HCM SCD risk algorithm cost-effectiveness analysis

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1 Introduction

Hypertrophic cardiomyopathy (HCM) is a common inherited heart muscle disorder and a leading cause of sudden cardiac death (SCD) in young adults. Patients at high risk of SCD need to be identified so they can be offered lifesaving treatment with an implantable cardioverter defibrillator (ICD). Contemporary guidelines recommend that the sudden death risk is assessed by evaluating clinical parameters that reflect the severity of the underlying myocardial disease. The presence or absence of these risk factors is then used to guide clinical decision-making with respect to prophylactic ICD implantation. Although observational cohort studies show that this approach identifies patients with the greatest risk of SCD, validation of current algorithms suggests that they overestimate risk, resulting in inappropriate prophylactic ICD implantation in a substantial number of patients. A previous study derived a new sudden death risk model that can be used to generate individualized risk estimates for SCD and improve the targeting of ICD therapy in patients with HCM (O'Mahony et al. 2014).

This paper aims to synthesise the key strengths of existing cost-effectiveness work in the area in order to answer the research question which is a notable gap in the current literature.

1.1 Previous work

There have been previous cost-effectiveness analyses of ICD implants (Magnusson and Wimo 2020; Boriani et al. 2014; Bryant et al. 2007; Caro et al. 2007; Cowie et al. 2009; García-Pérez et al. 2015; Mealing et al. 2016; Sanders, Hlatky, and Owens 2005; Smith et al. 2013)

Cost-effectiveness of a cardiovascular risk prediction algorithm. (Zomer et al. 2017) for statins interventions and people with severe mental illness.

(Yao et al. 2007) use a Markov model and consider multiple implantation attempts if unsuccessful. (Colquitt et al. 2014) is a Health Technology Assessment which compares optimal pharmacological therapy (OPT) with or without ICD. (Tomini 2016) is a review of economic evaluation models for cardiac resynchronization therapy with implantable cardioverter defibrillators in patients with heart failure. (Ommen et al. 2020) 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy.

2 Data

The data set has been described in detail elsewhere (see (O'Mahony et al. 2014)) so we will describe it briefly here. The main data set contains $n = 3672$ individuals follow-up data of patients with HCM who may have been given an ICD depending on clinical and patient factors.

Key cohort characteristics include the following. Patients were enrolled from the 6 health centres: Athens (474), Bologna (456), Coruna (590), London (1592), Murcia (404), Naples (156); The number of uncensored individuals was 197 (5%); The mean age (sd) was 48(16); The start of study data collection was in 1972 to 2011. Further plots are given in the Appendix.

Health and cost data were obtained from literature and expert opinion. Table 1 presents the unit cost and health values used in the model.

Table 1: Model parameter values. All cost are in pounds sterling and inflated to 2021 value where necessary. *either one-off/on state entry or recurring.

Description	Parameter	Value*	Range	Source
Health				
Manage with ICD	`q_icd`	0.88 QALY/year		Sanders, Hlatky, and Owens (2005)
HCM without ICD	`q_hcm`	0.88 QALY/year		Sanders, Hlatky, and Owens (2005)
Death	`q_death`	0 QALY/year		
Implantation procedure utility	`u_implant`	-0.016		Smith et al. (2013)
Shock utility	`u_shock`	-0.5		TODO
Cost				
ICD appointment	`c_appt`	£145		Cardiology Service (WF02A) Follow Up Attendance - Multi Professional. NHS England (2021)
Perform risk score	`c_rs`	£0		
Implant ICD	`c_implant`	£4,666		EY02B Tariffs
Implant complication	`c_compl`	£28,857		Formula derived
Non-fatal shock with hospitalisation	`c_shock`	£22,880		UK Stroke Assoc.
Lead infection	`c_inf`	£37,116		Thijssen et al. (2014)
Lead dislodgement	`c_dis`	£6,146		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`	0.02277		Thijssen et al. (2014)
lead dislodgement	`p_dis_init`	0.00828		Thijssen et al. (2014)
Time horizon	`T`	12 years		
Annual number of appointments	`n_appt`	2		

3 Methods

The individual-level patient data are first stratified in to two groups for each risk algorithm. The algorithms are

- Partition observed in data set: This is in principle number of risks factors > x but also incorporates

other factors such as patient preference [TODO]

- ICD given if Cox model risk score > 6%: Using the method from (O'Mahony et al. 2014).
- ICD given if Cox model risk score > 4%: Using the method from (O'Mahony et al. 2014).

3.1 Markov model

Th patient data provide starting state populations for HCM with ICD and HCM without ICD which will be different for each risk decision rule. Further, the transition probabilities from these states will differ because of the case mixes. We assume that shocked patients return to the HCM ICD state. A diagram of the cohort model is given in Figure 1.

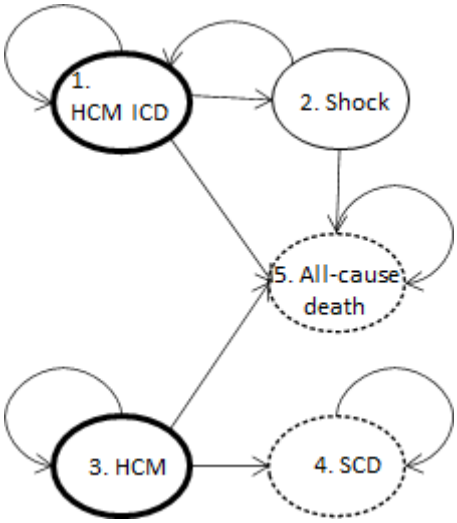


Figure 1: HCM ICD Markov model diagram. Bold circles represent starting states with and without ICD and dashed circles represent sink states.

Therefore, the transition matrix is the following.

$$\begin{pmatrix} p_{11} & p_{12} & 0 & 0 & p_{15} \\ 1-p_{15} & 0 & 0 & 0 & p_{15} \\ 0 & 0 & p_{33} & p_{34} & p_{35} \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

Model assumptions include the following: We assumed that an ICD patient has 2 annual appointments. All shocks are treated the same in terms of costs and health impact. Implantation can have complications and the cost of an implant complication is taken as a weighted sum of infection and dislodgement cost with values from (Smith et al. 2013). The time horizon was set at 12 years from time of implant, following (O'Mahony et al. 2014). The life cycle duration was one year. This was a balance between temporal fidelity and parsimony and was appropriate given the scale at which events occur. The full set of equations for calculating the health and cost values for each intervention are given in the Appendix.

3.2 Transition probability inference

Using the statistical software for Bayesian analysis, WinBUGS (Lunn et al. 2000) called from R (R Core Team 2021), each derived data set using each risk algorithm was used to generate posterior samples of transition probabilities. Details of the formulae for the Bayesian inference is provided in the Appendix.

4 Results

We give results of the model fitting and cost-effectiveness analysis.

4.1 Model fitting

The data set was stratified in to two subgroups for each intervention. Table 2 gives the model starting state populations. Uncertainty is presented for the Cox risk model values. These were obtained by using the frequentist confidence intervals from the risk score model fit in (O'Mahony et al. 2014) and simulating a sample of risk scores for each individual. The proportion of individuals for the observed and Cox model 6% threshold are similar but this does not necessarily mean that they are the same case-mix.

Table 2: Starting state populations by decision rule.

Risk rule	State	N (95% CI)	Proportion (95% CI)
Observed	HCM ICD	559	0.15
	HCM	3113	0.85
Cox risk >4%	HCM ICD	1103 (162, 2390)	0.3 (0.04, 0.65)
	HCM	2569 (1282, 3510)	0.7 (0.35, 0.96)
Cox risk >6%	HCM ICD	542 (61, 1777)	0.15 (0.02, 0.48)
	HCM	3130 (1895, 3611)	0.85 (0.52, 0.98)

Figures 2 gives densities of posterior distributions for state transition probabilities for groups with and without ICD implants using each risk decision rule. We see that the chance of remaining in the HCM state is lower for the ICD patients selected using the 6% risk threshold rule relative to the current approach. Also the chance of SCD or shock and all-cause death are higher. This indicates that the new method is better at selecting individuals to have an ICD.

4.2 Cost-effectiveness analysis

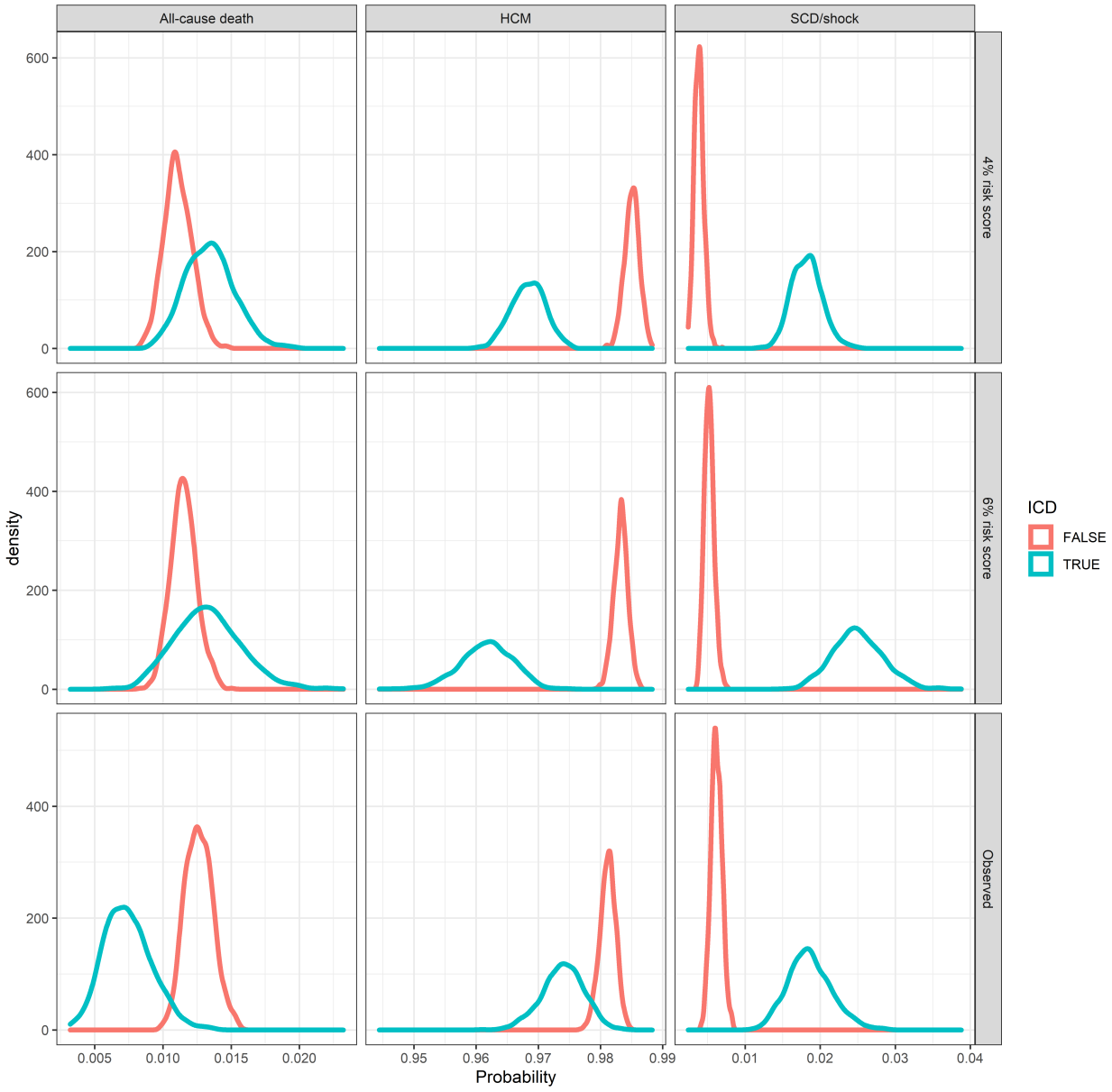


Figure 2: Density curves of posterior distributions for state transition probabilities from the starting state. Red lines are for ICD patients and blue lines are for non-ICD patients. Each row is for a particular decision rule of 4% and 6% threshold Cox model risk score and the observed in the data set.

Table 3: Cost-effectiveness statistics per enrolled study individual. The baseline intervention is that observed in the data.

Strategy	Cost, c (£)	Δc (£)	QALYs, e	Δe	ICER (£/QALY)
Baseline	8388.98		9.61		
Cox > 6%	7909.41	-479.57	9.65	0.04	-12,285
Cox > 4%	16,216	7826.78	9.66	0.05	156,463

Table 3 shows the cost-effectiveness mean summary statistics for baseline intervention of that observed in the data. We see that the 4% risk threshold intervention is approximately double the baseline expected total cost. This is expected because of the greater number of ICD patients. The expected total QALYs are very similar between interventions so that the relative cost-effectiveness is driven by the total costs. The 6% risk threshold intervention is both cheaper than the baseline and has marginally better health outcomes. This is the most cost-effective option with an ICER of 156,463. These conclusions are confirmed in the cost-effectiveness acceptability curve (CEAC) in Figure 3 and the cost-effectiveness plane in Figure 4.

4.2.1 Sensitivity analysis

Table 4: Sensitivity analysis input values.

scenario	q_hcm	q_icd	u_icd	u_shock	c_shock	c_icd	c_rscore	c_appt
1	0.88	0.88	-0.05	-0.5	22880	4666	0	145
2	0.50	0.88	-0.05	-0.5	22880	4666	0	145
3	1.00	0.88	-0.05	-0.5	22880	4666	0	145
4	0.88	0.50	-0.05	-0.5	22880	4666	0	145
5	0.88	1.00	-0.05	-0.5	22880	4666	0	145
6	0.88	0.88	-0.05	-0.8	22880	4666	0	145
7	0.88	0.88	-0.05	-0.2	22880	4666	0	145
8	1.00	0.00	0.00	0.0	0	1	0	0

c_inf	c_dis	p_compl	p_inf_init	p_dis_init
7116.02	6146.035	0.047	0.02277	0.00828
7116.02	6146.035	0.047	0.02277	0.00828
7116.02	6146.035	0.047	0.02277	0.00828
7116.02	6146.035	0.047	0.02277	0.00828
7116.02	6146.035	0.047	0.02277	0.00828
7116.02	6146.035	0.047	0.02277	0.00828
7116.02	6146.035	0.047	0.02277	0.00828
0.00	0.000	0.000	0.00000	0.00000

4.3 Discussion

Decision making as to whether to have the implant is shared between patient and medical professional. The SCD risk score is a support tool which contributes to the final decision. An SCD risk score of 6% provides a treatment recommendation for one patient versus another. There could be individual preferences that out-weighs the risk score and mean a patient chooses an alternative. Risk is viewed differently in shared decision making between patients and clinicians (and also between different clinicians).

Having more robust quality of life data will help to make such decisions. more embedded PROMs research

Informatics Consult (Lai et al. 2021) automation to scale evidence generation and to accelerate the return of

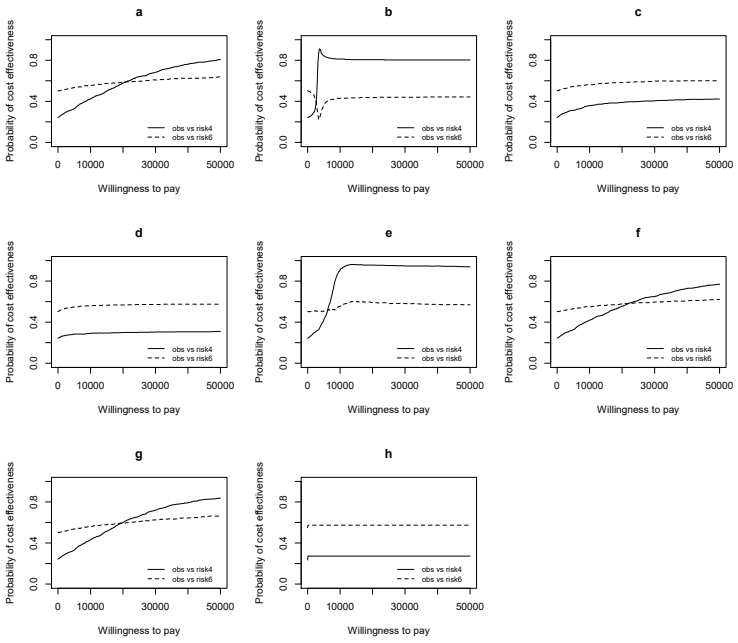


Figure 3: Cost-effectiveness acceptability curves (CEAC). Solid line is the 6% threshold Cox model and dashed line is the 4% threshold Cox model.

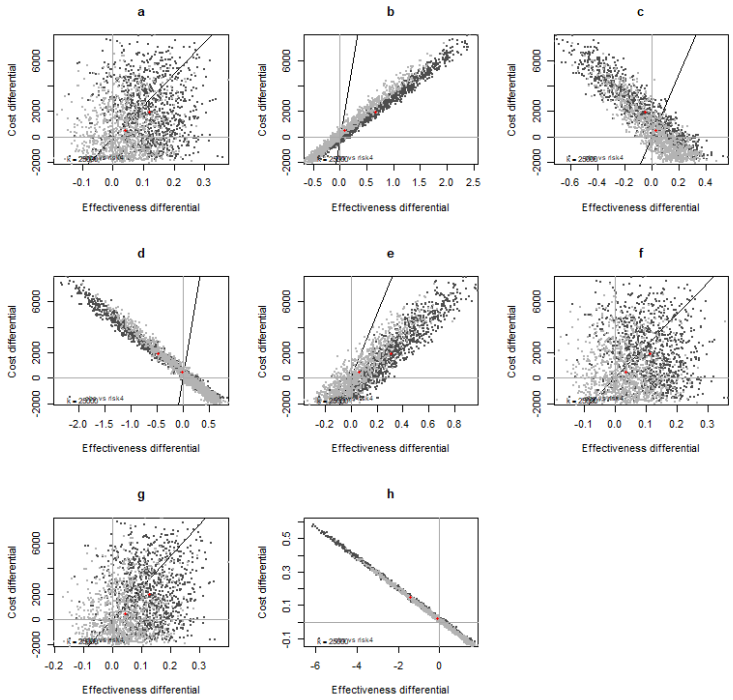


Figure 4: Cost-effectiveness planes. Black points are the 6% threshold Cox model and grey points are the 4% threshold Cox model. Mean values are indicated in red and a willingness to pay threhold for £25,000 is indicated with the diagonal line.

results within clinical time-scales.

We did not include CRT-D or s-ICD but that can be overcome by sensitivity analyses that show e.g. the main message is that conclusions about the ICER etc will be robust to most departures from base assumptions other than tweaks in utility (which are the part of the model based on the weakest data!)

(Olivotto et al. 2020) The role of new DMARDs and their ability to influence quality of life. So if both ICD and non-ICD patients experience significant increases in QoL, are these equally distributed?

Although this paper is anticipate to be of most interest to an HTA panel, the process of formally describing the development of the Markov model over time, such as for example how many reimplantations and QoL impact and unknowns etc that that could result in may in turn aid decision making.

The nascent field of s-ICD in HCM would have a time horizons for battery replacement lower than assumed for our analysis.

We could easily include the option of a fuzzy decision boundary such that near the threshold there is some random variation as to whether a patient received an ICD or not. Further this could formally incorporate expert knowledge which would require an elicitation exercise.

5 References

Boriani, Giuseppe, Paolo Cimaglia, Mauro Biffi, Cristian Martignani, Matteo Ziacchi, Cinzia Valzania, and Igor Diemberger. 2014. "Cost-effectiveness of implantable cardioverter-defibrillator in today's world." *Indian Heart Journal* 66 (SUPPL. 1): S101–4. https://doi.org/10.1016/j.ihj.2013.12.034.

Bryant, Jackie, Hakan Brodin, Emma Loveman, and Andrew Clegg. 2007. "Clinical effectiveness and cost-effectiveness of implantable cardioverter defibrillators for arrhythmias: A systematic review and economic evaluation." *International Journal of Technology Assessment in Health Care* 23 (1): 63–70. https://doi.org/10.1017/S0266462307051586.

Caro, J. Jaime, Alexandra Ward, H. Baris Deniz, Judith A. O'Brien, and Jenifer L. Ehreth. 2007. "Cost-benefit analysis of preventing sudden cardiac deaths with an implantable cardioverter defibrillator versus amiodarone." *Value in Health* 10 (1): 13–22. https://doi.org/10.1111/j.1524-4733.2006.00140.x.

Colquitt, Jill L, Diana Mendes, Andrew J Clegg, Petra Harris, Keith Cooper, Joanna Picot, and Jackie Bryant. 2014. "Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure: systematic review and economic evaluation." *Health Technology Assessment* 18 (56). https://doi.org/10.3310/hta18560.

Cowie, Martin R., Deborah Marshall, Michael Drummond, Nicole Ferko, Michael Maschio, Matthias Ekman, Luc De Roy, et al. 2009. "Lifetime cost-effectiveness of prophylactic implantation of a cardioverter defibrillator in patients with reduced left ventricular systolic function: Results of markov modelling in a european population." *Europace* 11 (6): 716–26. https://doi.org/10.1093/europace/eup068.

Cunningham, David, Richard Charles, Morag Cunningham, and Adel de Lange. 2012. "National Audit of Cardiac Rhythm Management Devices 2012," 1–185.

García-Pérez, Lidia, Pilar Pinilla-Domínguez, Antonio García-Quintana, Eduardo Caballero-Dorta, F. Javier García-García, Renata Linertová, and Iñaki Imaz-Iglesia. 2015. "Economic evaluations of implantable cardioverter defibrillators: a systematic review." *European Journal of Health Economics* 16 (8): 879–93. https://doi.org/10.1007/s10198-014-0637-x.

Lai, Alvina G, Wai Hoong Chang, Constantinos A Parisinos, Michail Katsoulis, M Ruth, Anoop D Shah, Vincent Nguyen, et al. 2021. "An Informatics Consult approach for generating clinical evidence for treatment decisions." *medRxiv*. https://doi.org/https://doi.org/10.1101/2021.01.10.21249331.

Lunn, D J, A Thomas, N Best, and David J. Spiegelhalter. 2000. "WinBUGS – a Bayesian modelling framework: concepts, structure, and extensibility." *Statistics and Computing* 10: 325–37.

Magnusson, Peter, and Anders Wimo. 2020. "Health economic evaluation of implantable cardioverter defibrillators in hypertrophic cardiomyopathy in adults." *International Journal of Cardiology* 311: 46–51. https://doi.org/10.1016/j.ijcard.2020.02.055.

Mealing, Stuart, Beth Woods, Neil Hawkins, Martin R. Cowie, Christopher J. Plummer, William T. Abraham, John F. Beshai, Helmut Klein, and Mark Sculpher. 2016. "Cost-effectiveness of implantable cardiac devices in patients with systolic heart failure." *Heart* 102 (21): 1742–49. https://doi.org/10.1136/heartjnl-2015-308883.

NHS England. 2021. "2021/22 National Tariff Payment System." https://www.england.nhs.uk/publication/national-tariff-payment-system-documents-annexes-and-supporting-documents/.

O'Mahony, Constantinos O, Fatima Jichi, Menelaos Pavlou, Lorenzo Monserrat, Aristides Anastasakis, Claudio Rapezzi, Elena Biagini, et al. 2014. "Myocardial disease A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD)." *European Heart Journal* 35: 2010–20. https://doi.org/10.1093/eurheartj/eht439.

Olivotto, Iacopo, Artur Oreziak, Roberto Barriales-Villa, Theodore P. Abraham, Ahmad Masri, Pablo Garcia-Pavia, Sara Saberi, et al. 2020. "Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial." *The Lancet* 396 (10253): 759–69. https://doi.org/10.1016/S0140-6736(20)31792-X.

Ommen, Steve R., Seema Mital, Michael A. Burke, Sharlene M. Day, Anita Deswal, Perry Elliott, Lauren L. Evanovich, et al. 2020. "2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy." *Circulation* 142 (25). https://doi.org/10.1161/cir.0000000000000937.

R Core Team. 2021. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing. https://www.R-project.org/.

Sanders, Gillian D, Mark A Hlatky, and Douglas K Owens. 2005. "Cost-Effectiveness of Implantable Cardioverter–Defibrillators," 1471–80.

Smith, Tim, Luc Jordaens, Dominic A. M. J. Theuns, Pascal F. Van Dessel, Arthur A. Wilde, and M. G. Myriam Hunink. 2013. "The cost-effectiveness of primary prophylactic implantable defibrillator therapy in patients with ischaemic or non-ischaemic heart disease: A European analysis." *European Heart Journal* 34 (3): 211–19. https://doi.org/10.1093/eurheartj/ehs090.

Thijssen, Joep, M. Elske Van Den Akker Van Marle, C. Jan Willem Borleffs, Johannes B. Van Rees, Mihály K. De Bie, Enno T. Van Der Velde, Lieselot Van Erven, and Martin J. Schalij. 2014. "Cost-effectiveness of primary prevention implantable cardioverter defibrillator treatment: Data from a large clinical registry." *PACE - Pacing Clin. Electrophysiol.* 37 (1): 25–34. https://doi.org/10.1111/pace.12238.

Tomini, F. 2016. "A review of economic evaluation models for cardiac resynchronization therapy with implantable cardioverter defibrillators in patients with heart failure." *Eur J Health Econ*, 1159–72. https://doi.org/10.1007/s10198-015-0752-3.

Yao, Guiqing, Nick Freemantle, Melanie J Calvert, Stirling Bryan, Jean-claude Daubert, and John G F Cleland. 2007. "The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator." *European Heart Journal*, 42–51. https://doi.org/10.1093/eurheartj/ehl382.

Zomer, Ella, David Osborn, Irwin Nazareth, Ruth Blackburn, Alexandra Burton, Sarah Hardoon, Richard Ian, et al. 2017. "Effectiveness and cost-effectiveness of a cardiovascular risk prediction algorithm for people with severe mental illness (PRIMROSE)." *BMJ Open*, 1–11. https://doi.org/10.1136/bmjopen-2017-018181.

6 Appendix

6.1 Health and cost equations

Subscript s denotes the state number and superscript denotes the intervention either ICD or not.

- Annual health:

$$
\begin{aligned}
e^i_{s=1}(t) &= q_{icd}, \quad i = 1, 2 \\
e^i_{s=3}(t) &= q_{hcm}, \quad i = 1, 2 \\
e^i_{s=2}(t) &= q_{hcm} - u_{shock}, \quad i = 1, 2 \\
e^i_s(t) &= 0, \quad i = 1, 2, \ s = 4, 5
\end{aligned}
$$

- Initial:

$$
\begin{aligned}
c^0_{s=1}(t = 0) &= c_{icd} + p_{compl} \times c_{compl} \\
c^1_{s=1}(t = 0) &= c_{icd} + c_{rscore} + p_{compl} \times c_{compl}
\end{aligned}
$$

should we include this?

$$
e^i_{s=1}(t = 0) = q_{hcm} - u_{implant} - p_{compl} \times u_{compl}, \quad i = 1, 2
$$

- Annual cost:

$$
\begin{aligned}
c^i_{s=1}(t) &= 2c_{appt}, \quad i = 1, 2, \\
c^i_{s=2}(t) &= c_{shock}, \quad i = 1, 2
\end{aligned}
$$

6.2 Bayesian inference of transition probabilities

Denote x as the observed number of transitions, p the probability of a transition and n as the total number of transitions from a given state. The hyperparameters α characterise the prior knowledge on p. Superscripts indicate the decision rule used.

$$
x^{(1)}_{i.} \sim \text{Multinomial}(p^{(1)}_{i.}, n^{(1)}_i), \quad i = 1, 3
$$

$$
x^{(2)}_{i.} \sim \text{Multinomial}(p^{(2)}_{i.}, n^{(2)}_i), \quad i = 1, 3
$$

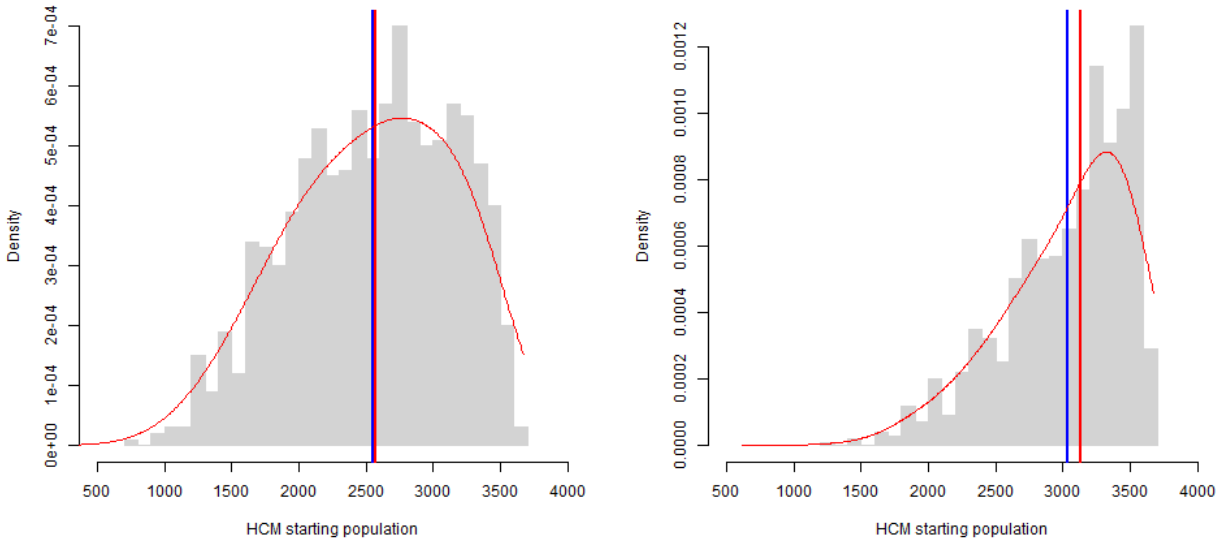
$$
p^{(1)}_{i.} \sim \text{Dirichlet}(\boldsymbol{\alpha}^{(1)}), \quad i = 1, 3
$$

$$
p^{(2)}_{i.} \sim \text{Dirichlet}(\boldsymbol{\alpha}^{(2)}), \quad i = 1, 3
$$

For all sink states,

$$
p^{(s)}_{ij} = \begin{cases} 1 & \text{if } i = j; \\ 0 & \text{if } i \neq j. \end{cases}
$$

\begin{figure}



\caption{Markov model initial HCM without ICD state population histograms for 4% and 6% risk score threshold. The uncertainty on the risk score model fit is propogated to the stratification step. Red vertical lines indicate the sample averages taking into account risk score model uncertainty and the blue vertical lines indicate the point estimates direct from the data. The smoothed densities are shown with the red curves.}
\end{figure}