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**RESEARCH ARTICLE**

# Predictors of sudden cardiac death in high-risk patients following a myocardial infarction

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**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 Myocardial Infarction in Patients With Left Ventricular Dysfunction trial (CAPRICORN) and the Valsartan in Acute Myocardial Infarction Trial (VALIANT) were used to create a SCD risk model (with non-SCD as a competing risk) in 13 202 patients. The risk model was validated in the Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS). The rate of SCD was 3.3 (95% confidence interval 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 ≤30%; atrial fibrillation; history of prior myocardial infarction, heart failure or diabetes; estimated glomerular filtration rate < 60 mL/min/1.73 $m^2$; 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 left ventricular ejection fraction. This score might be useful in identifying patients for future trials testing treatments to prevent SCD early after AMI.

**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

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1.4% per month to 0.14% 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 SCD in individuals with a left ventricular ejection fraction (LVEF) that remains reduced (≤35%) more than 40 days after AMI, despite optimized, evidence-based medical therapy (90 days or more in patients who undergo myocardial revascularisation).[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 3 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 four 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 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 LVSD, HF, or both, between 12 h 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 online supplementary *Table S1*. 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 randomisation, as time from AMI to randomisation was not available for all patients. Log-linearity was checked by plotting the beta estimates vs. the mean across deciles and then clinically relevant cut-offs 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 myocardial infarction, history of HF prior to randomisation, atrial fibrillation, peripheral arterial disease, hypertension, diabetes mellitus, previous stroke, reperfusion or revascularisation therapy for index myocardial infarction. Use of beta-blockers and mineralocorticoid receptor antagonists were not included for consideration in the model as information on randomised treatment allocation was not available in the high-risk myocardial infarction 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 implantable cardioverter-defibrillator 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 vs. 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 two or three 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 five 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 year, and 2 years. The cumulative incidence function was plotted by risk category. After fitting the competing risk regression model, we assessed time interaction using log[−log(survival)] curves for each category of risk vs. ln(time). The plotted lines were reasonably parallel, meaning that the proportional-hazards assumption had not

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

| | Alive ($n$ = 10 812) | 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 |
| ≤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 sex | 7738 (71.6%) | 556 (68.0%) | 977 (62.2%) | <0.001 |
| BMI ≥25 kg/m$^2$ | 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 class III/IV | 1749 (16.2%) | 220 (26.9%) | 499 (31.8%) | <0.001 |
| eGFR (mL/min/1.73 m$^2$) | | | | |
| ≤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 |

BMI, body mass index; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral arterial disease; SBP, systolic blood pressure; SCD, sudden cardiac death.

been violated (proportional-hazards Schoenfeld residuals by risk score quintiles, $P = 0.86$) (online supplementary *Figure S1*).

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

# Results

## Baseline characteristics

The derivation cohort included 13 202 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 online supplementary *Table S2*, 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 (CI) 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 myocardial infarction, atrial fibrillation, peripheral arterial disease, hypertension, diabetes, stroke, and HF prior to randomisation (*Table 1*). Body mass index and eGFR were lower, and systolic blood pressure and heart rate higher, in those experiencing SCD. Rates of coronary reperfusion or revascularizstion 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 bpm, active smoking, Killip class III/IV, LVEF ≤30%, atrial fibrillation, history of prior myocardial infarction, HF or diabetes mellitus, eGFR <60 mL/min/1.73 m$^2$ 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*).

**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 class 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/1.73 $m^2$ | 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 |

CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction.
C-index full model = 0.72 (95% CI 0.71–0.74).
C-index LVEF ≤ 35% alone = 0.54 (95% CI 0.53–0.55).

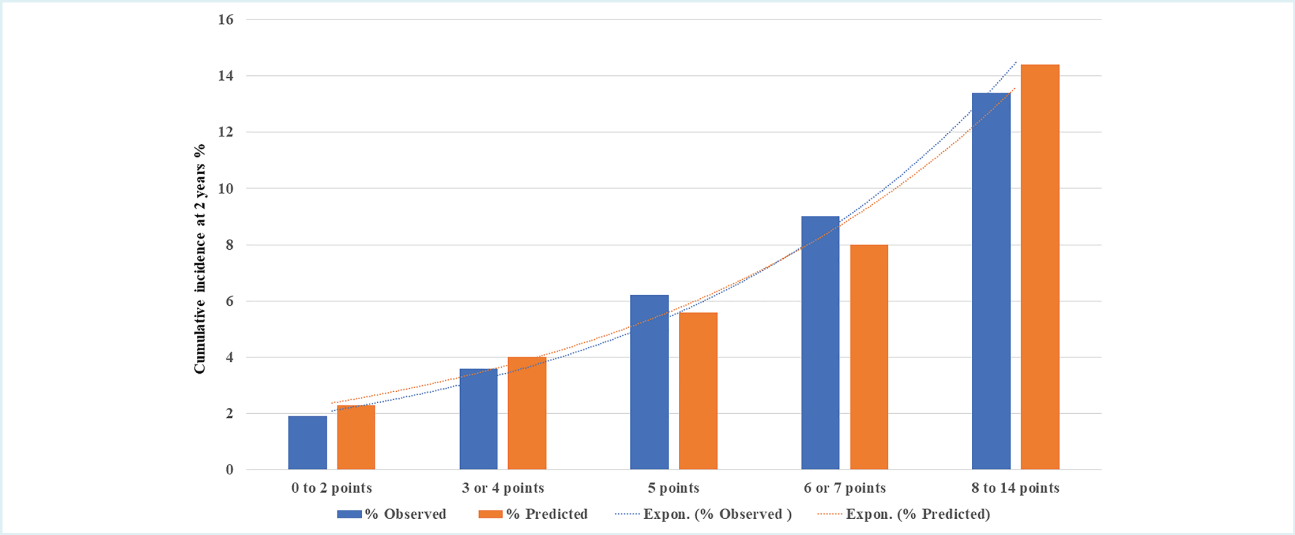


**Figure 1** Model calibration plot: percentage of observed vs. predicted risk of sudden cardiac death at 2 years according to quintile of risk score. The models were also well calibrated in the validation set: a steep gradient in risk by quintiles of predicted risk was observed (*Table 3*).

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; online supplementary *Table S3*). Patient characteristics were similar between the derivation and validation cohort (online supplementary *Table S4*).

## Risk model compared with left ventricular ejection fraction ≤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 predictive 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 reclassification of 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% (95% CI 1.6–2.8; $P < 0.001$).

## Event rates

The incidence rate per 100 person-years of SCD 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 1.1–1.9), respectively.

The observed 2-year incidence of SCD increased from 1.9% in the lowest to 13.4% in the highest quintile of risk score,

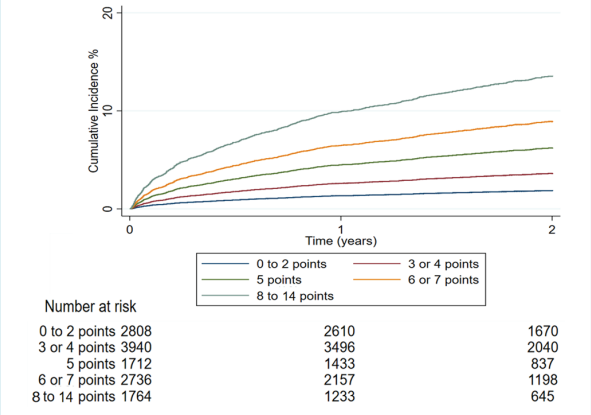


**Figure 2** Cumulative incidence function of sudden cardiac death accounting for the competing risk of non-sudden cardiac death plotted by quintile of risk score.

respectively (*Figure 2* and *Table 3*). This was consistent with the predicted event rates (*Table 3*). An online calculator (online supplementary *File S1*) is provided for calculation of the risk of SCD in patients with HF, LVSD, 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 randomisation 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 11 routinely collected clinical variables which were independent predictors of SCD. Importantly, our model accounted for the competing risk of non-SCD. Using the 11 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 HF. Together these are clearly related to the development of myocardial scar and LVSD, 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 HF 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 HF, 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 HF, LVSD 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

**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 |
| | | **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 |
| | | **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 |
| | | **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 |

SCD, sudden cardiac death.

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 SCD in patients with chronic HF with reduced ejection fraction.[29] The potential benefits of this pharmacological approach in patients with LVSD, HF, 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 HF 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 (online supplementary *Table S1*) and the maximum time from AMI from which randomisation was permitted, differed somewhat. 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 (95% CI 0.71–0.74); EPHESUS, 0.70 (95% CI 0.68–0.72)]. Patients with multiple co-morbidities may be at high risk of SCD but decision making regarding the appropriateness of therapies to prevent SCD such as an implantable cardioverter-defibrillator, should be made on a case by case basis taking into account the degree of co-morbidity and the competing risk of non-SCD. Furthermore, not all adjudicated SCDs 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. 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 practice 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 randomised controlled trial.

# Conclusion

We developed an easy to use score for predicting the risk of SCD in patients with HF, LVSD 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.

# Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Trial definitions of sudden cardiac death.

**Table S2.** Characteristics of the EPHESUS study population (replication cohort).

**Table S3.** External validation of the sudden cardiac death risk model in the EPHESUS dataset.

**Table S4.** Comparison of the derivation and replication sets.

**Figure S1.** Visual assessment of time interaction.

**File S1.** Online calculator for estimating the risk of sudden cardiac death in patients with heart failure, left ventricular systolic dysfunction, or both after acute myocardial infarction.

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