        |        |                      | Not cost-effective |
| Electrophysiologic study  | 20.461 | $30,823.79 | 0.17189 | $28,131.12 | $163,654.84 | 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**  |       |         |        |        |                      | Cost-effective |
| 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**  |       |         |        |        |                      | Not cost-effective |
| 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**  |       |         |        |        |                      | Not cost-effective |
| 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 | 81830 |

*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  | $3,755.62    | -      | -      | -                    | 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
| 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 | $137,110.19 | 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 |
| Scenario                      | Arrest rate 1.25%/yr | Arrest rate 1.50%/yr |
|-------------------------------|----------------------|----------------------|
| **Upfront ICD**               | 19.888               | 19.858               |
| **Cost**                      | $77,586.22           | $77,491.20           |
| **Observation**               |                      |                      |
| **Observation**               |                      |                      |
| **Baseline**                  |                      |                      |

**Arrest rate 1.25%/yr**

| Strategy                                      | Cost   | Effectiveness | Incremental Effectiveness Ratio | QALY Gained | ICER     |
|-----------------------------------------------|--------|---------------|---------------------------------|-------------|----------|
| 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**

| Strategy                                      | Cost   | Effectiveness | Incremental Effectiveness Ratio | QALY Gained | ICER     |
|-----------------------------------------------|--------|---------------|---------------------------------|-------------|----------|
| 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 | Electrophysiologic study | Upfront ICD |
|----------------|-------------|--------------------------|-------------|
|                | 490         | 27080                    | 99320       |
|                | 50          | 7370                     | 11690       |
|                | 110         | 8110                     | 29780       |
|                | 180         | 13520                    | 49710       |
|                | 3440        | 1970                     | 150         |
|                | 0           | 200                      | 720         |
|                | 3450        | 2160                     | 870         |
|                |             | 79890                    | 79640       |
| Age 60         | Observation | Electrophysiologic study | Upfront ICD |
|                | 320         | 26910                    | 99010       |
|                | 30          | 7020                     | 10440       |
|                | 60          | 6780                     | 25010       |
|                | 100         | 11310                    | 41700       |
|                |             | 2210                     | 90          |
|                |             | 0                        | 600         |
|                |             | 2210                     | 690         |
|                |             | 79170                    | 78700       |
| Age 65         | Observation | Electrophysiologic study | Upfront ICD |
|                | 200         | 26760                    | 98610       |
|                | 20          | 6670                     | 9230        |
|                | 30          | 5510                     | 20390       |
|                | 50          | 9210                     | 33910       |
|                |             | 1420                     | 50          |
|                |             | 0                        | 520         |
|                |             | 1420                     | 570         |
|                |             | 77770                    | 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 |
| Scenario                        | Age 60                  |  Age 65                  |
|--------------------------------|-------------------------|-------------------------|
| Observation (ICD if arrest)    | 14.643 $727.97          | 12.730 $459.81          |
| Electrophysiologic study (ICD if positive) | 14.541 $21,973.39  | 12.629 $19,422.31     |
| Upfront ICD                    | 14.066 $65,824.68       | 12.183 $56,974.69       |

*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
| 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
| 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  | $5,157.64      | -      | -        | -         | 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    |
| Age 45 | Electrophysiologic study (subcutaneous ICD if positive) | 19.321 | $29,372.50 | 0.16949 | $26,855.97 | $158,450.07 | Not cost-effective |
| Age 45 | Electrophysiologic study (transvenous ICD if positive) | 19.255 | $24,959.62 | - | - | - | Dominated |
| Age 45 | Observation (transvenous ICD if arrest) | 19.151 | $2,516.53 | - | - | - | Baseline |
| Age 45 | Observation (subcutaneous ICD if arrest) | 19.151 | $2,633.82 | - | - | - | Dominated |
| Age 45 | Upfront subcutaneous ICD | 18.797 | $73,131.91 | - | - | - | Dominated |
| Age 45 | 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 |
| Age 50 | Electrophysiologic study (transvenous ICD if positive) | 17.863 | $22,661.18 | - | - | - | Dominated |
| Age 50 | Observation (transvenous ICD if arrest) | 17.847 | $81,941.91 | - | - | - | Dominated |
| Age 50 | Upfront subcutaneous ICD | 17.256 | $67,070.69 | - | - | - | Baseline |
| Age 50 | Upfront transvenous ICD | 17.256 | $67,070.69 | - | - | - | Baseline |
| Age 55 | Observation (transvenous ICD if arrest) | 16.363 | $1,090.67 | - | - | - | Baseline |
| Age 55 | Observation (subcutaneous ICD if arrest) | 16.360 | $1,136.48 | - | - | - | Dominated |
| Age 55 | Electrophysiologic study (subcutaneous ICD if positive) | 16.304 | $24,445.98 | - | - | - | Dominated |
| Age 55 | Electrophysiologic study (transvenous ICD if positive) | 16.268 | $20,737.96 | - | - | - | Dominated |
| Age 55 | Observation (transvenous ICD if arrest) | 15.826 | $74,111.48 | - | - | - | Dominated |
| Age 55 | Observation (subcutaneous ICD if arrest) | 15.662 | $65,824.68 | - | - | - | Dominated |
| Age 60 | Observation (transvenous ICD if arrest) | 14.643 | $727.97 | 0.00312 | $21.88 | $7,023.15 | Cost-effective |
| Age 60 | Observation (subcutaneous ICD if arrest) | 14.640 | $706.08 | - | - | - | Baseline |
| Age 60 | Electrophysiologic study (subcutaneous ICD if positive) | 14.541 | $21,973.39 | - | - | - | Dominated |
| Age 60 | Electrophysiologic study (transvenous ICD if positive) | 14.505 | $18,771.85 | - | - | - | Dominated |
| Age 60 | Observation (transvenous ICD if arrest) | 13.933 | $54,106.17 | - | - | - | Dominated |
| Age 60 | Observation (subcutaneous ICD if arrest) | 13.930 | $459.81 | - | - | - | Dominated |
| Age 60 | Electrophysiologic study (subcutaneous ICD if positive) | 12.629 | $19,422.31 | - | - | - | Dominated |
| Age 65 | Observation (transvenous ICD if arrest) | 12.733 | $444.97 | - | - | - | Baseline |
| Age 65 | Observation (subcutaneous ICD if arrest) | 12.730 | $459.81 | - | - | - | Dominated |
| Age 65 | Electrophysiologic study (subcutaneous ICD if positive) | 12.629 | $19,422.31 | - | - | - | Dominated |
| Scenario                                      | Time  | Cost     | ICER  | QALY  | Preferred Strategy |
|----------------------------------------------|-------|----------|-------|-------|--------------------|
| Electrophysiologic study (transvenous ICD if positive) | 12.602| $16,960.64 | -     | -     | -                  |
| Upfront subcutaneous ICD                      | 12.183| $56,974.69 | -     | -     | -                  |
| Upfront transvenous ICD                       | 12.086| $47,804.15  | -     | -     | -                  |

*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            | △QALYs | △Costs   | 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       |
| **Baseline**                                        |         |                  |        |          |               |                 |
| **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       |
| **Baseline**                                        |         |                  |        |          |               |                 |
| **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       |
| **Baseline**                                        |         |                  |        |          |               |                 |
| **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  | $31,234.61       | 0.34642| $27,889.54   | $80,508.25        | Cost-effective              |
| Upfront subcutaneous ICD                                                | 20.164  | $26,693.45       | -      | -            | -                 | 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  | $31,234.61       | 0.43323| $27,663.54   | $63,853.95        | Cost-effective              |
| Upfront subcutaneous ICD                                                | 20.164  | $26,693.45       | -      | -            | -                 | 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**          | 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 |
| **Electrophysiologic study** | 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**           | Initial rate of arrest (%/year)         | 1.02       | 0.25        | 1.50        | -0.22               | 0.54                | Dominated below 0.75 | 41715              | 0.58            | 0.98            |
| Parameter                                | Value 1 | Value 2 | Value 3 | Value 4 | Value 5 | Decision 1 | Value 6 | Value 7 | Decision 2 |
|------------------------------------------|---------|---------|---------|---------|---------|------------|---------|---------|------------|
| 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 |
| 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 pattern48)
§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=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)

**Incremental Cost-Effectiveness Ratio**

- Initial yearly rate of arrest in BrS: 1.5% vs 0.950%
- Utility of subcutaneous ICD: 1 vs 0.948
- Probability of death from arrest (no ICD): 1 vs 0.785
- Utility of transvenous ICD: 0.9 vs 0.952
- Generator change interval for subcutaneous ICD: 4 vs 4.69
- Generator change interval for transvenous ICD: 4 vs 7.32
- Cost of EPS: 8000 vs 10000
- Cost of subcutaneous ICD: 20000 vs 30000
- Cost of transvenous ICD: 20000 vs 30000

**Incremental Cost-Effectiveness Ratio**

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

- Initial yearly rate of arrest in BrS: 1.5% vs 0.949%
- Probability of death from arrest (no ICD): 1 vs 0.781
- Generator change interval: 6 vs 4
- Cost of EPS: 5000 vs 10000
- Cost of ICD: 20000 vs 30000

**Incremental Cost-Effectiveness Ratio**

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

- Utility of ICD: 1 vs 0.945
- Probability of death from arrest (no ICD): 1 vs 0.820
- Initial yearly rate of arrest in BrS: 1.5% vs 0.983%
- Generator change interval: 8 vs 5.01
- Cost of EPS: 5000 vs 10000
- Cost of ICD: 20000 vs 30000
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

A. All Strategies

B. Subcutaneous ICD Strategies

C. Transvenous ICD Strategies
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