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ORIGINAL ARTICLE

A cost-effectiveness analysis of hypertrophic cardiomyopathy sudden cardiac death risk algorithms for implantable cardioverter defibrillator decision-making

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Aims To conduct a contemporary cost-effectiveness analysis examining the use of implantable cardioverter defibrillators (ICDs) for primary prevention in patients with hypertrophic cardiomyopathy (HCM).

Methods A discrete-time Markov model was used to determine the cost-effectiveness of different ICD decision-making rules for implantation. Several scenarios were investigated, including the reference scenario of implantation rates according to observed real-world practice. A 12-year time horizon with an annual cycle length was used. Transition probabilities used in the model were obtained using Bayesian analysis. The study has been reported according to the Consolidated Health Economic Evaluation Reporting Standards checklist.

Results Using a 5-year SCD risk threshold of 6% was cheaper than current practice and has marginally better total quality adjusted life years (QALYs). This is the most cost-effective of the options considered, with an incremental cost-effectiveness ratio of £834 per QALY. Sensitivity analyses highlighted that this decision is largely driven by what health-related quality of life (HRQL) is attributed to ICD patients and time horizon.

Conclusion We present a timely new perspective on HCM-ICD cost-effectiveness, using methods reflecting real-world practice. While we have shown that a 6% 5-year SCD risk cut-off provides the best cohort stratification to aid ICD decision-making, this will also be influenced by the particular values of costs and HRQL for subgroups or at a local level. The process of explicitly demonstrating the main factors, which drive conclusions from such an analysis will help to inform shared decision-making in this complex area for all stakeholders concerned.

Keywords Cost-effectiveness analyses • Risk prediction • HCM • ICD

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Key learning points

What is already known

- Hypertrophic cardiomyopathy (HCM) is a common heart muscle disorder and a leading cause of sudden cardiac death (SCD) in adults. Patients at high risk of SCD need to be identified so they can be offered an implantable cardioverter defibrillator (ICD).
- ICD implantation has significant variation across healthcare systems.

What this study adds

- The optimal decision, in terms of the cost-effectiveness of primary prevention ICD considered, is to adopt the >6% SCD risk threshold in a Cox regression algorithm (ICER £834/QALY) with up to approximately 70% probability.
- The cost-effectiveness and therefore optimal decision is dependent on the choice of time horizon and the relative utilities of the ICD and no ICD states, which have imprecise values.
- Future work is needed to quantify accurately utilities, especially for current, higher cost interventions such as subcutaneous ICD (S-ICD).

Introduction

Hypertrophic cardiomyopathy (HCM) is a common inherited heart muscle disorder and a leading cause of sudden cardiac death (SCD) in adults. Patients at high risk of SCD need to be identified so they can be offered lifesaving prophylactic treatment with an implantable cardioverter defibrillator (ICD). An ICD delivers an appropriate shock to terminate ventricular arrhythmia (anti-tachycardiac pacing excluded). Whilst contemporary guidelines[1,2] recommend that SCD risk is assessed to inform clinical decision-making with respect to primary prevention ICD implantation, their implementation in the real world demonstrates significant variation across healthcare systems.[3]

O'Mahony *et al.*[4] derived an SCD risk model to generate individualized, quantitative risk estimates to improve the targeting of ICD therapy in HCM patients. The implementation of such guidance is complex, with the interplay of evidence-based medicine and a patient's priorities, life philosophy, and background characteristics (e.g. gender, race/ethnicity, and socioeconomic status) ('patient values') determining the outcome of any shared decision. The use of health economic analyses and, in particular, cost-effectiveness analyses (CEAs) can supplement clinical outcomes research. CEAs can impact decision-making in terms of modelling the system-level effect of ICD in HCM and thereby influence funding decisions for the availability of the treatment. They require associated costs and health-related quality of life (HRQL) data. HRQL can be defined as those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment. In addition, they rely on clinical outcomes for use as input data in any modelling. In scenarios where mortality is a rare event, the reporting of patient welfare through HRQL can have a large effect on their conclusions. Despite a number of previous CEAs in this field[5–8] uncertainty still remains about the cost1-effectiveness of primary prevention ICDs given the different methodology and input data used.

Given the changing pattern of ICD implantation rates across different geographies and populations, there is a need to re-examine the question of cost-effectiveness as well as the underlying assumptions used in modelling to derive an answer to such a question. This paper therefore presents an updated cost-effectiveness analysis of primary prevention ICD in HCM. The CEA reflects contemporary practice with a range of ICD implantation rates.

Methods

A discrete-time Markov model was used to determine cost-effectiveness of different ICD decision-making algorithms. We investigated several alternative scenarios, including the case of current practice in the UK and Europe, defined as observed ICD implantation in the study dataset based on ACC/ESC 2003 guidelines (prior to ESC 2014 guidelines/HCM Risk SCD). Two other scenarios used the Cox regression model for 5-year HCM-SCD risk prediction from.[4] Two criteria for ICD implantation were used based on either >6% or >4% 5-year SCD predicted risk. Current practice, i.e. what was observed in the raw data, was used as the reference group to make direct comparisons of cost-effectiveness statistics with other algorithms. The time horizon for simulated patient follow up was set at 12 years from time of ICD implant, following.[4] The time cycle length was 1 year, in order to capture the rate of occurrence of events. A UK National Health Service (NHS) health service provider perspective was taken and only costs directly incurred by the NHS were included, obtained from expert knowledge, NHS National Tariffs, and previous CEAs and reviews (see below). The discount rate used was the standard 3.5% for both costs and utilities.[9] The willingness to pay (WTP) threshold was set at £25 000 as commonly used by the UK National Institute for Health and Care Excellence (NICE).[10] Health outcomes were based in utilities using quality-adjusted life-years (QALYs), which are a measure of the state of health of a person, where one QALY is equal to 1 year of life in perfect health. Costs were all in pounds sterling in 2022. The Consolidated Health Economic Evaluation Reporting Standards[11] checklist was followed and is provided in the Supplementary Material.

Study data

The data set used in our analysis has been described in detail elsewhere (see[4]). In brief, 3672 individuals with HCM were followed up from the point of HCM diagnosis, of whom some had been given an ICD depending on clinical and patient factors. Patients were enrolled from six health centres in Greece, Italy, England, and Spain: Athens (474), Bologna (456), Coruna (590), London (1592), Murcia (404), and Naples (156). The mean age (SD) was 48.[16]

The main survival analysis in[4] was based on a composite end point consisting of aborted SCD, appropriate ICD shock therapy and survived cardiac arrest. After a median follow up of 5.7 years (IQR, 2.8–9.2), 197 patients (10.6% of total cohort) reached the composite study end point (SCD, 117 (6.3%); appropriate shock, 53 (2.9%); survived cardiac arrest, 27 (1.5%)); 1.4% of patients died of other cardiovascular (CV) causes; 144 patients (3.9%) died of non-CV causes.

Model structure

The Markov model comprised five states: (1) HCM ICD; (2) ICD-Shock; (3) HCM without ICD; (4) SCD; and (5) all-cause death. Each base case scenario was represented by different starting state populations and different transition probabilities. The transition probabilities were assumed constant through time (time-homogeneous). A diagram of the Markov model is given in *Figure 1*.

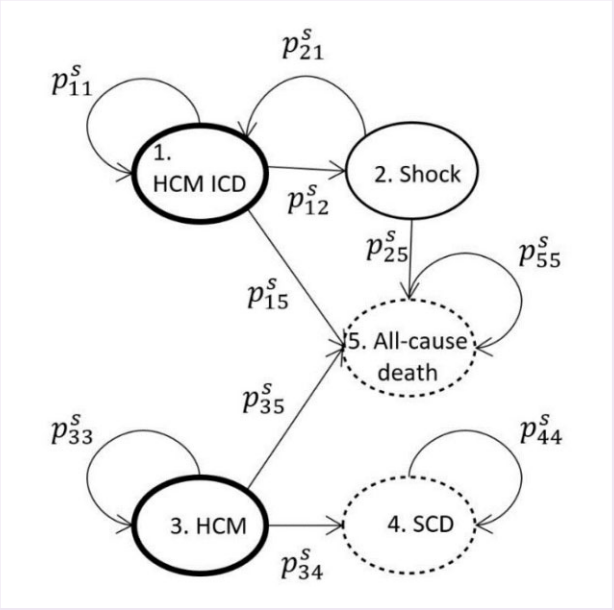

Figure 1 HCM ICD Markov model diagram. Bold circles represent starting states with and without ICD and dashed circles represent sink states. HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; SCD, sudden cardiac death.

We assumed that shocked patients either died from all-causes or returned to the HCM-ICD state at the next cycle. The negative health impact of a shock lasts for one cycle and then an individual returns to a pre-shock health state. All shocks were treated the same in terms of costs and health impact. We did not include a possible transition from HCM to HCM-ICD because age had a negative effect on the SCD risk score and thus the proportion of the cohort eligible for an ICD at each time step was a decreasing subset of those given an ICD at the outset. Other risk factors in the Cox model could also have changed over time, but we did not have access to this information and so assumed that they remained constant. The full set of equations for calculating the health and cost values for each scenario are given in the Appendix.

Parameter estimation

Predicted SCD risk from the model using patient data produced ICD stratified group sizes for each scenario, which were used for starting state populations in the Markov model for HCM with ICD and HCM without ICD (in contrast to other stratification approaches not using cohort data).[12] The event times of shock or SCD and all-cause death in each stratified group for each scenario were used to estimate posterior distributions of transition probabilities p^s_{ij} for each scenario s and pair of states i, j. All computation were carried-out in the statistical software for Bayesian analysis, WinBUGS,[13] called from R.[14] Details of the formulae and results for the Bayesian inference are provided in the Appendix.

Cost-effectiveness input data

Health, resource use, and cost data were obtained from literature and expert opinion. *Table 1* presents the unit cost and health-base case values used in the primary analysis. The primary analysis uses parameter values most likely to occur. The effect of changes to these values was explored in sensitivity analyses. The shock utility proportion is the ratio of shock utility and non-shock utility of 0.7/0.8 from.[15] Similarly, the manage with ICD proportion is 0.8/0.88, which is consistent with values found elsewhere.[8,16] We assumed that an ICD patient followed routine practice and had six monthly appointments. Implant complications and their associated costs were taken as a weighted sum of infection and dislodgement cost with values from.[17]

All code is made publicly available on GitHub at https://github.com/n8thangreen/HCM-SCD-CE-analysis/.

Sensitivity analyses

We performed two types of sensitivity analyses. First, a one-way deterministic sensitivity analysis varying the cost and health parameter values one at a time to investigate what impact this would have on the model output and conclusions. We then conducted a probabilistic sensitivity analysis (PSA), using a global first-order variance-based sensitivity analysis.[19] Variance-based sensitivity indices use the variance to describe the model output uncertainty, capturing the influence of the full range of variation in each parameter.

Results

Starting state population sizes

Table 1 gives the Markov model starting state population sizes. The uncertainty for the populations estimated using the Cox 5-year SCD risk algorithm was obtained by using the frequentist confidence intervals from the model fit in[4] assuming a normal distribution and simulating a sample of 5-year SCD risk probabilities for each individual. We observed that a decrease of 2% in risk threshold corresponds to a more than doubling of the number of ICD patients. The proportion of individuals given ICDs was the same in the observed study data and for the 5-year SCD risk threshold of >6%, but this does not necessarily mean that they have the same case-mix. That is, the characteristics of each group may be different, which would in turn lead to different transition probabilities.

Cost-effectiveness analysis

The Markov model simulation produced state population counts, costs and QALYs over time. Plots and tables for state occupancy and total person-years in states are given in the Appendix. In particular, the number of ICD shocks up to the time horizon of 12 years was 188, 129, and 110 for the >4% 5-year SCD risk, >6% 5-year SCD risk, and observed scenarios, respectively. Relative to the initial number of ICD patients this is 17, 23, and 20% of those with implants.

Table 2 shows the cost-effectiveness mean summary statistics for the primary analysis using observed data. The standard cost-effectiveness analysis outcome statistics of incremental net benefit, $\text{INB} = k\ \Delta e\ -\Delta c$, and incremental cost-effectiveness ratio, $\text{ICER} = \Delta c/\Delta e = (c1 - c0)/(e1 - e0)$, are reported, where k is the WTP threshold and $c0$ ($e0$) and $c1$ ($e1$) are the expected total cost (health) for the reference intervention and alternative, respectively. The reference intervention in the analyses is that observed in the study data unless otherwise stated.

Figure 2 shows the cost-effectiveness plane and cost-effectiveness acceptability curves for the two scenarios. We see that the >4% 5-year SCD risk threshold scenario has approximately doubled the expected total cost of the reference intervention. This follows intuitively because of the greater number of ICD patients. The expected total QALYs are similar between scenarios so that the relative cost-effectiveness is largely driven by the total costs. This is due to the incurred costs being mostly up-front, whereas the QALY benefit due to ICD implants is deferred due to death prevented following shocks. For a 12-year time horizon, a smaller number of excess QALYs are accrued, relative to those if a longer lifetime horizon was used. The >6% 5-year SCD risk threshold scenario is both cheaper than the reference group and has marginally better health outcomes. This is the most cost-effective of the options considered, with an ICER of £834/QALY and INB of £747. The total person-years in each state gives further intuition to this since these counts are multiplied by the

Table 1 Primary analysis Markov model parameter values

Description	Parameter	Value	Source
Health			
HCM without ICD	q_hcm	0.88 QALY/year	Sanders *et al.* [2005]
Manage with ICD proportion	u_icd	0.9	Magnusson and Wimo [2020]; Holbrook *et al.* [2020]
Death	q_death	0 QALY/year	
Implantation procedure decrement	u_implant	−0.048	Holbrook *et al.* [2020]
Implantation complication decrement	u_compl	−0.096	Holbrook *et al.* [2020]
Shock utility proportion	u_shock	0.875	Buxton *et al.* [2006]
Cost			
ICD appointment	c_appt	£145	(WF02A) [NHS England, 2021]
Perform risk score	c_rs	£0	
Implant ICD	c_icd	£4666	(EY02B) [NHS England, 2021]
Implant complication	c_compl	£28 857	Formula derived
Non-fatal shock with hospitalisation	c_shock	£165	Thijssen *et al.* [2014]
Lead infection	c_inf	£37 116	Thijssen *et al.* [2014]
Lead dislodgement	c_dis	£6146	Thijssen *et al.* [2014]
HCM without ICD	c_hcm	0	
Sudden cardiac death (SCD)	c_scd	0	
All-cause death	c_death	0	
Probabilities			
Initial implant complication	p_compl	0.043	Cunningham *et al.* [2012]
Lead infection	p_inf_init	0.02 277	Thijssen *et al.* [2014]
Lead dislodgement	p_dis_init	0.00 828	Thijssen *et al.* [2014]
Cohort size	N	3672	
Time horizon	T	12 years	Expert input
Annual number of appointments	n_appt	2	Expert input

All cost are in pounds sterling and inflated to 2021 value where necessary.

Table 2 Cost-effectiveness statistics per enrolled study individual

Scenario	Cost, c (£)	Δc (£)	QALYs, e	Δe	ICER (£/QALY)	INB† (£)
Observed (reference)	1899		7.77			
Cox 5-year SCD risk >4%	3569	1670	7.73	−0.04	−38 616	−2750
Cox 5-year SCD risk >6%	1925	26	7.80	0.03	834	747

The reference scenario is that observed in the original data.
†Incremental net benefit (INB) for WTP £25 000.

health and cost values for each state to estimate total cost and QALYs (see Appendix).

Sensitivity analyses

The input values for the deterministic analyses are given in *Table 3*. These values were obtained from the range of values used in relevant literature and clinical judgement. In some cases, we take the upper or lower bounding value, either 0 or 1, and balance this by using a similar difference on the other side of the central base case value. From the sensitivity analysis in[18] the lower bound HRQL for HCM QALYs (q_hcm) was 0.75. They also assumed that quality of life did not change as a result of the implantation of an ICD so the upper value for ICD utility (u_icd) was set at 1. The ICD device cost (converted from euros) was £13 788, much higher than £4666 from EY02B Tariffs.[19]

The input values for the probability analyses placed uniform distributions on the model parameters with minimum and maximum values taken from *Table 3*. The primary analysis employed a PSA on transition probabilities (using posterior samples). For this analysis, the mean posterior transition probabilities were used to focus on the uncertainty related to the cost and health parameter inputs. We also calculated the expected value of perfect partial information (EVPPI) in order to explore the differences in optimal interventions when knowing perfectly the value of each input parameter.

Further, we investigated the starting state population size uncertainty due to uncertainty in the Cox model. The uncertainty about the model coefficients was propagated forward to uncertainty about

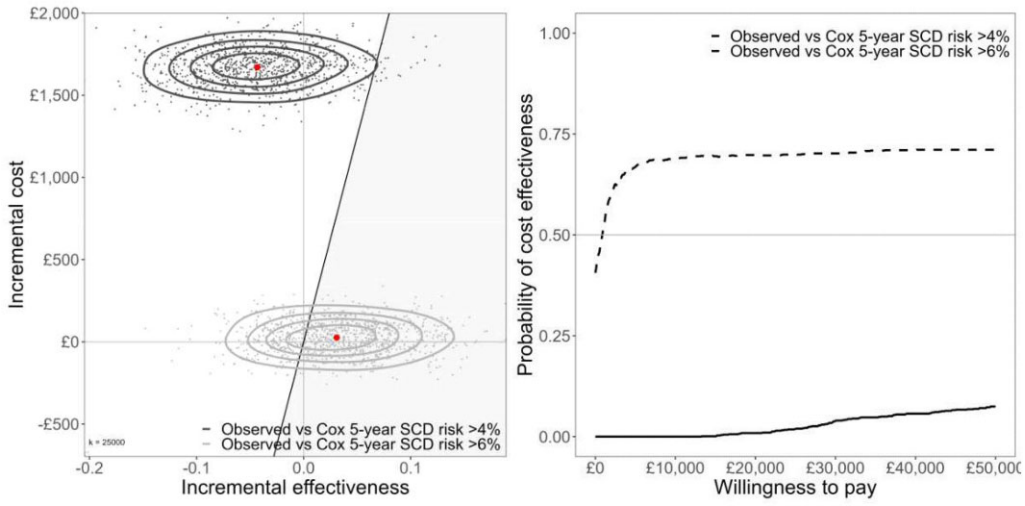

Figure 2 Plots of cost-effectiveness results with for the primary analysis. The reference scenario follows the decision-making observed in the cohort data. Solid line/black points are the >4% 5-year SCD risk threshold Cox algorithm and dashed line/grey points are the >6% 5-year SCD risk threshold Cox algorithm. (*A*) Cost-effectiveness plane. ICERs are indicated with red dots and a WTP threshold for £25 000 is indicated with the diagonal line. (*B*) Cost-effectiveness acceptability curve.

Table 3 One-way deterministic sensitivity analysis model input values

ID	q hcm	u icd	u shock	u implant	c icd (£)
1	**0.6**	0.9	0.875	−0.048	4666
2	**1**	0.9	0.875	−0.048	4666
3	0.88	0.9	0.875	**−0.096**	4666
4	0.88	0.9	0.875	**0**	4666
5	0.88	**0.8**	0.875	−0.048	4666
6	0.88	**1**	0.875	−0.048	4666
7	0.88	0.9	0.875	−0.048	**2333**
8	0.88	0.9	0.875	−0.048	**13788**
9	0.88	0.9	**1**	−0.048	4666
10	0.88	0.9	**0.5**	−0.048	4666

The bold font indicates the lower and upper values in the range, relative to the central values used in the primary analysis.

the decision to receive an ICD depending on whether an individual is above or below the 5-year SCD risk threshold.

Figure 3 shows tornado plots of the one-way deterministic sensitivity analysis for expected incremental benefit (EIB) with WTP £25 000 for the 4% and 6% 5-year SCD risk threshold Cox algorithm. We see that the 4% 5-year SCD risk threshold scenario had EIB most sensitive to the proportion reduction in utility due to ICD and the EIB was significantly less sensitive to changes in the other parameters. For the 6% 5-year SCD risk threshold algorithm, the EIB was also sensitive to the QALYs for an individual in the HCM non-ICD state. This makes sense because for this model there are more people in the HCM non-ICD state than in the 4% 5-year SCD risk threshold algorithm.

Furthermore, results for global first-order variance-based probability sensitivity analyses for incremental benefit (IB) with WTP £25 000 for the 4% and 6% 5-year SCD risk threshold Cox scenarios correspond with the deterministic analysis. The proportion reduction in utility due to ICD was a significantly larger proportion of the total variance than any of the other model parameters. For the >4% 5-year SCD risk threshold scenarios, this was almost all of the variation. For the >6% 5-year SCD risk threshold scenarios, some of the variation was also not trivially explained by the QALYs for an individual in the HCM non-ICD state. The EVPPI was 0 for all parameters except proportion reduction in utility due to ICD. Learning the other parameters to any more accuracy would not alter our algorithm decision. The Appendix provides the bar plots for this analysis.

Figure 4 shows the probability of each scenario being the most cost-effective across all scenarios simultaneously using the primary analysis parameters (ICD state 90% of non-ICD HRQL) and for an alternate set of inputs parameters where the ICD state was assigned 95% of non-ICD HRQL. We see that for the primary analysis parameter values, even at £50 000 WTP, the 6% 5-year SCD risk threshold algorithm only had approximately a 25% chance of being cost-effective, whereas for the alternative input parameters, the 6% 5-year SCD risk threshold scenario was cost-effective at £30 000 WTP.

The emphasis on the HRQL in the HCM states can be further demonstrated by extending the time horizon. To show the sensitivity to the time horizon, we repeated the baseline analysis but with a 30-year time horizon rather than 12 years. Reimplantation was again not included and so this analysis can be considered to provide a lower bound for total costs. The resulting plots are shown in the Appendix. We found that now the 6% 5-year SCD risk threshold algorithm was marginally cost saving as well as beneficial to health, and the 4% 5-year SCD risk threshold algorithm was on the decision boundary meaning, we would be indifferent to either the observed or new algorithm from a cost-effectiveness perspective. At WTP over £10 000, the 6% 5-year SCD risk threshold algorithm was optimal out of all alternatives including the do nothing option. Additional results to assess model fitting are also given in the Appendix.

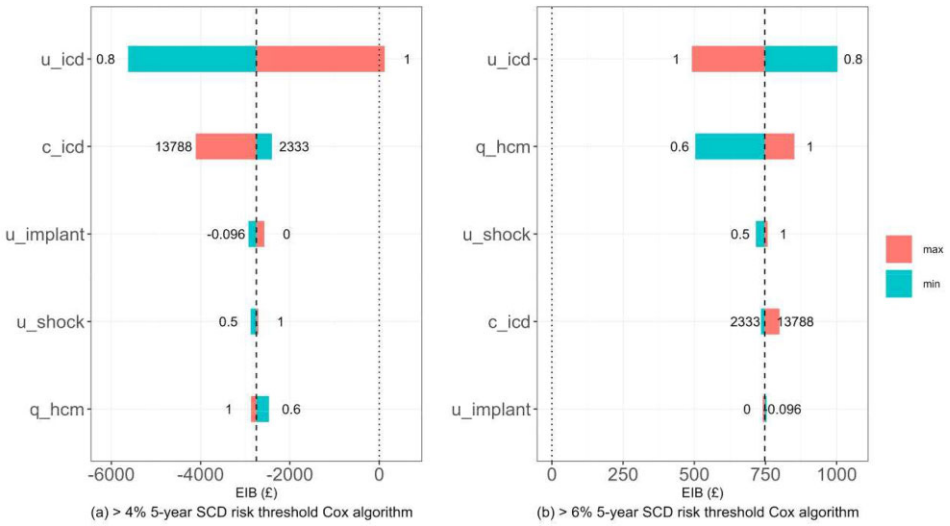

Figure 3 Tornado plots of one-way deterministic sensitivity analysis for EIB of 5-year SCD risk threshold Cox algorithms, with WTP £25 000. Mean values are indicated by the dashed line.

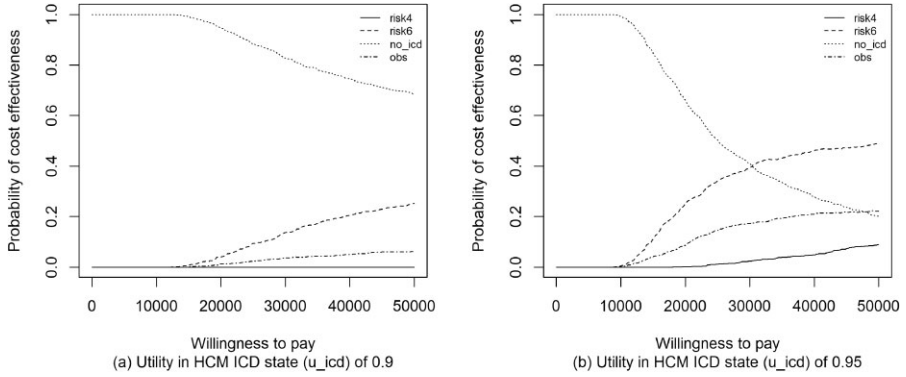

Figure 4 Cost-effectiveness acceptability curves for a sensitivity analysis of utility in ICD state. Comparing all scenarios simultaneously rather than pairwise against a reference. (*a*) All parameter values from base case. (*b*) Base case parameter values except with utility of HCM ICD at 95% of non-ICD HRQL instead of 90% from base case.

Discussion

In this paper, we have demonstrated that across a range of different ICD implantation scenarios, the optimal decision, in terms of cost-effectiveness of primary prevention ICD, varies between current observed practice and using a Cox regression algorithm for >6% 5-year SCD risk threshold. We found that for a 12-year time horizon and WTP threshold of £25 000 in the primary analysis, the decision rule in the observed data is more cost-effective than the 4% 5-year SCD risk threshold regardless of the size of budget since it is both more costly and more harmful in total (ICER −£38 616/QALY). The 6% SCD risk threshold is cost-effective (ICER £834/QALY) with up to approximately 70% probability and even at small WTP values. In other words, implanting fewer HCM patients with ICDs is a more cost-effective strategy compared to the decision rule observed in the study data, when assessed using a 12-year time window.

This headline is driven by two major factors. (1) High costs predominantly incurred at the outset for ICD implantation and its possible complications, balanced against any health benefits, which are accrued later in time. In our sensitivity analysis, we found that extending the time horizon to 30 years resulted in the 4% SCD risk threshold being borderline cost-effective relative to current practice with WTP threshold of £25 000 (ICER £26 820/QALY; INB −£146) and the 6% SCD risk threshold always being cost-effective since now it is both cost-saving and providing positive health impact (ICER −£270/QALY; INB £2 113). For longer time horizons, the cohort life expectancy becomes more of a key factor for CEA. When costs and health impact are accrued at different times in this way NICE guidance is to consider differential discounting with a smaller discounting for health benefit at 1.5%. This was explored but the impact was minimal given the second main driver of the model conclusions: (2) Quality of life values for the different health states such as having an ICD or experiencing a shock (either appropriate or inappropriate). The fact that in the 6% scenario,

an improvement in QALYs from 0.79 to 0.84 (proportion of non-ICD HRQL from 0.9 to 0.95) in the sensitivity analysis would alter the conclusion from not cost-effective to cost-effective at WTP £30 000 emphasizes this latter point.

Comparison with literature

In terms of cost-effectiveness of ICDs in general,[5] provided a systematic literature review (SLR) of relevant work, which updated a previous review.[15] CEAs for ICD decision-making have tended to use Markov models,[8,17,18] with some exceptions such as with a series of regression models[7] or a discrete-event simulation.[20] Direct comparisons between these studies is complicated by the fact that the design of the analyses and cohort study characteristics have important differences, including in terms of nationality, age, and health status. Previous work often uses a no ICD strategy as the reference group, which we decided was unrealistic. For example, cost-effectiveness estimates include the following: The ICER comparing ICD to no ICD strategies for Swedish adults with HCM was €15 119 per QALY gain.[8] For European patients with a reduced left ventricular ejection fraction (LVEF),[18] the ICER for ICD against conventional treatment lifetime cost was €46 413 per 1.57 QALYs. For patients with systolic heart failure with reduced ejection fraction based on a range of clinical characteristics,[7] the ICD strategy was cost-effective for all patients with QRS duration <120 ms, who were able to carry out any physical activity without discomfort at a £30 000 WTP threshold. Finally, for a cohort of patients with a LVEF < 40% of ischaemic or non-ischaemic aetiology,[17] gave an ICER of €43 993/QALY gained compared with the 'no ICD strategy'. The SLR in[5] contains summary tables of the differences between reviewed CEAs and their ICER results.

Different model assumptions

Considering model inputs, all-cause mortality in the literature is commonly defined as a point value using mortality rates from external sources, e.g. life tables. For example,[8] used a fixed yearly mortality rate for ICD patients taken from a national cohort study and included as an input parameter to the model a proportion reduction in mortality due to ICD. The simulation length of economic models varied between studies, ranging from a lifetime horizon,[7,17,21] to 12 years.[8] Further idiosyncrasies of individual studies included different care pathways, e.g. more detailed states, and multiple end points[22]; use of multiple implantation attempts if unsuccessful and[18] specific defined categories of death. All models must balance the trade-off between degree of detail, data quality, and assumptions made.

Challenges and considerations

We have highlighted that the utility in each state is particularly important in determining cost-effectiveness in this context. The relative utility (and cost) of the HCM with and without ICD state dominate modelling conclusions, with the shock state being less of a factor because it is a rare event. Importantly, the annual probability of occurrence of SCD or shock was estimated directly from the cohort data in the Bayesian model rather than using external references.

An aim of this CEA work was to highlight that for analyses with either a clinical or health economic focus, the value of patient reported outcome measures (PROMs), specifically the quantification of HRQL using validated instruments, play a crucial role in the assessment of both clinical- and cost-effectiveness for the vast majority of individuals involved in the ICD primary prevention decision-making space. We focused the modelling on one part of the patient journey with HCM. Additional therapeutic interventions can be considered, including more complex models of HCM care, and the global clinical and cost-effectiveness of HCM therapies. It is of note that separate evaluations of e.g. HRQL set within a particular context do not account for co-interventions or other indirect consideration that happen elsewhere, which can have a material impact to clinical and economic outcomes.[23,24]

Thus, changes in HRQL within a specific model such as ICD implantation may be confounded by other treatment strategies, e.g. medications, other surgical procedures, and a limited number of studies have used different models such as[25] in a Health Technology Assessment (HTA) compared optimal pharmacological therapy with or without ICD[20] compares ICD vs. amiodarone. Depending on the chosen perspective, the other relevant clinical factors that can bias the model results changes.

We have shown that model outcomes are particularly sensitive to state health values. This makes the current paucity of reliable and appropriate HRQL data particularly concerning. This is compounded by a lack of validated conversion scales for quantifying important events such as the effect of a shock and translating this, e.g. the Florida shock scale but does not convert to utilities.[26] Currently, most model inputs use data from trials, and other groups have demonstrated that identifying patients through routine care is feasible.[27] Such analyses could in future be directly connected to system-level analyses to harness the potential power of national electronic health records in the UK to identify and perform unbiased analysis of rare conditions and outcomes.

Limitations

In producing our cost-effectiveness analysis several assumptions were made. All patients within our Markov model were considered to have the same mean cohort age. Incorporating a distribution of ages would require a different modelling approach. However, given that other risk factors are a stronger determinant of SCD in HCM, this simplification does not detract from our overall analysis and results. We elected for a simple model with less reliance on data extrapolation for several reasons—(i) for HCM, the field has evolved dramatically over the last few decades, which has partly informed why we elected for a time horizon of 12 years to omit reimplantation considerations, given the unknown device technology including batteries that could appear in the next decade. Modelling for additional complexity based on expert-opinion and little patient-generated data was a deliberately chosen trade-off. We also did not include subcutaneous ICD (S-ICD) in our analyses. This was decided partly because the technology was not available during the study data collection period, and because of a lack of long-term follow up and outcomes data. For example, only 10% of S-ICD patients in the Effortless registry had HCM,[38] so there remains significant uncertainties regarding cost and HRQL. No medications were modelled, including side effects.[28] We implicitly assumed that they are in equal proportion and dose. The model parameters used in the cost-effectiveness analysis were particular to the cohort on which they were fit. Although there are other notable sources of HRQL utilities, including[29–31] these use condition specific HRQL scales that do not convert to a utility, such as country-specific views that are decades old[32] or suffer from small sample sizes.[33] In any case, the effects of changes in state utilities were demonstrated by our sensitivity analyses.

We assumed that the missingness in the original study data was assumed missing at random, as also assumed in the original paper.[4] In this case, the data were simply used directly in the Bayesian analysis to estimate transition probabilities. Further, the SCD risk estimates used in this work were provided from[4] which had addressed the missing data in the original study by using multiple imputation with chained equations.

Subgroup analyses could be further investigated, but the intention of this work was to investigate a priority real-world case-mix of patients. Symptomatic atrial fibrillation was not modelled though known to be particularly troubling for a group of HCM patients.[1] In these

individuals, ICD implantation may have a far smaller impact on HRQL than adequate rate or rhythm control.

We did not include a possible transition in the model between non-ICD and ICD states because an individual's 5-year SCD risk reduced with an increase in age. However, this behaviour was a result of fixing the other SCD risk factors at their baseline values for increasing age. This assumption was made because we did not have any follow up data available with which to model the relationship between the other SCD risk factors and age. Ideally, the collection of individual-level data over time could be used to do this.

Finally, we selected a health system perspective for this work, but a more expansive analysis could consider a patient or societal perspective, which may include cost due to patient time, transportation costs, caregiver time, productivity loss, and other non-healthcare sector impacts. This type of analysis is much less common and significantly more difficult to carry out.

Implications for practice

These results support conclusions made in the 2014 ESC guidelines, which advocate risk stratification using a risk prediction model to estimate risk of SCD within 5 years.[4,34] We have shown that from a systems perspective the new prediction model is also cost-effective for a 6% 5-year SCD risk threshold and WTP below a NICE recommended value of £20 000. Collective decision-making is aided by CEAs often with aggregated data but shaped by local context—price sensitive or QALY sensitive for each local population. Collecting more robust, relevant HRQL data will aid with the latter, which is a main driver of most utility analyses where the event rate for mortality (or other adverse events) is low.[35] More embedded PROMs research within other projects and systems provides an opportunity for this. Even with quantification of risk such as that employed by the SCD risk algorithm, the understanding and interpretation of risk differ from individual to individual (both professional and patient). The risk algorithm considered in this work adopted from[4] is for a 5-year risk. Patients or other colleagues may wish to consider a different time frame. The crux of such decisions is that an ICD offers delayed benefits for the few and a high initial upfront cost for all who receive it. However, the final decision to implant is more than an economic calculation and includes 'value based'/individual preferencing. Scaling evidence generation and embedding the result of such decisions within routine care in the form of Informatics Consult[36] represent rich areas for future work. Precision medicine is an active area of research aiming to more formally integrate individual variations and considerations in to the decision process. The type of analysis in this paper should be used in conjunction with a range of hard and soft evidence to inform a personalized decision. As advancements in care continue, including discovery of new therapeutic agents,[28] there may be further changes to functional status and HRQL in patients with HCM, which can affect any CEA in this field, including evaluations of ICD.[37]

As newer devices, such as S-ICD, become available to both providers and a subset of patients, a move towards implanting more patients may occur given the benefits of avoiding intravascular complications, such as infection, swelling, bleeding, bruising, and blood vessel damage. How this may impact a CEA analysis remains to be seen, especially when there is both an increase in cost and health benefit. Achieving the vision of systematic appropriate use of ICDs in HCM will require greater reporting of welfare impacts (quality of life) as well as its effect on reducing sudden cardiac death. This is timely given the latest data on variation in real-world practice and the rise of newer modalities including (S-ICD) technology.[38]

Conclusion

We have presented a timely new perspective on HCM-ICD cost-effectiveness, using methods, which reflect real-world ICD practice. We have shown that the >6% 5-year SCD risk Cox algorithm provides the best cohort stratification to aid ICD decision-making of the options considered but that this conclusion is sensitive to model assumptions, including the utility for ICD patients and the time horizon under consideration. This is pertinent at a local level where a CEA will be shaped by local data and so sensitive to price or QALYs for each local population. This paper may be of particular interest to policy makers or an HTA panel, but the process of explicitly demonstrating the main factors, which drive conclusions from an analysis should also inform front line shared decision-making.

Supplementary material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

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Data availability

The data and code underlying this article are available in the GitHub repository EHJ-QCCO-analysis, at https://github.com/n8thangreen/EHJ-QCCO-analysis.

Ethical and/or legal approval prior to conducting the research was not required.

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