Cost-Effectiveness Analysis of Iodine-123 Meta-Iodobenzylguanidine Imaging for Screening Heart Failure Patients Eligible for an Implantable Cardioverter Defibrillator in the USA

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Abstract

Background Many guideline-eligible heart failure (HF) patients do not receive a survival benefit from implantable cardioverter defibrillators (ICDs). Improved risk stratification may help to reduce costs and improve the cost effectiveness of ICDs.

Objective To estimate the potential outcomes, costs, and cost effectiveness of using iodine-123 meta-iodobenzylguanidine (I-mIBG) to screen HF patients eligible for an ICD.

Methods A decision-analytic model was developed to compare screening with I-mIBG imaging and no screening over 2-year and 10-year time horizons from a US payer perspective. Data on I-mIBG imaging and risk stratification were obtained from the ADMIRE-HF/HFX (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) trial. Data on ICD effectiveness for prevention of sudden cardiac death (SCD) were obtained from a meta-analysis. Costs of ICDs and costs of generator and lead procedures were obtained from the Agency for Healthcare Research and Quality National Inpatient Sample. Age-specific mortality was modeled using US life tables and data from the ACT (Advancements in ICD Therapy) Registry on risks of SCD and non-SCD mortality. Sensitivity analyses were conducted.

Results In the analysis, screening with I-mIBG imaging was associated with a reduction in ICD utilization of 21%, resulting in a number needed to screen to prevent 1 ICD implantation of 5. Screening reduced the costs per patient by US$5,500 and US$13,431 (in 2013 dollars) over 2 and 10 years, respectively, in comparison with no screening and resulted in losses of 0.001 and 0.040 life-years, respectively, over 2 and 10 years. Screening was decrementally cost effective, with savings of US$5,248,404 and US$513,036 per quality-adjusted life-year lost over 2 and 10 years, respectively. In subgroup analyses, cost savings were greater for patients with an ejection fraction (EF) of 25–35% than for those with an EF <25%.

Conclusions According to the model, screening of guideline-eligible patients selected for ICDs with I-mIBG imaging may be cost effective and may help reduce costs associated with implantation of ICDs, with a minimal impact on survival.

Key Points for Decision Makers

Over 2 and 10 years, this analysis found that screening had the potential to reduce costs by US$5,500 and US$13,431, respectively, with less than 1 day and 2 weeks of life lost, respectively, per patient.

Screening was cost effective, with savings of US$5,248,404 and US$513,036 per quality-adjusted life-year lost, respectively, over 2-year and 10-year horizons.

Screening improved the cost effectiveness of implantable cardioverter defibrillators (ICDs) by approximately 10%.

Iodine-123 meta-iodobenzylguanidine (I-mIBG) screening may help healthcare policy makers control costs associated with provision of ICDs to guideline-eligible patients, with a minimal impact on patient mortality.
1 Introduction

Sudden cardiac death (SCD) accounts for 300,000–400,000 deaths annually in the USA [1]. Risk factors for SCD include age, male sex, coronary artery disease, a prior coronary event, and heart failure (HF) [2]. American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) guidelines recommend implantable cardioverter defibrillators (ICDs) for primary prevention of SCD in patients with New York Heart Association (NYHA) class II or III HF and a left ventricular ejection fraction (LVEF) ≤35 % due to prior myocardial infarction and in patients with non-ischemic dilated cardiomyopathy and NYHA class I HF of ischemic etiology and an LVEF <30 % [3].

Selection of patients for an ICD is heavily influenced by the ejection fraction (EF), given its use in guidelines (≤35 % for NYHA class II–III or ≤30 % for ischemic NYHA class I) and the corresponding evidence base from clinical trials demonstrating efficacy of ICDs in HF patients with a reduced EF [4–6]. Cost-effectiveness analyses, including a recent systematic review, have generally found ICDs to be cost effective [7]. However, a substantial proportion of patients receiving ICDs will obtain no survival benefit from the device, as they will die of other causes prior to any ICD shocks. As the ICD-eligible patient population includes individuals at varying risk of arrhythmic death, additional risk stratification of patients may help to reduce costs and improve the cost-effectiveness of ICDs by identifying patients at lower risk of arrhythmic death or at higher risk of non-arrhythmic death who are not likely to obtain a meaningful benefit from ICDs [8–10].

Iodine-123 meta-iodobenzylguanidine (I-¹²³IBG) is a molecular imaging agent, which received US Food and Drug Administration (FDA) approval in 2013 for scintigraphic imaging assessment of sympathetic innervation of the myocardium to assist in the evaluation of adult patients with NYHA class II or III HF and an LVEF ≤35 % to help identify patients with lower 1- and 2-year mortality risks as indicated by a heart/mediastinum (H/M) ratio ≥1.6. The ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) trial prospectively studied I-¹²³IBG imaging in predicting prognosis for significant cardiac events [11]. Patients in ADMIRE-HF with an H/M ratio ≥1.6 had significantly reduced risks of a cardiac event [hazard ratio (HR) 0.40, P < 0.001], HF progression (HR 0.49; P = 0.002), potentially life-threatening arrhythmia (HR 0.37; P = 0.020), and cardiac death (HR 0.14; P = 0.006) in comparison with patients with an H/M ratio <1.6 [11]. The addition of I-¹²³IBG to a number of multivariable risk models, including the Seattle Heart Failure Model, was found to improve risk stratification in comparison with the risk models alone [12, 13].

In selecting HF patients for an ICD, clinicians and patients must balance potential survival benefits against potential risks. Identification of patients at low risk of a significant cardiac event with I-¹²³IBG imaging may help to provide decision support to clinicians regarding patients who may not want an ICD or where there is uncertainty about whether the risks associated with an ICD may outweigh the potential benefits. The objectives of this study were to assess the potential clinical and economic impact of I-¹²³IBG imaging in screening guideline-eligible patients referred for an ICD and to assess the costs, outcomes, and cost effectiveness of screening.

2 Methods

2.1 Model Description

A decision analytic model was developed using Microsoft Excel® 2010 software to estimate the costs, outcomes, and cost-effectiveness of I-¹²³IBG imaging for risk stratification of HF patients with an LVEF ≤35 % who were referred for ICD implantation on the basis of current guidelines. The model compared outcomes [the ICD implantation rate, survival, life-years (LYs), and quality-adjusted life-years (QALYs)] and costs (in 2013 dollars) of current practice versus a one-time screening with I-¹²³IBG imaging from a US payer perspective over short-term (2-year) and long-term (10-year) time horizons, incorporating direct medical costs. Subgroup analyses were conducted to assess outcomes and costs for patients with an LVEF <25 % and for those with an LVEF of 25–35 %.

A Markov cohort analysis was used to model survival of patients over time in terms of SCD mortality, non-SCD cardiac mortality due to HF, and other mortality (Fig. 1). In the no-screening arm, all patients were assumed to receive an ICD, as the patient population consisted of guideline-eligible patients referred for an ICD. In the screening arm, patients underwent screening with I-¹²³IBG imaging. Patients with an H/M ratio ≥1.6 (low risk) were assumed to forgo an ICD, while patients with an H/M ratio <1.6 (non-low risk) were assumed to receive an ICD. In subsequent cycles, patient mortality was modeled as a function of SCD, non-SCD cardiac mortality, and other mortality (i.e., non-cardiac causes). For mortality calculations in the model, patients were stratified into low-risk and non-low-risk groups based on the H/M ratio, with the low-risk group incurring a reduced risk of SCD. All patients receiving ICDs incurred an additional reduced risk of SCD. The model utilized a monthly cycle over the duration of the modeled time horizon.
2.2 Model Outcomes

The primary model outcomes were LYs, QALYs, and healthcare costs. LYs were calculated on the basis of overall survival, and QALYs were calculated on the basis of overall survival, a utility adjustment for HF, and age-weighted utilities. Costs (in 2013 US dollars) included the initial costs of screening, ICD implantation, generator and lead procedures, ICD evaluation, medical costs for surviving HF patients, and end-of-life care for dying patients. Costs and outcomes were discounted using a standard 3% discount rate, with undiscounted LYs also presented. An incremental cost-effectiveness ratio (ICER) was computed as the ratio of the difference in costs divided by the difference in discounted LYs or QALYs between screening and no screening. Other model outcomes included the ICD implantation rate, cumulative mortality, and the number needed to screen to prevent 1 ICD implantation. An additional analysis was also conducted to estimate the contribution that screening made to the overall cost effectiveness of ICDs by evaluating the ICER of ICDs versus no ICDs in a screening scenario in comparison with the ICER of ICDs versus no ICDs in a no-screening scenario.

2.3 Model Inputs

2.3.1 Patient Characteristics and Screening Effectiveness

The model used data from the ADMIRE-HF and HFX prospective studies of I-mIBG imaging \[11, 15\]. Accordingly, the characteristics of the modeled patient population included a mean age of 62 years, NYHA class II–III HF (83% of patients were in NYHA class II), LVEF ≤35, 80% male, and a late H/M ratio <1.6 in 79% of patients.

In ADMIRE-HF, patients underwent I-mIBG imaging and clinical follow-up to document the occurrence of cardiac events, including non-fatal arrhythmias (sustained ventricular tachycardia, resuscitated cardiac arrest, and appropriate ICD activations), cardiac death, and all-cause mortality. The HRs for arrhythmia and cardiac death during a median 17-month follow-up period were 0.37 \((P = 0.02)\) and 0.14 \((P = 0.006)\), respectively. ADMIRE-HFX extended the follow-up for study subjects to a median of 24 months. For the purposes of this model, a separate analysis was conducted to estimate the HR for patients with a sudden cardiac event (SCE), consisting of SCD or an appropriate ICD shock (defibrillation) as determined by the study adjudication committee. Because the ADMIRE study population included patients with ICDs, this composite endpoint was used as a surrogate measure to account for SCD events that might have been prevented by the ICDs present in 20% of ADMIRE subjects at baseline (increasing to 43% of subjects during the course of ADMIRE-HFX). In SCD-HeFT (the Sudden Cardiac Death in Heart Failure Trial), the annual ICD shock rate was 7.5 versus a 1.4% reduction in all-cause mortality; thus, only 1 in 5 ICD shocks were likely lifesaving. In MADIT-II (the Multicenter Automatic Defibrillator Implantation Trial II),
the annual ICD shock rate was ~35 % (420 ICD shocks in 720 patients over 20 months) versus an ~3.4 % annual reduction in all-cause mortality; thus, only 1 in 10 ICD shocks were likely lifesaving. Longer detection intervals have shown that 91 % of fast ventricular tachycardias and 67 % of ventricular fibrillations may self-terminate and not require an ICD shock [16]. To account for the fact that <3.3 % of ICD shocks are lifesaving, the SCE rate was adjusted conservatively to include only 50 % of ICD defibrillations for the base-case analysis. Additional analyses were conducted assuming that 33 and 66 % of ICD defibrillations were lifesaving in the sensitivity analysis. The screening inputs are presented in Table 1.

2.3.2 ICDs

ICD efficacy inputs reflecting the relative risk reduction of SCD for patients with ICDs were obtained from a meta-analysis [17] of randomized, controlled ICD trials, identified by a clinical expert as the best estimate of the overall treatment effect of ICDs, and were assumed to apply equivalently to patients with late H/M ratios of <1.6 and ≥1.6. The perioperative mortality risk of an ICD procedure was obtained from a published analysis [18].

2.3.3 Mortality

Life tables representing all-cause mortality by age and sex were obtained from the National Center for Health Statistics [19]. To avoid double-counting the mortality associated with HF, life tables were adjusted by removal of the proportion of deaths due to HF [20]. To account for age-specific risks associated with non-SCD and SCD mortality as the model cohort aged, the baseline risks of mortality due to non-SCD and SCE from the ADMIRE study were multiplied by the age-specific relative risk of non-SCD and SCD mortality. According to data from a registry, the relative risks of non-SCD and SCD mortality are 1.48 and 0.49, respectively, for 60- to 69-year-olds, 2.39 and 0.89, respectively, for 70- to 79-year-olds, and 2.17 and 1.91, respectively, for 60- to 69-year-olds, 2.39 and 0.89, respectively, for 60- to 69-year-olds [21]. Thus, in the model, mortality risks associated with HF due to non-SCD steadily increased with age, while risks associated with SCD were U shaped. Annual mortality rates were then adjusted to monthly mortality rates.

2.3.4 Costs

The cost of screening with I-123MBG imaging included both the cost of the drug, based on the average sales price, and the imaging test cost of a cardiovascular nuclear examination [Current Procedural Terminology (CPT) code 78499]. The weighted average costs of the ICD device and the implantation procedure in patients with (22 %) and without (78 %) complications [Diagnosis-Related Groups (DRG) 226 and 227, respectively], ICD generator replacement (DRG 245), and ICD lead replacement (DRG 265) were based on data from the Agency for Healthcare Research and Quality 2010 National Inpatient Sample [22]. Generator and lead-replacement procedures were assumed not to occur in the first 2 years after ICD implantation; thereafter, generators were replaced once every 5 years, on average, with lead procedures being performed in 0.8 % of patients per year [23, 24]. ICD evaluation was assumed to occur 3 times per year, on average, and was assumed to be conducted remotely [25]. The cost of ICD evaluation was based on the Centers for Medicare and Medicaid Services (CMS) 2013 reimbursement for CPT codes 93295 and 93296. The proportion of ICD patients experiencing inappropriate shocks was 2.8 % per year [26]. Inappropriate shocks were assumed to be evaluated in the emergency department, and costs were obtained from the 2010 Agency for Healthcare Research and Quality Medical Expenditure Panel Survey [27]. The monthly follow-up healthcare costs of HF patients were obtained from a study estimating the annual total medical costs of HF patients, excluding those who died in the prior year [28]. End-of-life costs were based on a study examining healthcare resource use in HF patients in the final 6 months of life [29]. All costs were inflated to 2013 US dollars, using the Medical Care Component of the Bureau of Labor Statistics Consumer Price Index.

2.3.5 Utilities

The baseline utility of an HF patient aged 55–64 years was obtained from the literature and estimated to be 0.808, based on the EQ-5D in US patients [30]. Age-specific utility weights were obtained from the literature, and the utilities of patients as they aged in the model were adjusted accordingly [31]. It was assumed in the model that there was no change in utility for patients with an ICD versus those with no ICD, consistent with other evaluations of ICDs [23] and based on a systematic review that identified conflicting studies on whether or not ICDs improve quality of life [7].

2.4 Sensitivity Analyses

A univariate deterministic sensitivity analysis was conducted by varying model inputs around the base-case value bounded by the lower and upper values as indicated in Table 1. The discount rate was varied between 1 and 5 %.
A probabilistic sensitivity analysis (PSA) was conducted to assess the impact of varying all model parameters simultaneously on the model outcomes. Each model parameter was sampled from an appropriate distribution (beta distribution for proportions and utilities, log-normal distribution for relative risks, and gamma distribution for costs) using the mean and standard error over 1000 simulations to estimate the joint uncertainty. On the basis of the PSA, 95 % CIs for the model outcomes were estimated. A cost-effectiveness acceptability curve was also developed.
to show the probability that screening was more cost effective than no screening across a range of willingness-to-pay thresholds.

3 Results

3.1 Model Validation

Multiple methods were used to validate the model. See the Appendix for the model validation results.

3.2 Costs, Outcomes, and Cost Effectiveness of Screening

A total of 5 patients (rounded up from 4.8, per standard practice for reporting the number needed to treat) would need to be screened with I-mIBG imaging to prevent 1 ICD implantation. The reduction in ICD implantations resulted in estimated total cost savings of US$5500 and US$13,431 per screened patient over 2-year and 10-year time horizons, respectively. In comparison with no screening, screening resulted in −0.001 LYs (−0.5 life-days) and −0.001 QALYs (−0.4 quality-adjusted life-days) per patient over a 2-year horizon and −0.040 LYs (−14.7 life-days) and −0.026 QALYs (−9.6 quality-adjusted life-days) per patient over a 10-year horizon. Figure 2 shows lifetime survival curves for use of no ICDs (i.e., assuming no patients received an ICD), ICDs without screening, and ICDs with screening. Disaggregated costs and outcomes are shown in Table 2 for 2 and 10 years (lifetime outcomes are shown in the Appendix). Given these differences in costs and outcomes over a 2-year time horizon, screening saved US$4,033,719 per LY lost and US$5,248,404 per QALY lost, in comparison with no screening, and over a 10-year horizon, screening saved US$334,178 per LY lost and US$513,036 per QALY lost, in comparison with no screening.

3.3 Subgroup Analyses

The results of the subgroup analyses of LVEF 25–35 % and LVEF <25 % are shown in Table 3. The numbers needed to screen to prevent one ICD implantation were 5 (rounded up from 4.1) in the LVEF 25–35 % subgroup and 9 (rounded up from 8.1) in the LVEF <25 % group. In comparison with no screening, screening resulted in greater cost savings over a 2-year horizon in patients with LVEF 25–35 % (US$6838) than in patients with LVEF <25 % (US$1947). In the LVEF 25–35 % subgroup, screening resulted in −0.001 LYs (−0.5 life-days) and −0.001 QALYs (−0.4 quality-adjusted life-days) per patient, in comparison with −0.001 LYs (−0.4 life-days) and −0.001 QALYs (−0.3 quality-adjusted life-days) per patient in the LVEF <25 % subgroup. In the LVEF 25–35 % subgroup, screening would save US$4,864,621 per LY lost and US$6,337,756 per QALY lost, in comparison with no screening. In the LVEF <25 % subgroup, screening would save US$1,592,033 per LY lost and US$2,063,871 per QALY lost, in comparison with no screening.

Fig. 2 Survival outcomes of modeled treatment arms. ICD implantable cardioverter defibrillator
3.4 Impact of Screening on the Cost Effectiveness of ICDs

We also conducted an analysis to assess the impact of screening on the cost effectiveness of ICDs. With screening and risk stratification of patients for ICDs, patients at low risk of SCD may forgo an ICD, resulting in potentially improved cost effectiveness of ICDs in a population of patients at comparatively higher risk of SCD. First, the model was reconfigured to compare the cost effectiveness of ICDs and no ICDs in a no-screening scenario. This resulted in ICERs per QALY of US$1,688,124, $3209, and $1,869, respectively. The number of life years (LYs) and QALYs were also calculated for the screening and no-screening scenarios. The results are summarized in Table 2 and Table 3.

| Outcomes                  | 2 years No ICD | ICD Screening | Difference between screening and no screening | 10 years No ICD | ICD Screening | Difference between screening and no screening |
|---------------------------|----------------|---------------|-----------------------------------------------|----------------|---------------|-----------------------------------------------|
| ICD (%)                   | 0.0            | 100.0         | 79.1                                          | 0.0            | 100.0         | 79.1                                          |
| Mortality (%)             | 11.2           | 8.1           | 8.3                                          | 47.8           | 39.3          | 40.0                                          |
| LYSs                      | 1.922          | 1.953         | 1.952                                         | 7.508          | 8.072         | 8.032                                         |
| LYSs; discounted          | 1.866          | 1.896         | 1.895                                         | 6.598          | 7.068         | 7.035                                         |
| QALYS; discounted         | 1.508          | 1.532         | 1.531                                         | 5.243          | 5.454         | 5.411                                         |
| Costs ($)                 |                |               |                                               |                |               |                                               |
| Screening                 | 0              | 0             | 3209                                         | 0              | 0             | 3209                                          |
| ICD                       | 0              | 41,486        | 32,815                                       | 0              | 41,486        | 32,815                                       |
| Battery/lead replacement   | 0              | 0             | 0                                            | 0              | 0             | 0                                             |
| ICD evaluation            | 0              | 611           | 482                                          | 0              | 2313          | 1814                                         |
| Medical costs             | 31,217         | 30,177        | 30,268                                       | 113,278        | 116,560       | 116,370                                      |
| Total                     | 31,217         | 72,274        | 66,774                                       | 113,278        | 193,781       | 180,351                                      |

The numbers may not sum because of rounding.

ICD implantable cardioverter defibrillator, LYS life-year, QALY quality-adjusted life-year

Table 3 Subgroup analyses; 2-year horizon

| LVEF 25–35 % | No ICD | ICD Screening | Difference between screening and no screening | LVEF ≤25 % | No ICD | ICD Screening | Difference between screening and no screening |
|--------------|--------|---------------|-----------------------------------------------|-----------|--------|---------------|-----------------------------------------------|
| ICD (%)      | 0.0    | 100.0         | 75.9                                          | 0.0       | 100.0  | 87.6          | −12.4                                         |
| Mortality (%)| 9.4    | 6.9           | 7.1                                          | 16.0      | 11.1   | 11.3          | 0.1                                           |
| LYSs         | 1.942  | 1.966         | 1.964                                         | 1.869     | 1.920  | 1.919         | −0.001                                        |
| LYSs; discounted | 1.885  | 1.908         | 1.907                                         | 1.815     | 1.865  | 1.863         | −0.001                                        |
| QALYS; discounted | 1.523  | 1.542         | 1.541                                         | 1.467     | 1.507  | 1.506         | −0.001                                        |
| Costs ($)    |        |               |                                               |           |        |               |                                               |
| Screening    | 0      | 0             | 3209                                         | 0         | 0      | 3209          | 3209                                          |
| ICD          | 0      | 41,486        | 31,488                                       | 0         | 41,486 | 36,342        | −5144                                         |
| Battery/lead replacement | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ICD evaluation | 0 | 615          | 466                                          | 0         | 600    | 525           | −76                                           |
| Medical costs | 30,713 | 29,581        | 29,952                                       | 32,510    | 31,012 | 31,075        | −63                                           |
| Total        | 30,713 | 72,274        | 66,774                                       | 32,510    | 73,098 | 71,150        | −1947                                         |

The numbers may not sum because of rounding.

ICD implantable cardioverter defibrillator, LVEF left ventricular ejection fraction, LYS life-year, QALY quality-adjusted life-year

3.4 Impact of Screening on the Cost Effectiveness of ICDs

We also conducted an analysis to assess the impact of screening on the cost effectiveness of ICDs. With screening and risk stratification of patients for ICDs, patients at low risk of SCD may forgo an ICD, resulting in potentially improved cost effectiveness of ICDs in a population of patients at comparatively higher risk of SCD. First, the model was reconfigured to compare the cost effectiveness of ICDs and no ICDs in a no-screening scenario. This resulted in ICERs per QALY of US$1,688,124, $3209, and $1,869, respectively. The number of life years (LYs) and QALYs were also calculated for the screening and no-screening scenarios. The results are summarized in Table 2 and Table 3.
US$217,155, and US$126,193 over 2-year, 10-year, and lifetime horizons, respectively. Then the model was adjusted to compare the cost effectiveness of ICDs and no ICDs in a screening scenario. This resulted in ICERs per QALY of US$1,527,818, US$194,673, and US$113,904 over 2-year, 10-year, and lifetime horizons, respectively. The analysis showed that screening patients with I-mIBG imaging improved the cost effectiveness of ICDs and reduced the ICERs by approximately 10%.

### 3.5 Sensitivity Analyses

The results of the one-way sensitivity analysis are displayed in the tornado diagrams for the 2-year (Fig. 3a) and 10-year (Fig. 3b) analyses. The output for the one-way sensitivity analysis was the incremental cost per patient of screening versus no screening (base-case value, reductions of US$5,500 over 2 years and US$13,431 over 10 years). Over 2 years, the model results were most sensitive to the

| Incremental Costs | Low Input | High Input |
|-------------------|-----------|------------|
| Proportion of patients H/M <1.6 | -$6,585 | -$4,462 |
| ICD implant cost | -$5,929 | -$5,081 |
| I-mIBG drug cost | -$5,777 | -$5,209 |
| Relative risk of SCE of patients with H/M ≥1.6 | -$5,536 | -$5,427 |

| Incremental Costs | Low Input | High Input |
|-------------------|-----------|------------|
| Proportion of patients H/M <1.6 | -$15,503 | -$11,448 |
| Frequency of generator replacement (years) | -$15,163 | -$12,266 |
| Discount Rate Costs | -$14,381 | -$12,611 |
| ICD generator replacement cost | -$14,128 | -$12,765 |
| ICD implant cost | -$13,860 | -$13,011 |
| Non-SCD heart failure death rate (2 years) | -$13,698 | -$13,122 |
| AdreView drug cost | -$13,708 | -$13,140 |
| ICD efficacy for patients with H/M ≥1.6 (RR of SCD) | -$13,576 | -$13,185 |
| Frequency of ICD evaluation (per year) | -$13,566 | -$13,295 |
| Relative risk of SCE of patients with H/M ≥1.6 | -$13,539 | -$13,375 |

*Fig. 3* One-way sensitivity analyses: a over 2 years; b over 10 years. *H/M* heart/mediastinum ratio, *ICD* implantable cardioverter defibrillator, *I-mIBG* iodine-123 meta-iodobenzylguanidine, *RR* relative risk, *SCD* sudden cardiac death, *SCE* sudden cardiac event

*Adis*
proportion of patients with an $H/M$ ratio <1.6, ICD implant cost, I-mIBG drug cost, and relative risk of SCE in patients with an $H/M$ ratio ≥1.6. Over 10 years, the model results were most sensitive to the proportion of patients with an $H/M$ ratio <1.6, frequency of generator replacement, and discount rate for costs. Assuming that 33 or 66% of ICD shocks were lifesaving had little impact on cost differences over 2 years (savings of US$5510 and US$5490, respectively) and 10 years (savings of US$13,416 and US$13,445, respectively), little impact on mortality differences over 2 years (0.2%), and minimal impact over 10 years (0.8% and 0.7%, respectively). The sensitivity analysis showed that screening with I-mIBG imaging was cost saving across the full range of tested model parameters, with a minimum expected cost saving of US$4462 over 2 years and US$11,448 over 10 years.

The results of the PSA estimated cost savings of US$5508 (95% CI US$4395–6839) over 2 years and US$13,498 (95% CI US$10,976–16,474) over 10 years. In the PSA, screening with I-mIBG imaging had a 100% probability of being more cost effective than no screening, up to a willingness-to-pay threshold of US$1,000,000 per QALY over a 2-year time horizon. Over a 10-year time horizon, screening was more likely cost effective than no screening, up to a willingness-to-pay threshold of over US$500,000 per QALY (Fig. 4). It has been suggested that cost-saving innovations may improve overall outcomes, even when they are slightly less effective, under conditions of resource constraint [32]. A “decrementally cost-effective” intervention is defined as one in which there are savings of at least US$100,000 per QALY lost. However, decrementally cost-effective medical innovations are rare, with only 8 innovations identified in 887 publications. Screening HF patients with I-mIBG imaging would be an example of a decrementally cost-effective intervention, with savings of US$5,248,404 per QALY lost over a 2-year time horizon and savings of US$513,036 per QALY lost over a 10-year time horizon. Generally, healthcare payers, clinicians, and patients are accustomed to incrementally cost-effective interventions. However, payers, in particular, may want to offer clinicians and patients the option of screening in cases where the clinician is uncertain about the risk/benefit profile of an ICD or where the patient has significant reservations in order to control or limit costs.

4 Discussion

This analysis found that screening NYHA class II or III HF patients who are eligible on the basis of ACC/AHA/HRS guidelines for primary-prevention ICD implantation with I-mIBG imaging has the potential to reduce costs associated with ICDs, with a minimal impact on patient mortality. In the model, screening resulted in approximately one in every 5 patients being identified as low risk for SCD. On the basis of data from the ADMIRE-HF/HFX studies, patients with an $H/M$ ratio ≥1.6 had a lower risk of SCD and mortality over 2 years. Assuming these patients forgo an ICD, the high costs of the device, surgical implantation, and subsequent generator and lead replacement can be reduced significantly at a population level while maintaining the beneficial impact of ICDs in reducing SCD and extending life (Fig. 2). With screening, overall per-patient costs were reduced by US$5500 over 2 years and by US$13,431 over 10 years, while expected LYs per patient for the modeled cohort were reduced by less than a day over a 2-year horizon and by about 2 weeks over a 10-year horizon.
rate in those who met the criteria. Screening with I-
ICD shock rate that was approximately one quarter of the
not meet guideline criteria for ICD use had a subsequent
B use at the time of generator replacement, defined as EF
25 % of patients who received an ICD for primary pre-
vention may no longer meet guideline indications for ICD
patients in deciding to forgo an ICD.
The overall cost of ICDs to the healthcare system is
significant. According to the AHA, about 100,000 ICDs
are implanted each year in the USA [33]. At a cost of
about US$40,000 per device, this translates into an annual
cost of approximately US$4.0 billion. These high costs
are incurred despite the fact that most guideline-eligible
patients do not receive an ICD [34]. The result is a con-
cern among healthcare payers that adherence to treatment
guidelines and a corresponding increase in ICD utilization
would further increase costs [35]. The use of I-mIBG
imaging has the potential to contain or reduce the use of
ICDs by identifying patients at lower risk of SCD who are
likely not to derive a meaningful benefit from an ICD.
Even if ICDs are cost effective as currently used,
screening would help to improve their cost effectiveness
and allow policy makers to make better use of limited
healthcare resources [7].
Patients who might be appropriate candidates for
screening include those considered for a primary-preven-
tion ICD where the clinician or patient is unsure whether
the risks (e.g., the procedure, device complications, and
inappropriate shocks) outweigh the benefit of the ICD in
preventing SCD. Our analysis indicates that screening in
patients with an EF of 25–35 % resulted in greater cost
savings with a similar minimal effect on survival, in
comparison with patients with an EF ≤25 %. This was
primarily the result of identifying a greater proportion of
patients with an H/M ratio ≥1.6 in the EF 25–35 % group
who were at lower risk of SCD. The EF may therefore be a
useful marker to select patients for screening with I-mIBG
imaging. Targeting patients in the EF 25–35 % group is
also consistent with recent evidence from the National
Cardiovascular Data Registry showing a lesser benefit of
ICDs among patients with higher EFs [36]. Additionally,
25 % of patients who received an ICD for primary pre-
vation may no longer meet guideline indications for ICD
use at the time of generator replacement, defined as EF
≤35 % or a prior appropriate shock [37]. Patients who did
not meet guideline criteria for ICD use had a subsequent
ICD shock rate that was approximately one quarter of the
rate in those who met the criteria. Screening with I-mIBG
imaging may be useful in identifying patients with an EF
≤35 % without a prior appropriate ICD shock, who may be
candidates for ICD generator explantation versus
replacement.

4.1 Limitations
This study had several limitations. Data on the effective-
ness of I-mIBG imaging were obtained from the ADMIRE-
HF/HFX prospective studies [11, 15]. For the purposes of
this model, an analysis was conducted to estimate the
baseline rate and HR of SCE, defined as SCD or an
appropriate ICD shock (i.e., defibrillation). This was nec-
essary since the ADMIRE-HF/HFX study populations
included patients with ICDs (most of whom never received
an appropriate ICD shock), and ICDs prevent SCD only via
an appropriate shock. But appropriate ICD firing is not
equivalent to SCD, as fewer than one in three such events
are likely to be lifesaving [26]. Therefore, in the model, we
adjusted for the baseline risk of SCE by using a conser-
vative assumption that 50 % of appropriate firings were
lifesaving (and we tested a range of values from 33 to 66 %
in a sensitivity analysis). The SCE relative risk (0.29;
95 % CI 0.16–0.52) used in the model was a proxy for the
ture relative risk of SCD, which is not known, but this SCE
estimate was consistent with the HRs from the ADMIRE-
HF study for arrhythmic events (0.37) and cardiac death
(0.14). Additionally, the proportion of defibrillations
among trial subjects with ICDs (8.5 %) was less than twice
that of SCD among trial subjects without ICDs (4.6 %),
suggesting that the SCE endpoint with an adjustment for
non-lifesaving defibrillations provides a reasonable
approach and is preferable to ignoring the effect of ICDs or
treating all ICD activations as equivalent to SCD preven-
tion. Finally, the model results in the sensitivity analysis
were robust across the tested range for the SCE relative
risk.
The ADMIRE-HF study had a 2-year study duration
[11]. ICDs are generally recommended only in patients
with a minimum 1-year expected survival, as patients with
short-term expected survival are unlikely to benefit from
ICDs, as they are at markedly increased risk of non-SCD-
related mortality. Moreover, cost-effectiveness analyses,
including this analysis, have found that the cost-effective-
ness ratios for ICDs are substantially more favorable over a
longer time horizon. Consequently, it was necessary to
extrapolate the time horizon of the model beyond the
2-year study duration. In extrapolating, we assumed that
the prognostic value of I-mIBG imaging persisted over the
duration of the analysis and, as in other models of ICDs, we
also assumed that the relative risk reduction of ICDs per-
sisted over the duration of the analysis. A long-term study
in Japan found that a single I-mIBG imaging test was
predictive of mortality over a 10-year period [38]. Addi-
tionally, to address the potential limitations associated with
extrapolation, we conducted a short-term (2-year) analysis
in addition to a long-term (10-year) analysis and found that
screening was cost saving and cost effective over all
modeled time horizons. See the Appendix for additional information on validation of the model predictions over the extrapolated time period and lifetime analyses.

We did not account for the possibility of serial screening, where low-risk patients who do not receive an ICD may undergo a repeat test after a period of time. Additional analyses are necessary to assess the potential impact of serial screening on clinical outcomes and costs when sufficient data on disease progression are available. In the meantime, the finding that screening was cost effective over a 2-year time horizon suggests that serial screening may be cost effective in an appropriate patient population; however, the impact will depend on the frequency of rescreening and the rate of disease progression, which affect the durability of the prognostic information provided by the test. Additionally, the Japanese analysis by Nakata et al. [38] found that a single I-mIBG imaging test with a high $H/M$ ratio was predictive of a low mortality risk over a 10-year period. This suggests that a longer rescreening interval may be appropriate, assuming no changes in other clinically relevant indicators, which would improve the cost effectiveness of a screening program in comparison with one with a shorter rescreening interval. Nor did we account for the possibility that patients who are screened and do not receive an ICD may receive one subsequently, thus only delaying the costs of ICDs. However, there is an economic benefit from delaying the costs of the device and reducing the number of generator and lead procedures. Additionally, in this patient population, it is also likely that some screened patients will die of non-arrhythmic causes prior to being reconsidered for an ICD.

Finally, this modeling study provided a population-level analysis and does not necessarily apply to any particular individual patient. The clinical risks and benefits of I-mIBG imaging for screening HF patients to identify those at low risk of SCD will need to be assessed by clinicians on the basis of the specific characteristics of individual patients. However, on the basis of the subgroup analyses we conducted, screening would generally be more effective and cost effective in patients with an LVEF of 25–35 % in comparison with patients with an LVEF <25 %.

4.2 Conclusion

According to the model, incorporating I-mIBG imaging into the assessment of guideline-eligible patients selected for ICDs may reduce costs associated with implantation of ICDs, with a minimal impact on patient outcomes. This modeling study found that screening reduced costs, in comparison with no screening, by US$5500 and US$13,431 per patient over 2 and 10 years, respectively. Additional studies are warranted to further evaluate the costs and effectiveness of screening.

Author contributions All authors were involved in the conception and design of the study, data collection, and critical revision of the manuscript. Ken O’Day developed the model, ran the analyses, and drafted the manuscript.

Compliance with Ethical Standards

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Conflict of interest disclosure statements Ken O’Day is an employee of the consulting company Xcenda, LLC, which received funding from GE Healthcare US to conduct this research. Wayne Levy is an employee of the University of Washington and a consultant to GE Healthcare US. He is the local investigator in the ADMIRE-HF trial and a steering committee member of a potential ICD trial using MIBG imaging. He is also a consultant to Biotronik and has received research funding from Medtronic. Meridith Johnson is an employee of GE Healthcare US. At the time of this research, Arnold Jacobson was an employee of GE Healthcare US.

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Appendix

Model Validation

Multiple methods were used to attempt to validate the model predictions and results.

First, the model results were cross-validated against a published decision model estimating the cost effectiveness of ICDs [23]. The Sanders model utilized data from multiple ICD trials to estimate the cost effectiveness of ICDs over a lifetime horizon and found that, depending upon the data source used, an ICD would add between 1.01 and 2.99 QALYs and between US$68,300 and US$101,500 in costs over a lifetime horizon, resulting in ICERs ranging from US$34,000 to US$70,200 per QALY. Accordingly, we reconfigured our model inputs to estimate the cost effectiveness of an ICD versus no ICD (as opposed to screening versus no screening), and we modified the cost and utility inputs in the model with values from the analysis by Sanders et al. while leaving all mortality-related inputs intact. With these inputs, over a lifetime horizon, our model estimated a gain of 1.00 QALY (1.8 undiscounted LYs) and a cost increase of US$67,183, resulting in an
For the base-case analysis, the median EF in ADMIRE was 27 versus 23% and 25% in MADIT-II and SCD-HeFT, respectively. In ADMIRE, only 17% of patients were in NYHA class III, versus 24% in MADIT-II (with an additional 5% in class IV) and 30% in class III in SCD-HeFT. The effect sizes for ICDs were similar across all three populations, with a 5-year predicted relative risk of 0.75 in our model and observed HRs of 0.66 and 0.77, respectively, in MADIT-II and SCD-HeFT. Varying these parameters within the sensitivity analyses did not substantially change the model results.

Lifetime outcomes for patients with an LVEF ≤35% are listed in Table 4.

**Table 4** Lifetime outcomes for patients with a left ventricular ejection fraction ≤35%  

| Outcomes            | No ICD  | ICD  | Difference between screening and no screening |
|---------------------|---------|------|---------------------------------------------|
| ICD (%)             | 0.0     | 100.0| 79.1                                        |
| Mortality (%)       | 100.0   | 100.0| 100.0                                       |
| LYs                 | 11.726  | 13.532| 13.377                                      |
| LYs; discounted     | 9.232   | 10.430| 10.331                                      |
| QALYs; discounted   | 7.236   | 8.153 | 8.077                                       |

**Costs ($)**

|              | No     | ICD    | Difference between screening and no screening |
|--------------|--------|--------|---------------------------------------------|
| Screening    | 0      | 0      | 3209                                       |
| ICD          | 0      | 41,486 | 32,815                                     |
| Battery/lead replacement | 0      | 55,148 | 42,776                                     |
| ICD evaluation| 0     | 3420   | 2661                                       |
| Medical costs | 164,997| 180,669| 179,391                                   |
| Total        | 164,997| 280,724| 260,853                                   |

The numbers may not sum because of rounding.

HF = heart failure, ICD = implantable cardioverter-defibrillator, LY = life-year, QALY = quality-adjusted life-year.

ICER of US$67,265 per QALY for ICDs. These results are comparable to the results obtained by Sanders et al.

Second, in our model, mortality due to SCD was separated from mortality due to pump failure and other causes of death. For the measure of ICD effectiveness, we utilized the relative risk of SCD mortality (0.40) in patients receiving ICDs in a large meta-analysis [17]. The same published meta-analysis reported a relative risk of 0.73 for ICD all-cause mortality, which was consistent with our model’s estimated relative risk of 0.75 for all-cause mortality in patients with ICDs over 5 years, thereby validating the proportion of deaths due to SCD versus other causes in our analysis.

Finally, we compared survival outcomes from our analysis with the outcomes from the MADIT-II and SCD-HeFT clinical trials. The observed 5-year mortality rates among no-ICD and ICD patients were 43 and 33%, respectively, in MADIT-II, and 36 and 29%, respectively, in SCD-HeFT [4, 5]. Over 5 years, our model predicted mortality rates of 26% in patients not receiving an ICD and 19% in patients receiving an ICD. The somewhat higher mortality rates in MADIT-II and SCD-HeFT, in comparison with our analysis, can be accounted for by the lower-risk patient population in ADMIRE, which was used for the base-case analysis.

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