Institution: University College London

Unit of Assessment: 10 – Mathematical Sciences

Title of case study: A risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy patients (HCM Risk-SCD)

Period when the underpinning research was undertaken: 2010 - 2017

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Rumana Omar	Professor of Medical Statistics	2000 - present
Menelaos Pavlou	Post-doctoral research fellow/lecturer	2013 - 2016, 2017 - present

Period when the claimed impact occurred: August 2013 – December 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact (indicative maximum 100 words)

Hypertrophic cardiomyopathy (HCM) is an inherited heart muscle disorder and a leading cause of sudden cardiac death (SCD) in young adults affecting 1 in 500 adults in the general population. Professors Omar and Elliott from UCL developed the first risk model to predict SCD risk for HCM patients. This algorithm was incorporated into the European Society of Cardiology (ESC) guidelines and is currently used by cardiologists in at least 25 countries to risk stratify HCM patients during their clinical assessment and decide on the best treatment option for individual patients. The HCM SCD-risk model has good predictive ability and is a major landmark in the management of cardiomyopathy providing an improved treatment decision-making tool.

2. Underpinning research (indicative maximum 500 words)

As part of Professor Rumana Omar's (Head of Biostatistics Group, UCL Department of Statistical Science) research programme on risk prediction models, she developed and validated the first risk prediction model to predict SCD risk for HCM patients, in collaboration with Professor Elliott (UCL Institute of Cardiovascular Science) (**R1**). HCM patients who are at high risk of SCD need to be identified so they can be offered lifesaving treatment with an implantable cardioverter defibrillator (ICD). Previous clinical guidelines (2003 American College of Cardiology/ European Society of Cardiology (ESC) and 2011 American College of Cardiology Foundation/AHA clinical guidelines) used for assessing the risk of SCD in HCM patients were based on a simple summation of five clinical patient characteristics. This simplistic approach that had not been statistically justified, provided low predictive accuracy (positive predictive value of 10.5 to 23.3%), resulting in unnecessary and potentially harmful prophylactic ICD implantation in a substantial number of patients who are at intrinsically low risk of SCD. Therefore, it was essential to use statistical models to develop a risk tool to provide more accurate and individualised risk estimates for SCD that would enable more objective and targeted ICD therapy in HCM patients.

Omar and Elliott (Professor of Cardiovascular Medicine, UCL) had joint leadership roles in this research and supervised a clinical research fellow (O'Mahony) for acquiring and interpreting data and two statistical research fellows (Jichi, and Pavlou, from the Biostatistics Group led by Omar) for the statistical modelling and validation work. In the first phase of the research (2010-2013), Omar designed a cohort study with adequate sample size to develop the risk model and established an international cohort of HCM patients through the HCM-RISK Consortium collaboration, which includes clinicians and health researchers from Europe, North America, Israel and the Far East. The cohort consisted of 3,675 HCM patients from six European centres: (i) The Heart Hospital, London, UK, (ii) A Coruña University Hospital, Spain, (iii) Unit of Inherited Cardiovascular diseases, University of Athens, Greece, (iv) Institute of Cardiology, University of

Bologna, Italy, (v) University Hospital Virgen, Spain, and (vi) Monaldi Hospital, Second University of Naples, Italy.

Typically, risk models used in clinical practice are developed using only complete data and without appropriately addressing important statistical issues, such as the degree of censoring in survival data, sample size and model over-fitting. Omar (with Rahman, PhD student and Ambler, Associate Professor, UCL Statistical Science) conducted parallel research to evaluate model performance measures and penalised regression methods for prediction of survival outcomes using simulation studies to address these problems for the HCM data. Omar's research on performance measures (**R2**) showed that the routinely used Harrell's C index to assess discrimination in risk prediction studies with survival outcomes was affected by the degree of censoring present in the data; providing high values when there is moderate to high levels of censoring and thus an over-optimistic view of a model's discriminatory ability. Uno's C-index was shown to be more reliable (in terms of bias) in the presence of moderate censoring and was used to assess the discriminatory ability of the HCM-SCD risk model. Omar's research on penalised methods (**R3**) showed that significant improvements were achieved by using a penalised modelling approach over standard Cox model for rare outcomes. The Lasso penalised regression was shown to perform well when variable selection is involved and was used to develop the HCM-SCD model when the number of SCD events was small. The predictive performance of the risk model was internally validated using bootstrapping on the entire dataset, which required evaluating and choosing the most optimal strategy to combine bootstrapping validation with multiple imputation required for handling missing predictor values.

The risk model was incorporated into the ESC guidelines, a non-profit medical society with member decision-makers drawn from scientists, clinicians, nurses and allied professionals working in cardiology. The ESC guidelines present relevant evidence to help physicians weigh the benefits and risks of a particular diagnostic or therapeutic procedure. Nevertheless, for the HCM-SCD risk prediction tool to be used widely in clinical practice for SCD prevention, it was essential to validate its performance externally on a large independent patient group to confirm whether the model predictions hold in diverse populations. In the second phase of the research (2015-2017), Omar designed a validation cohort study and data on a further 3,703 patients were obtained from a geographically diverse cohort recruited from 14 centres from the United States, Europe, the Middle East and Asia (**R4**). This was the largest external model validation study carried out to date for an HCM risk prediction tool. The study demonstrated that the risk model performed very well in this external cohort. The model demonstrated a higher discriminatory ability to separate patients into high and low risks of SCD as measured by the C-index, 0.70 (95% CI: 0.68, 0.72) compared to the pre-2014 guidelines C=0.54 (95% CI: 0.51, 0.56). The model also showed good calibration (**R4**).

Statistical team: Rumana Omar, Professor of Medical Statistics, Head of Biostatistics Group, UCL Department of Statistical Science (2000- to date). Dr Menelaos Pavlou, currently Lecturer, Department of Statistical Science (2013 to date). Fatima Jichi, Senior Research Associate, (Biostatistics Group (2012-2017).

3. References to the research (indicative maximum of six references)

R1. O'Mahony C, **Jichi F, Pavlou M**, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, **Omar RZ**, Elliott PM (2014). A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J* 35:2010–2020. https://doi.org/10.1093/eurheartj/eht439
R2. Rahman MS, Ambler G, Choodari-Oskooei B, **Omar RZ** (2017). Review and evaluation of performance measures for survival prediction models in external validation settings. *BMC Med Res Methodology* 17(1):60. doi:10.1186/s12874-017-0336-2
R3. Ambler, G & Seaman, S & **Omar, RZ** (2012). An evaluation of penalised survival methods for developing prognostic models with rare events. *Statistics in Medicine* 31:1150-61. doi:10.1002/sim.4371

R4. O'Mahony C, **Jichi F**, Ommen SR, Christiaans I, Arbustini E, (...), **Omar RZ**, Elliott PM (2017). International External Validation Study of the 2014 European Society of Cardiology Guidelines on Sudden Cardiac Death Prevention in Hypertrophic Cardiomyopathy (EVIDENCE-HCM). *Circulation* 137(10),1015-1023. doi:10.1161/circulationaha.117.030437.

4. Details of the impact (indicative maximum 750 words)

HCM is an inherited heart disease affecting 1 in 500 people globally (approximately 36 million people). SCD remains the most devastating and feared clinical event for both HCM patients and their cardiologists. Effective prevention of SCD using ICD therapy significantly reduces SCD events and has provided HCM patients with the chance of normal life expectancy. However, ICD implantation carries a substantial risk of major complications for patients. The risk model developed by Professors Omar and Elliott accurately predicts the risk of SCD in HCM patients and is now used in the clinical management of HCM patients to make treatment decisions regarding optimal implantation of ICDs.

Improved clinical guidelines with more accurate and individualised SCD risk prediction for HCM patients

The risk prediction tool has been incorporated in to the 2014 ESC guidelines for the management of HCM patients endorsed in 57 countries (**S1, S2**). The ESC unites all national cardiac societies from around the world and disseminates evidence-based scientific knowledge to cardiovascular professionals so they can better care for their patients. Professor Omar and collaborators subsequently conducted a meta-analysis summarising all available published data relevant to the 2014 ESC guideline performance for SCD prevention. The meta-analysis showed that HCM-risk-SCD model provides accurate SCD risk estimates that can be used to guide ICD therapy in accordance with the 2014 ESC guidelines (**S3**). In addition, the HCM Risk-SCD tool was validated independently in a wider patient group including HCM patients who had treatment with alcohol septal ablation - a non-surgical procedure to treat obstruction. This international multicentre cohort study also showed good predictive ability of the risk tool (**S4**).

The risk model's use is recommended to clinicians during the "first evaluation and re-evaluation at 1-2 years of HCM patients, as well as whenever there is a change in clinical status" (**S1**). The ESC has classified the risk algorithm as a class I tool, which means that its recommendation by ESC is based on "evidence and/or general agreement that a given treatment or procedure is beneficial, useful and effective" (**S1**). This tool was also recommended in "Essential Messages" memo (2014) by the ESC, called for informing practitioners about the newest recommendations in an easily interpretable manner. The essential messages released by the ESC on hypertrophic cardiomyopathy in the "take home messages" section stated: "The use of a new risk calculator (HCMRisk-SCD) (http://doc2do.com/hcm/webHCM.html) is recommended to guide the use of implantable cardioverter defibrillators (ICD)" (**S1**).

The risk calculator has been made globally accessible through two different routes:

- Free online access of the risk stratification tool (http://doc2do.com/hcm/webHCM.html)
- Free downloadable application on apple and google store, available since 2015. (https://play.google.com/store/apps/details?id=com.icreadomain.hcmcaluculator&hl=fr&rrdi=com.icreadomain.hcmcaluculator)

Improved clinical decision making for the management of HCM patients

ICD implantation carries a significant risk (estimated to be 9%) of major complications requiring intervention or further hospitalisation of the patient. Furthermore, ICDs can lead to poor quality of life, especially when patients receive inappropriate shocks which can be painful and estimated to occur in 11% of patients. ICD implantation should therefore only be considered for patients for whom the potential benefits of ICD implant outweighs the potential harms. The pre-2014 clinical guidelines used for assessing the risk of SCD in HCM patients had a low predictive accuracy (positive predictive value of 10.5 to 23.3%), resulting in unnecessary and potentially harmful prophylactic ICD implantation in a substantial number of patients who are at intrinsically low risk of SCD. It has been estimated that 85% of HCM patients who get an ICD never receive an appropriate, life-saving shock (**S5**). Using the HCM-SCD risk tool to classify patients into SCD risk groups (low, moderate or severe) based on their predicted probabilities enables clinicians to provide targeted management of patients in whom ICD has the greatest potential to prevent

SCD and allows reassurance for the large majority of patients who are at very low risk. The risk prediction tool complements clinical reasoning by providing objective individualised prognostic information.
The Medical Director of the Sarver Heart Center at the University of Arizona affirmed that the guideline algorithm identifies a group with substantially elevated risk for sudden cardiac death, which is important for patients that are young, as the complications associated with an ICD at a young age are significant. She states "Accurately identifying that patient at risk is terribly important clinically" (**S6**). Physicians can download an app to their phone or computer "to help you [physician] with a patient at high risk and whether you [physician] should counsel that patient about the risks and benefits of defibrillator implantation" (**S6**).
The HCM Risk-SCD tool, therefore, offers improved decision-making for clinicians and is a major landmark in the management of cardiomyopathy. The tool is currently used in cardiac centres worldwide and is mentioned in patient referral letters. 695 cardiologists from across 25 countries participated in a survey conducted by the ESC on the use of the risk tool in clinical practice between February 27th and April 1st 2019 (**S7**). The survey revealed that there is a widespread use of the tool with 76.3% of the respondents reporting using the tool between 1-5 times in a 6 month period, 12.5% reported using it of 6-10 times and 11.2% reported using it more than 10 times in 6 months. Approximatively 82% of the respondents reported that the tool has improved clinical decision making (**S7**). The Clinical Lead for cardiomyopathy at the Guy's and St Thomas NHS Foundation Trust attested that they "(...) use the sudden death risk prediction model (HCM Risk-SCD) in routine clinical practice" and found that the tool "(…) helps in clinical management of patients with hypertrophic cardiomyopathy" (**S6**). Additional supporting letters are available from 2 other cardiac centres including from the clinical lead for heart failure and inherited cardiac conditions at Oxford University Hospitals, which has also confirmed the utility of the tool in their practice "(…) the HCM risk-SCD calculator are fundamental to our daily practice as we strive towards improving patient outcomes in this area. (…) we have adopted (…) HCM Risk-SCD and use it routinely in our clinical practice to guide the risk assessment in our large population of HCM patients and to help rationalise the management of patients with this condition" (**S6**).

Improved care and communication for patients facilitating a shared decision making process with their clinicians

It is estimated that for every 13 high-risk patients who receive an ICD as recommended by the 2014 ESC guidelines based on this risk prediction tool, 1 patient could potentially be saved from SCD. The tool also saves unnecessary and potentially harmful ICD implantations in patients who are at intrinsically low risk of SCD.
The tool provides information to patients that empowers them by helping to understand the relative merits of the primary preventative treatment with ICD and their risk of SCD, for example, the implications of no ICD; and the benefits and the risks of treatment with an ICD. It facilitates patient involvement and enables a shared decision making process on treatment between patients and their clinicians, offering patients more personalised care based on their individual risk assessment. The aforementioned ESC survey showed that approximately 77% of the 695 cardiologists who responded from 25 countries worldwide, routinely discuss the risk estimates from the risk algorithm with their patients and that the tool helped in their communication with patients (**S7**). This meets the NHS Long Term plan recommendations in improving patient satisfaction through the delivery of a better integrated care involving patients, which has been set has a new challenge for the government in a recent report released by the Health and Social Care Committee (committee appointed by the House of Commons) (**S8**). The Chief Executive of Cardiomyopathy UK (the heart muscle charity for patients) said: "This new research shows that this tool, which is already making a real difference to the lives of people with cardiomyopathy, should now be rolled out worldwide so more people can make informed decisions about the treatment options that are best for them" (**S9**).

Reducing NHS costs

The underpinning research (**R4**) showed that the HCM Risk-SCD tool can be used to avoid unnecessary ICD implants. A very low number of SCDs was observed in HCM patients who had a 5-year predicted risk of SCD of <4% supporting the 2014 ESC recommendation not to implant an ICD in these patents. Consequently, an optimal management of ICD implantations in HCM

patients balancing with their SCD risks can be achieved using this tool. The ICD implantation rate in the UK rose sharply until about 2014 and then has been reducing gradually. England showed a 10% drop in the number of ICDs implanted for the year 2017/18 compared to previous years which corresponds to approximatively 1,000 fewer ICD implantations, potentially resulting in cost saving of at least GBP10,000,000 (one ICD device costs the NHS approximatively GBP10,000, then there is additional cost of hospital equipment and stay) (**S10**).

Contribution to the understanding of the relationship between patients' characteristics and SCD

The risk prediction tool has allowed a better understanding of the relationship between the left ventricular maximal wall thickness (MWT), one of the risk factors of SCD, and the risk of SCD. Until recently, the clinical perception was that the more severe the thickening of the heart muscle is the higher the risk of SCD and MWT was one of several clinical features used to guide prophylactic ICD therapy. The development of the risk tool has revealed a non-linear relationship between MWT and the risk of SCD, suggesting that the risk of SCD increases with increase in the thickness of the heart muscle to reach a plateau and declines thereafter (**S11**). Thus, the tool has contributed to a better understanding of pathophysiological mechanisms and an improvement on the guidance of ICD implantations, recommending that ICD implantation should not be guided solely on the severity of the left ventricular hypertrophy but a more global SCD risk assessment integrating other risk factors should be used (**S11**).

5. Sources to corroborate the impact (indicative maximum of 10 references)

S1. "2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy" (29/08/2014) and "Essential Messages from ECS Guidelines" (2014) corroborate recommendation of the HCM Risk-SCD tool by the ECS.
S2. List of ECS National Cardiac Societies corroborates the number of countries endorsing ECS Guidelines.
S3. Article published in Open Heart journal (17/02/2015) corroborates accuracy of SCD risk estimates by HCM-risk-SCD model.
S4. Validation study of the HCM Risk-SCD model in patients with HCM following alcohol septal ablation published in EP Europace (September 2019) corroborates a good predictive ability of the risk tool in this patient group.
S5. An article (22/01/2016) published in CHEST Physician corroborates the accuracy of conventional risk predictors of SCD in HCM patients.
S6. Supporting statements from Medical Director of the Sarver Heart Centre at the University of Arizona (video on Medpage Today accessed on 20/12/2020), Clinical Lead for Cardiomyopathy at the Guy's and St Thomas NHS Foundation Trust, Clinical Lead for Heart Failure & Inherited Cardiac Conditions at Oxford University Hospitals and Consultant Cardiologist at Belfast Heart Centre corroborate statements provided.
S7. Results of the ESC online survey 'Hypertrophic Cardiomyopathy HCM Risk Tool Survey 2019' conducted from February 25th to April 1st 2019 corroborate the adoption of the HCM Risk-SCD tool to clinical practice.
S8. The UK Parliament's report "Integrated care: organisations, partnerships and systems" (11/06/2018) and a statement from the Department of Health and Social Care (12/03/2019) corroborate that the application of the HCM Risk-SCD tool fulfils recommendations for a better integrated care.
S9. Article "Preventing Sudden Death in Hypertrophic Cardiomyopathy" (29/03/2018) published on Cardiomyopathy UK website corroborates the statement from the Chief Executive on the HCM Risk-SCD tool.
S10. Statement from State for Health and Social Care (25/06/2018) corroborates the number of new implantable cardioverter defibrillators from 2015 to 2018; NICE guidance "Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure" (25/06/2014) corroborates the cost of ICD implantations.
S11. Article published in Circulation: Arrhythmia and Electrophysiology (June 2016) corroborates that the tool contributes to a better understanding of pathophysiological mechanisms and guidance of ICD implantation.