Title: Predictors of sudden cardiac death in high risk patients following a myocardial infarction

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## ABSTRACT

### Aims

To develop a risk model for sudden cardiac death (SCD) in high-risk acute myocardial infarction (AMI) survivors.

### Methods and Results

Data from the Effect of Carvedilol on Outcome After MI in Patients With Left Ventricular Dysfunction trial (CAPRICORN) and the Valsartan in Acute MI Trial (VALIANT) were used to create a SCD risk model (with non-SCD as a competing-risk) in 13202 patients. The risk model was validated in the Eplerenone Post–Acute MI Heart Failure Efficacy and Survival Study (EPHESUS).

The rate of SCD was 3.3 (95%CI 3.0-3.5) per 100 person-years over a median follow-up of 2.0 years. Independent predictors of SCD included age >70 years; heart rate ≥70 bpm; smoking; Killip class III/IV; left ventricular ejection fraction (LVEF) ≤30%; atrial fibrillation; history of prior MI, heart failure or diabetes; estimated glomerular filtration rate <60ml/min/1.73m$^2$; and no coronary reperfusion or revascularisation therapy for index AMI. The model was well calibrated and showed good discrimination (C-statistic = 0.72), including in the early period after AMI. The observed 2-year event rates increased steeply with each quintile of risk score: 1.9%, 3.6%, 6.2%, 9.0%, 13.4%, respectively.

**Conclusion**

An easy to use SCD risk score developed from routinely collected clinical variables in patients with heart failure, left ventricular systolic dysfunction or both, early after AMI was superior to LVEF. This score might be useful in identifying patients for future trials testing treatments to prevent SCD early after AMI.

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**Keywords:** Acute myocardial infarction; sudden cardiac death; risk model; left ventricular systolic dysfunction; heart failure.

## INTRODUCTION

Early reperfusion in patients with acute myocardial infarction (AMI) has greatly reduced short-term case-fatality.[1] However, the survivors remain at risk of sudden cardiac death (SCD) over the subsequent weeks, months and years, despite secondary preventive pharmacotherapy with beta-blockers, antiplatelet therapy, statins, angiotensin converting enzyme inhibitors/angiotensin receptor blockers and mineralocorticoid receptor antagonists. Indeed, SCD accounts for between 20-40% of all deaths after discharge and the risk is especially high in the first year after AMI.[2,3] For example, a *post-hoc* analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT) reported that the risk of SCD was 10-fold higher in the 30 days following AMI than later, falling from 1.4 percent per month to 0.14 percent per month after 2 years in patients with heart failure (HF), left ventricular systolic dysfunction (LVSD), or both, complicating their index event.[4] Therefore, the identification and treatment of patients at high-risk of SCD after AMI remains a clinical priority.

Current guidelines advocate the use of an implantable cardioverter defibrillator (ICD) for primary prevention of sudden cardiac death (SCD) in individuals with a left ventricular ejection fraction (LVEF) that remains reduced ($\leq$35%) more than 40 days after AMI, despite optimized, evidence-based, medical therapy (90 days or more in patients who undergo myocardial revascularization).[5,6] Conversely, implantation of a device before 40 days is *not* recommended because two randomised controlled trials failed to show any benefit of an ICD during that early period in patients with a depressed LVEF and markers of impaired autonomic function (elevated heart rate, depressed heart-rate variability or non-sustained ventricular tachycardia).[7,8] More recently, a third trial showed no benefit of a wearable cardioverter-defibrillator in the first three months following AMI in patients with LVEF

≤35%.[9] Nevertheless, the question remains whether selected individuals at particularly high risk of SCD can be identified, as they might still benefit from more targeted use of an ICD early after AMI.

The aims of this study were to characterise patients who experienced SCD after AMI and develop a calibrated and validated risk score for SCD using routinely collected clinical variables in patients with an AMI complicated by HF, LVSD or both.

## METHODS

### Patients

The high-risk AMI initiative was a collaborative undertaking by the chairpersons of the steering committees of 4 randomized controlled trials to provide a large, comprehensive and statistically robust dataset to help further understanding of outcomes in high-risk survivors of AMI.[10] The dataset was composed of the following trials: the Effect of Carvedilol on Outcome After Myocardial Infarction in Patients With Left Ventricular Dysfunction (CAPRICORN) trial[11,12]; the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)[13,14]; the Optimal Trial in Myocardial Infarction With Angiotensin II Antagonist Losartan (OPTIMAAL)[15,16]; and the Valsartan in Acute Myocardial Infarction Trial (VALIANT).[17,18] OPTIMAAL was excluded from the present analysis because data on LVEF were not collected. The three remaining trials, CAPRICORN, EPHESUS and VALIANT enrolled patients with left ventricular systolic dysfunction, heart failure, or both, between 12 hours and 21 days following an AMI. The full details of the enrolled patients, the inclusion and exclusion criteria and the results for each individual trial are published.[12,14,18] The pooled dataset did not include information regarding the randomised treatment allocations for each trial.[10] All trials were conducted in accordance with the Declaration of Helsinki and were approved by ethics committees. All participants gave written informed consent to participate in the trials.

### Outcomes

The primary outcome of interest in this study was SCD. The definitions for SCD used in each individual trial are detailed in Supplementary Table 1. Mortality due to causes other than SCD was considered the competing risk event.

## Statistical methods

Continuous variables are expressed as means ± standard deviations and categorical variables as frequencies and percentages. Differences in baseline characteristics according to the occurrence or not of SCD were assessed using the Student's t-test and the chi-square test for continuous and categorical variables, respectively.

Time-to-event analysis was conducted using a competing risk model as described by Fine and Gray with SCD as outcome event and mortality due to any other cause as a competing risk.[19] Time-to-event was calculated as time from randomization, as time from AMI to randomization was not available for all patients. Log-linearity was checked by plotting the beta estimates versus the mean across deciles and then clinically relevant cutoffs were chosen for the candidate variables. Variables were entered in the multivariable model in a backward stepwise regression analysis with the p value to enter and stay in the model set to $p \leq 0.1$ and $p < 0.05$, respectively. Variables considered to be of potential prognostic import were age, sex, body mass index, systolic blood pressure, heart rate, LVEF, Killip class, estimated glomerular filtration rate (eGFR, calculated using the Chronic Kidney Disease Epidemiology Collaboration formula), previous MI, history of HF prior to randomization, atrial fibrillation (AF), peripheral artery disease, hypertension, diabetes mellitus, previous stroke, reperfusion or revascularization therapy for index MI. Use of beta-blockers and MRA were not included for consideration in the model as information on randomized treatment allocation was not available in the HRMI dataset. Sodium, potassium, and anaemia (defined as haemoglobin <13 g/dL or 12 g/dL for men and women, respectively) were not included in the models due to high proportion of missing values (>80%). Patients with missing LVEF measurements were excluded from the models (15%). Multiple imputation for missing values was not

performed. Patients with an ICD at baseline (n=96; 0.3%) were excluded for the purposes of these analyses.

The competing risk regression model was derived from a cohort of patients from the VALIANT and CAPRICORN trials. Model discrimination was determined by calculation of the C- statistic and the Hosmer-Lemeshow test. Assessment of model calibration was performed by plotting the cumulative incidence of observed versus expected SCD events derived from the competing risk model across quintiles of the predicted risk. The ability of the model to reclassify events compared to the use of LVEF ≥35% alone was assessed with a 10-fold cross-validation with 1000x bootstrap net reclassification improvement (NRI) and integrated discrimination improvement (IDI) statistics for the outcome of SCD. External validation of the model was performed in the EPHESUS trial cohort.

A simple, easy-to-use integer risk score was created with integer points assigned to each prognostic variable in the model based on the log-hazard ratio estimates. For continuous variables included in the model, clinically relevant cut-offs were used to create either 2 or 3 groups. The risk score for each patient was calculated by totalling the points across all chosen prognostic variables. From the overall distribution of the risk score we formed 5 categories of risk. Within each risk score category, we calculated the number of events and the cumulative event incidence at 40 days, 90 days, 1 years, and 2 years. Kaplan-Meier plots were drawn showing the cumulative incidence curves by risk category. After fitting the competing risk regression model, we assessed time interaction using log[−log(survival)] curves for each category of risk versus ln(time). The plotted lines were reasonably parallel,

meaning that the proportional-hazards assumption had not been violated (proportional-hazards Schoenfeld residuals by risk score quintiles, p=0.86 [Supplementary Figure 1]).

All analysis was performed with STATA software version 15 (StataCorp, College Station, Texas). All p-values are two-sided and a p-value <0.05 was considered statistically significant.

## RESULTS

### Baseline characteristics

The derivation cohort included 13202 patients from VALIANT and CAPRICORN. The external validation cohort comprised 6632 patients from EPHESUS. The baseline characteristics of the patients of the derivation and validation cohorts are shown in Table 1 and Supplementary Table 2, respectively.

In the derivation cohort, the mean age was 64.1 ± 11.8 years and 29.8% were female. There were 2390 (18.1%) deaths during a median follow-up of 2.0 years (interquartile range: 1.5-2.5 years), of which 818 (34.2%) were due to SCD. The overall incidence rate of SCD was 3.3 (95% confidence interval [C.I.] 3.0-3.5) per 100 patient years.

Compared to patients alive at end of follow-up, those who experienced SCD were older, more often female, more commonly had a history of previous MI, atrial fibrillation, peripheral arterial disease, hypertension, diabetes, stroke and heart failure prior to randomization (Table 1). Body mass index and estimated glomerular filtration rate (eGFR) were lower, and systolic blood pressure and heart rate higher, in those experiencing SCD. Rates of coronary reperfusion or revascularization for the index AMI were lower in those with SCD compared to those surviving to end of follow-up.

### Risk Model

The variables included in the final predictive model for SCD are detailed in Table 2. Age >70 years, heart rate ≥70 beats per minute, active smoking, Killip class III/IV, LVEF ≤30%, atrial

fibrillation, history of prior MI, heart failure or diabetes mellitus, eGFR <60ml/min/1.73m$^2$ and no reperfusion or revascularisation for the index AMI were independently associated with a higher risk of SCD. The risk score derived from these predictive variables ranged from 0 to 14 points (Table 2).

The final model was well calibrated with a steep gradient in risk observed when plotted by quintiles of predicted risk (Figure 1). The model discrimination was good with a C-statistic of 0.72 and the Hosmer-Lemeshow goodness-of-fit test gave a p-value of 0.33 supporting the good calibration of the model. When externally validated in EPHESUS, the model retained good calibration with good discrimination (C-statistic=0.70 [Supplementary Table 3]). Patient characteristics were similar between the derivation and validation cohort (Supplementary Table 4).

**Risk Model compared with LVEF ≤35% alone**

To compare the derived risk score with what is recommended in current guidelines, we also calculated the C-statistic using LVEF ≤35% as the sole predictor variable in a competing risk model. An LVEF of ≤35% alone was a poor discriminator of the risk of SCD with a C-statistic of 0.54. The addition of the variables identified in the risk model, greatly improved the reclassification of the SCD events compared to an LVEF ≤35% alone, with a continuous NRI of 50.9% (95% CI 42.9-57.8; p<0.001) and an IDI of 2.1% (1.6-2.8; p<0.001).

**Event Rates**

The incidence rate per 100 person-years of sudden cardiac death in the 1st, 2nd and 3rd year following AMI was 4.8% (95% CI: 4.4-5.2), 2.0% (95% CI: 1.7-2.3), and 1.5% (95% CI: 1.2-2.0), respectively.

The observed two-year incidence of SCD increased from 1.9% in the lowest to 13.4% in the highest quintile of risk score, respectively. This was consistent with the predicted event rates (Table 2). An online calculator {LINK to supplement excel file} is provided for calculation of the risk of SCD in patients with heart failure, left ventricular systolic dysfunction or both after AMI.

To further explore the performance of the model in the period immediately following AMI, we calculated the predicted rates of SCD at 40 and 90 days after randomization and found these to calibrate well against the observed rates with moderate/good discrimination and a C-statistic of 0.70 and 0.72, respectively (Table 3).

## DISCUSSION

In this *post-hoc* analysis of the high-risk AMI database, we identified eleven routinely collected clinical variables which were independent predictors of SCD. Importantly, our model accounted for the competing risk of non-sudden death. Using the eleven variables identified, we created a simple risk score which performed well (C-statistic=0.72), both early and later after AMI. By contrast, we found that a LVEF of ≤35%, by itself, was a poor predictor of the risk of SCD (C-statistic=0.54).

The latter finding is consistent with the evidence from three trials showing no benefit from an implanted or wearable defibrillator in patients with a low LVEF early after AMI.[7–9] Yet, arguably, it is in the early period after AMI that interventions to reduce the risk of SCD are needed most. This is because proximity to the acute coronary event is also an important predictor of the risk of SCD. For example, in VALIANT, the rate of SCD was higher during the first 30 days after AMI in patients with a LVEF >40% than in those more than 90 days after AMI with a LVEF ≤30%.[4] Collectively, these findings highlight the need to identify variables, other than LVEF, which will improve SCD risk stratification early after AMI. Such a strategy could allow better targeting of defibrillators (or other treatments) to the patients most likely to benefit from them. The risk score described here may offer that possibility.

However, a first step is to consider whether the variables in the score proposed are biologically plausible. The independent predictors of SCD we identified included absence of coronary reperfusion, prior myocardial infarction and history of heart failure. Together these are clearly related to the development of myocardial scar and left ventricular systolic

dysfunction, as well as myocardial ischaemia, each of which is a powerful substrate for ventricular arrhythmias; each also interacts with the others to amplify risk.

We also found that renal dysfunction and diabetes mellitus were associated with a higher risk of SCD. This was also unsurprising, given that both these conditions increase the risk of all the substrates for electrical instability described above.[20–22] Moreover, renal dysfunction and diabetes each reduce the potential protection offered by coronary revascularisation as both conditions are associated with a diffuse coronary artery disease phenotype and a lower probability of successful percutaneous and surgical revascularisation.[23] Each of renal dysfunction and diabetes also increases the risk of developing heart failure after AMI, a further way in which they likely augment the risk of SCD.[24,25] Autonomic dysfunction is also a recognised complication of diabetes, itself increasing the risk of cardiac electrical instability. Both renal dysfunction and diabetes cause electrolyte abnormalities, particularly hyperkalaemia, which may also potentiate the risk of arrhythmias. The risks of heart failure, diabetes, renal impairment and more extensive coronary disease are also associated with more advanced age (and older individuals are less likely to undergo coronary reperfusion and revascularisation).

Another predictor of SCD was elevated heart rate, which may be a marker of autonomic instability.[26] Smoking at the time of index AMI was also associated with risk of SCD, possibly because of the risk of further coronary events and earlier failure of coronary revascularisation in patients who continue to smoke.[27]

Even if biologically plausible, any risk score of this type must also identify a relatively small and high-risk group of patients, to make any intervention based on it potentially cost-effective. How discriminating might our risk score be in clinical practice? Robust epidemiological data demonstrate that no more than one-third of patients with AMI develop heart failure, left ventricular systolic dysfunction or both within 3 months of their event i.e. the denominator for use of this risk score is no more than a third of all patients with AMI.[28] If only patients with a risk score in the top two quintiles are considered further, just one third of the initial patients (i.e. 10% of all patients with AMI) would be considered at sufficiently high risk of SCD to potentially merit further intervention. Specifically, in the derivation cohort, the risk of SCD in these individuals was 8.2% at 90-days and 22.4% at 2-years i.e. an approximately 1-in-12 patients experienced SCD at 90-days and 1-in-5 at 2 years. Targeted defibrillator (or other) therapy should be feasible and potentially cost-effective in such an enriched subgroup of AMI survivors.

Of course, the key question is whether a score like the one proposed identifies patients with a *modifiable* risk of SCD. The only way to test this is to conduct an intervention trial. However, if such a trial were based on the score we propose, it would require a considerable divergence form conventional thinking about primary prevention of SCD. This is because 40% of the patients in highest two quintiles of risk-score had a baseline LVEF >30%, yet current guidelines for use of defibrillators is focussed on patients with a low LVEF.[5,6]

It might also be possible to improve upon our score and to consider alternative interventions to a defibrillator. The addition of neprilysin inhibition to renin-angiotensin system blockade reduces the risk of sudden cardiac death in patients with chronic HF with reduced ejection

fraction (HFrEF).[29] The potential benefits of this pharmacological approach in patients with LVSD, heart failure, or both following AMI is currently being examined in the PARADISE-MI trial (ClinicalTrials.gov identifier NCT02924727). The burden of ventricular scar and replacement fibrosis, detected by cardiac magnetic resonance imaging, is associated with the risk of ventricular arrhythmias in patients with heart failure and other cardiomyopathies, and may help identify individuals, irrespective of LVEF, who are at increased risk of SCD.

**Limitations**

This was a *post-hoc* analysis and the patients analysed were selected through enrolment in clinical trials. Ideally, our score should be validated in a less selected population. The definition of SCD in each trial (Supplementary Table 1) and the maximum time from AMI from which randomization was permitted, differed somewhat. Furthermore, not all adjudicated sudden cardiac deaths represent events where a ventricular arrhythmia occurred and are potentially preventable by use of prophylactic defibrillators e.g. recurrent AMI, ventricular rupture or pulmonary embolism. Moreover, these other events should have reduced the predictive accuracy of the model yet it still performed well. To explore the potential for any bias due to these differences we calculated the C-statistic for each trial individually and found that the model performed equally as well in all three trials individually (CAPRICORN, 0.68 [95% CI 0.67-0.70]; VALIANT, 0.72 [0.71-0.74]; EPHESUS 0.70 [0.68-0.72]). Patients with multiple comorbidities may be at high risk of SCD but decision making regarding the appropriateness of therapies to prevent SCD such as ICD, should be made on a case by case basis and taking into account the degree of comorbidity and the competing risk of non-SCD. Our risk score did not take account of how variables changed over time after AMI. Furthermore, we were unable to account for the use of implantable cardioverter defibrillators following randomisation, a factor which may

modify the subsequent risk of SCD. Some potentially relevant variables (e.g. potassium) were not available. A further limitation is that information regarding treatment with renin-angiotensin aldosterone system inhibitors and beta-blockers was not available therefore the risk model does not take into account those patients who did not receive these treatments known to reduce the risk of SCD. The variables considered for inclusion in the risk model are routinely collected in clinical with the aim of making the risk score easy to calculate. This approach may ignore other variables which are potentially associated with the risk of SCD e.g. burden of myocardial scar and markers of impaired autonomic function. The trials providing the data used in the analysis are over 15 years old and may not therefore, represent contemporary clinical practice; in particular, increased use of primary reperfusion therapy may mean that modern rates of SCD are lower than those presented. We used classical methods of risk modelling but it may be that more complex, and potentially more accurate, models could be constructed by using machine learning approaches and may be an area for further research.[30] The proposed use of this score, to target interventions to reduce the risk of sudden death, needs to be tested in a prospective randomized controlled trial.

**Summary**

We developed an easy to use score for predicting the risk of SCD in patients with heart failure, left ventricular systolic dysfunction or both, early after AMI. The score uses routinely collected clinical variables and is superior to (and additive to) LVEF on its own. This score might be useful in identifying patients for future trials testing treatments aimed at reducing the risk of SCD early after AMI.

## Conflicts of interest

Dr. Sharma reports grants and personal fees from Boeringer-Ingelheim and Roche, grants from Takeda and personal fees from Akcea during the conduct of the study; grants and personal fees from Alberta Innovates Health Solution Clinician Scientist fellowship and grants from CCS-Bayer Vascular award outside the submitted work. Dr. Girerd reports personal fees from Novartis and Boeringer outside the submitted work. Dr. Gregson reports personal fees from Amarin Corporation, Edwards LifeSciences, MVRX and Biosensors outside the submitted work. Dr. Jhund reports personal fees from Novartis during the conduct of the study; grants from Boheringer Ingelheim and personal fees from Boehringer Ingelheim, Vifor Pharma and Cytokinetics outside the submitted work. Dr. Pfeffer reports grants and personal fees from Novartis, personal fees from AstraZeneca, DalCor, GlaxoSmithKline, NovoNordisk, Sanofi, Roche, Jazz Pharmaceuticals, MyoKardia, Servier and Takeda outside the submitted work. Dr. Pitt reports personal fees from Bayer, Astra Zeneca and KBP pharmaceuticals outside the submitted work; In addition, Dr. Pitt has a patent US Patent # 9931412 issued. Dr. Rossignol reports personal fees from Relypsa, Inc. and Vifor Pharma Group Company during the conduct of the study; grants and personal fees from AstraZeneca, Bayer, CVRx and Novartis and personal fees from Fresenius, Grunenthal, Servier, Stealth Peptides, Vifor Fresenius Medical Care Renal Pharma, Idorsia and NovoNordisk outside the submitted work; and is a co-founder of CardioRenal. Dr. Zannad reports personal fees from Janssen, Bayer, Novartis, Boston Scientific, Resmed, Amgen, CVRx, General Electric, Boehringer, AstraZeneca and Vifor Fresenius outside the submitted work; and is a co-founder of CardioRenal and CVCT. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## FIGURES

**Figure 1:** Model calibration plot: percentage of observed versus predicted risk of sudden cardiac death at 2-years according to quintile of risk score

Legend: SCD, sudden cardiac death. Note: The models were also well calibrated in the validation set: a steep gradient in risk by quintiles of predicted risk was observed (Table 2).

**Figure 2:** Kaplan-Meier failure cumulative incidence curve by quintile of risk score

## TABLES

**Table 1:** Baseline characteristics of the study population (derivation set: CAPRICORN and VALIANT)

**Table 2:** Multivariable competing risk model for sudden cardiac death (derivation set: CAPRICORN and VALIANT)

**Table 3:** Cumulative incidence of sudden cardiac death at 2-years by quintile of risk score (derivation set: CAPRICORN and VALIANT)

**Table 1: Baseline characteristics of the study population (derivation set: CAPRICORN and VALIANT)**

| | **Alive n=10812** | **SCD n=818** | **Non-SCD n=1572** | **p-value** |
|---|---|---|---|---|
| Age (years) | 62.9±11.7 | 66.9±11.2 | 70.5±10.5 | <0.001 |
| Age (years) | | | | |
| ≤60 | 4418 (40.9%) | 225 (27.5%) | 265 (16.9%) | <0.001 |
| 61-70 | 3241 (30.0%) | 237 (29.0%) | 410 (26.1%) | |
| >70 | 3153 (29.2%) | 356 (43.5%) | 897 (57.1%) | |
| Male | 7738 (71.6%) | 556 (68.0%) | 977 (62.2%) | <0.001 |
| BMI ≥25 kg/m² | 7630 (72.1%) | 542 (67.8%) | 973 (64.4%) | <0.001 |
| Current smoking | 3642 (33.7%) | 255 (31.2%) | 367 (23.5%) | <0.001 |
| SBP ≥140 mmHg | 1843 (17.1%) | 182 (22.4%) | 290 (18.5%) | <0.001 |
| Heart rate ≥70 bpm | 7448 (69.3%) | 605 (74.5%) | 1207 (77.2%) | <0.001 |
| LVEF (%) | 35.5±9.8 | 32.0±9.8 | 32.7±10.0 | <0.001 |
| LVEF ≤30% | 3332 (30.8%) | 389 (47.6%) | 733 (46.6%) | <0.001 |
| Killip III/IV | 1749 (16.2%) | 220 (26.9%) | 499 (31.8%) | <0.001 |
| eGFR (ml/min/1.73m2) | | | | |
| ≤45 | 1209 (11.3%) | 171 (21.3%) | 477 (30.6%) | <0.001 |
| 46-60 | 2282 (21.4%) | 227 (28.2%) | 420 (27.0%) | |
| >60 | 7192 (67.3%) | 406 (50.5%) | 661 (42.4%) | |
| Sodium ≤135 mmol/L | 215 (13.8%) | 15 (14.3%) | 24 (18.0%) | 0.41 |
| Potassium (mmol/L), | | | | |
| <4 | 134 (8.7%) | 11 (10.5%) | 12 (9.0%) | 0.30 |

| | | | | |
|---|---|---|---|---|
| 4-5 | 1169 (75.5%) | 70 (66.7%) | 96 (72.2%) | |
| >5 | 246 (15.9%) | 24 (22.9%) | 25 (18.8%) | |
| Previous MI | 2700 (25.0%) | 366 (44.7%) | 685 (43.6%) | <0.001 |
| HF history | 1055 (9.8%) | 202 (24.7%) | 390 (24.8%) | <0.001 |
| Atrial fibrillation history | 1224 (11.3%) | 176 (21.5%) | 350 (22.3%) | <0.001 |
| PAD history | 795 (7.4%) | 92 (11.3%) | 226 (14.4%) | <0.001 |
| Hypertension history | 6075 (56.2%) | 530 (64.8%) | 1016 (64.6%) | <0.001 |
| Diabetes history | 2571 (23.8%) | 265 (32.4%) | 583 (37.1%) | <0.001 |
| Stroke history | 729 (6.7%) | 90 (11.0%) | 204 (13.0%) | <0.001 |
| Anaemia | 397 (25.9%) | 47 (45.6%) | 49 (36.6%) | <0.001 |
| Reperfusion during index event | 6021 (55.7%) | 274 (33.5%) | 582 (37.0%) | <0.001 |

Legend: BMI, body mass index; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; HF, heart failure; PAD, peripheral artery disease.

**Table 2: Multivariate competing risk model for sudden cardiac death (derivation set: CAPRICORN and VALIANT)**

| Retained variable | HR (95%CI) | Coefficient | P-value | Integer |
|---|---|---|---|---|
| Age >70 years | 1.24 (1.02-1.51) | 0.22 | 0.030 | +1 |
| Heart rate ≥70 bpm | 1.18 (1.01-1.39) | 0.17 | 0.038 | +1 |
| Smoking (active) | 1.32 (1.10-1.58) | 0.28 | 0.003 | +1 |
| Killip III/IV | 1.20 (1.02-1.42) | 0.19 | 0.027 | +1 |
| LVEF ≤30% | 1.55 (1.34-1.79) | 0.44 | <0.001 | +2 |
| Previous MI | 1.53 (1.31-1.79) | 0.43 | <0.001 | +2 |
| Atrial fibrillation | 1.45 (1.22-1.73) | 0.37 | <0.001 | +1 |
| HF history | 1.36 (1.14-1.63) | 0.31 | 0.001 | +1 |
| Diabetes | 1.19 (1.02-1.38) | 0.17 | 0.026 | +1 |
| eGFR <60 ml/min/1.73m$^2$ | 1.36 (1.16-1.59) | 0.31 | <0.001 | +1 |
| No index reperfusion | 1.87 (1.60-2.18) | 0.62 | <0.001 | +2 |

C-index full model=0.72 (95% CI:0.71-0.74)

C-index LVEF alone=0.54 (95% CI:0.53-0.55)

Abbreviations as per Table 1.

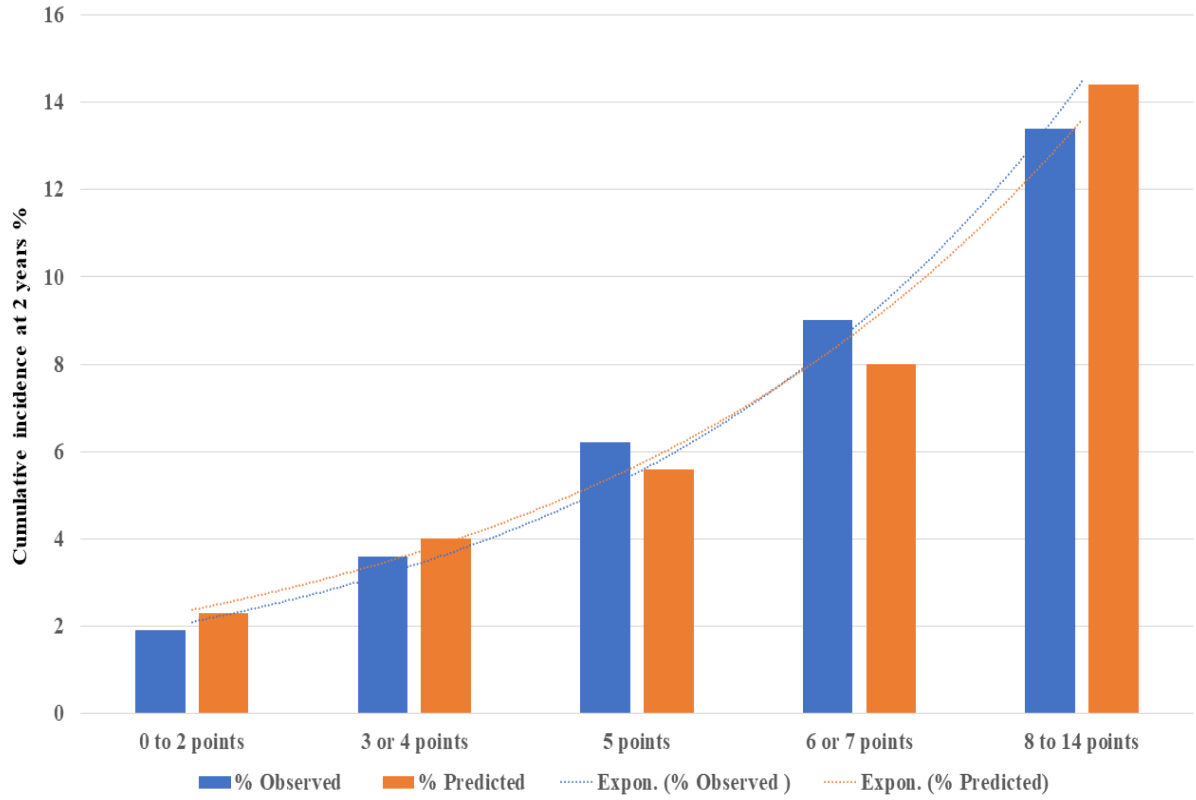
**Table 3: Cumulative incidence of sudden cardiac death by quintile of risk score (derivation set: CAPRICORN and VALIANT)**

| **Risk score quintiles** | **Baseline, n** | **Censored before 40 days, n** | **Non-SCD at 40 days, n** | **SCD at 40 days, n** | **SCD observed cumulative incidence at 40 days, %** | **SCD predicted cumulative incidence at 40 days, %** |
|---|---|---|---|---|---|---|
| 1 (0-2 points) | 2808 | 3 | 20 | 13 | 0.5 | 0.4 |
| 2 (3-4 points) | 3940 | 5 | 84 | 26 | 0.7 | 0.7 |
| 3 (5 points) | 1712 | 2 | 54 | 16 | 0.9 | 1.1 |
| 4 (6-7 points) | 2736 | 3 | 104 | 54 | 2.0 | 1.8 |
| 5 (8-14 points) | 1764 | 2 | 120 | 60 | 3.4 | 3.5 |
| **Risk score quintiles** | **Baseline, n** | **Censored before 90 days, n** | **Non-SCD at 90 days, n** | **SCD at 90 days, n** | **SCD observed cumulative incidence at 90 days, %** | **SCD predicted cumulative incidence at 90 days, %** |
| 1 (0-2 points) | 2808 | 4 | 26 | 19 | 0.7 | 0.7 |
| 2 (3-4 points) | 3940 | 10 | 109 | 43 | 1.1 | 1.3 |
| 3 (5 points) | 1712 | 5 | 71 | 36 | 2.1 | 1.9 |
| 4 (6-7 points) | 2736 | 6 | 158 | 84 | 3.1 | 2.8 |
| 5 (8-14 points) | 1764 | 3 | 165 | 90 | 5.1 | 5.3 |

| **Risk score quintiles** | **Baseline, n** | **Censored before 1 year, n** | **Non-SCD at 1 year, n** | **SCD at 1 year, n** | **SCD observed cumulative incidence at 1 year, %** | **SCD predicted cumulative incidence at 1 year, %** |
|---|---|---|---|---|---|---|
| 1 (0-2 points) | 2808 | 111 | 50 | 37 | 1.3 | 1.6 |
| 2 (3-4 points) | 3940 | 163 | 177 | 105 | 2.7 | 2.8 |
| 3 (5 points) | 1712 | 70 | 131 | 78 | 4.6 | 4.1 |
| 4 (6-7 points) | 2736 | 112 | 304 | 169 | 6.2 | 5.8 |
| 5 (8-14 points) | 1764 | 38 | 319 | 174 | 9.9 | 10.5 |
| **Risk score quintiles** | **Baseline, n** | **Censored before 2 years, n** | **Non-SCD at 2 years, n** | **SCD at 2 years, n** | **SCD observed cumulative incidence at 2 years, %** | **SCD predicted cumulative incidence at 2 years, %** |
| 1 (0-2 points) | 2808 | 1023 | 75 | 50 | 1.9 | 2.3 |
| 2 (3-4 points) | 3940 | 1520 | 255 | 135 | 3.6 | 4.0 |
| 3 (5 points) | 1712 | 599 | 179 | 101 | 6.2 | 5.6 |
| 4 (6-7 points) | 2736 | 879 | 432 | 232 | 9.0 | 8.0 |
| 5 (8-14 points) | 1764 | 432 | 459 | 229 | 13.4 | 14.4 |

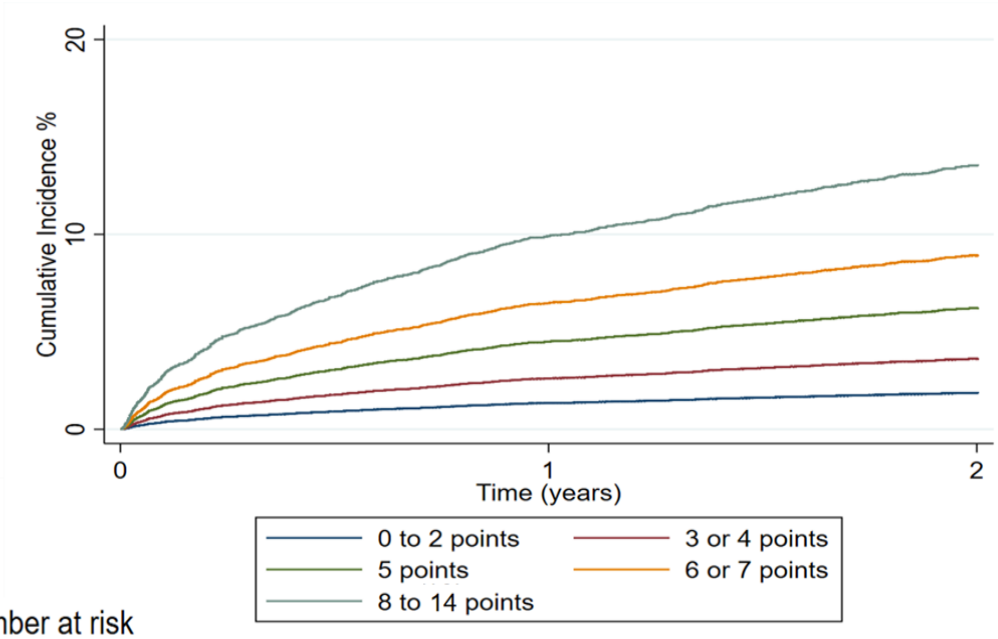
Abbreviations as per Table 1

**Figure 1: Model calibration plot: percentage of observed versus predicted risk of sudden cardiac death at 2-years according to quintile of risk score**




Note: The models were also well calibrated in the validation set: a steep gradient in risk by quintiles of predicted risk was observed (Table 2).

**Figure 2: Kaplan-Meier failure cumulative incidence curve by quintile of risk score**




Number at risk

| | | | |
|---|---|---|---|
| 0 to 2 points | 2808 | 2610 | 1670 |
| 3 or 4 points | 3940 | 3496 | 2040 |
| 5 points | 1712 | 1433 | 837 |
| 6 or 7 points | 2736 | 2157 | 1198 |
| 8 to 14 points | 1764 | 1233 | 645 |