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Predictors of sudden cardiac death change with time after myocardial infarction: results from the VALIANT trial

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Aims To determine whether predictors of sudden cardiac death (SCD) vary with time after myocardial infarction (MI).

Methods and results We analysed 11 256 patients enrolled in VALIANT. Landmark analysis and Cox proportional hazards modelling were used to predict SCD during hospitalization, from discharge to 30 days, 30 days to 6 months, and 6 months to 3 years. The cumulative incidence of SCD was 8.6% ($n = 965$). Initially, higher baseline heart rate [HR 1.20 per 10 b.p.m. (95% CI 1.06–1.37)] and impaired baseline creatinine clearance [HR 0.82 per 10 mL/min (95% CI 0.74–0.91)] were stronger predictors of SCD. With long-term follow-up, prior MI [HR 1.71 (95% CI 1.39–2.10)], initial left ventricular ejection fraction <40% [HR 0.67 per 10% (95% CI 0.58–0.78)], and recurrent cardiovascular events [HR 1.47 for rehospitalization (95% CI 1.17–1.86)] were more robust risk stratifiers for SCD. Atrial fibrillation post-MI was associated with an increased risk of SCD over the entire follow-up period. As time passed, the associations between baseline clinical characteristics and SCD decreased and time-updated assessments became more important.

Conclusion Predictors of SCD change with time after MI. Future studies of risk stratification for SCD should account for changes in these factors with time after MI.

Keywords Arrhythmia • Sudden death • Heart failure • Natural history

Introduction

Despite improvements in the care of patients with acute coronary syndromes, sudden cardiac death (SCD) remains a lethal complication of myocardial infarction (MI). The risk of SCD after MI is most pronounced in patients with heart failure (HF) and left ventricular (LV) dysfunction.[1,2] The VALsartan In Acute myocardial iNfarcTion trial (VALIANT) Trial, which enrolled patients with acute MI complicated by LV dysfunction and/or HF demonstrated that the risk of SCD changes with time after MI, and that the risk of SCD is greatest in the first 30 days following MI.[3,4] Despite this observation, both prospective and retrospective studies of implantable cardioverter defibrillators have failed to show a reduction in all-cause mortality in the days to first month after MI.[5,6] This discrepancy reflects the limits of current risk stratification techniques and highlights the need for an improved understanding of the factors which contribute to SCD and their temporal relation after MI, particularly in patients with HF.

While many risk factors for SCD have been described, little is known about whether and how predictors of SCD vary with time after MI. Better understanding of the predictors of SCD as a function of time may allow for improved risk stratification and prevention of SCD. We conducted a retrospective study of SCD in the VALIANT trial using landmark follow-up periods after MI to identify predictors of SCD as a function of time.

Methods

VALIANT was a double-blind, randomized, controlled trial of treatment with valsartan, captopril, or both in 14 703 patients with acute MI complicated by HF, LV dysfunction [ejection fraction (EF) ≤40%],

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Table 1 Candidate variables

Baseline clinical and demographic characteristics
Age, sex, race
Weight, height
Systolic and diastolic BP
Heart rate
CrCl at enrolment
Clinical evidence of heart failure
LVEF at enrolment
Radiographic evidence of pulmonary oedema
Abnormal biomarkers (CK, CKMB, or troponin)
Killip classification
Q-wave MI
Location of MI (anterior, inferior, or other)
New LBBB
Smoking status (never, current, past)
Region of the world (East Europe, West Europe, South America, North America, other)
Any hospitalization in the prior 6 months
Randomized treatment (valsartan or valsartan with captopril)
Aspirin
Statin
Beta-blocker
Past medical history (factors occurring before the enrolling MI)
Hypertension
Dyslipidaemia
Diabetes mellitus
History of angina pectoris
Unstable angina
Prior MI
PCI
CABG
Heart failure
TIA
Stroke
Atrial fibrillation
Peripheral vascular disease
Chronic obstructive pulmonary disease
Chronic renal insufficiency
Chronic alcohol abuse
Cancer within 5 years
In-hospital events and updated post-randomization variables
Time from qualifying MI to randomization (hours)
Cardiac catheterization
Primary PCI in association with qualifying MI
Subsequent PCI
IABP use
CABG
Pacemaker use
Hypertension
Dyslipidaemia
New diagnosis of diabetes
Renal insufficiency
Atrial fibrillation
Sustained ventricular tachycardia
Ventricular fibrillation
Resuscitated cardiac arrest
Post-infarct angina
Unstable angina
MI
Stroke
Clinical evidence of heart failure (or recurrent)
NYHA class
Heart transplant
Systolic and diastolic BP
Heart rate
Rehospitalization for any cause
Aspirin
Statin
Beta-blocker

BP, blood pressure; CABG, coronary artery bypass grafting; CrCl, creatinine clearance; IABP, intraaortic balloon pump; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

or both. Patients were enrolled at 931 hospitals in 24 countries between December 1998 and June 2001. A detailed description of the protocol, including the inclusion and exclusion criterion, has been published previously.[3] For the purpose of this analysis, patients without left ventricular ejection fraction (LVEF) quantification ($n = 3353$) and with an implantable cardioverter defibrillator at randomization were excluded ($n = 94$). After randomization, 222 ICDs were implanted during follow-up: $n = 62$ in-hospital, $n = 29$ between discharge and 30 days, $n = 42$ between 30 days and 6 months, and $n = 89$ between 6 months and 3 years (some patients were implanted more than once). Patients with an ICD at the beginning of each interval were censored and therefore are not included in the landmark analysis for that interval ($n = 59$ at hospital discharge, $n = 27$ at 30 days, and $n = 40$ at 6 months). The final cohort was 11 256 patients.

Endpoint definitions

The primary endpoint for this analysis was SCD, including resuscitated SCD. We included patients who experienced resuscitated SCD in subsequent analysis (the next landmark period). A central, blinded adjudication committee reviewed all key endpoints including SCD and resuscitated SCD using source documents. Sudden cardiac death was expressly defined as death that occurred suddenly and unexpectedly in a patient who was otherwise clinically stable.[4] Both witnessed and unwitnessed deaths (if the patient was known to be well and seen within 24 h of death) were included. Deaths that were preceded by symptoms of HF or MI were adjudicated as non-sudden cardiovascular deaths. Finally, resuscitated sudden death was defined as any cardiac arrest from which the patient was successfully resuscitated with intact cognitive function.

Candidate variables

A total of 63 candidate variables were used to develop the models and included clinical, demographic, and historical characteristics available at baseline, during the MI hospitalization (pre- and post-randomization), and at each subsequent follow-up period (*Table 1*). Intercurrent clinical events (including recurrent MI and HF) were added to the model at each time point. In addition to the randomized study treatment, baseline (at each landmark period) evidence-based medications, including aspirin, beta-blocker, and statin therapy, were included in the model.

The LVEF was determined prior to randomization (median of 5 days after MI) in 11 256 patients with echocardiography ($n = 9095$), radionuclide ventriculography ($n = 272$), or contrast ventriculography ($n = 1889$). Patients for whom no LVEF was recorded were excluded. Creatinine clearance was estimated prior to randomization using the Modification of Diet in Renal Disease equation.[7]

Statistical analysis

Baseline characteristics were summarized as percentages for categorical variables and medians with 25th and 75th percentiles for continuous variables. Comparisons of baseline characteristics were made according to outcome (resuscitated sudden death, SCD, both, or none) using the Chi-square test and the Kruskal–Wallis test for categorical and continuous variables, respectively.

Cox's proportional hazards models at different time points were fit to identify the risk factors for SCD or resuscitated sudden death as a function of time after MI.[8–10] This approach was used to estimate the probability of event before the next office visit and then long term. Specifically, for each of the following four periods: initial hospitalization, discharge to 30 days, 30 days to 6 months, and 6 months to 3 years, we developed a Cox's proportional hazards model to determine important risk factors among all available information at the beginning of the period. These models evaluated events between the start of the period and the beginning of the next period (for the final model, this was the 3 year follow-up time). In addition to those variables deemed to be clinically significant, we used three variable selection techniques: (i) forward selection, (ii) step-wise selection, and (iii) backwards elimination. In order to assure robust model architecture, we included any variable selected by any of the three techniques (at the $P < 0.05$ level) in our final, non-parsimonious model. For example, if variable X was selected using forward selection technique but was eliminated in the other two techniques, it was retained in the final model. The three different selection techniques (all selecting at $P < 0.05$) led to similar sets of risk factors.

A restricted cubic spline transformation method was used to check the linearity assumption for continuous variables, and whenever the assumption was violated, a transformation of the variable suggested by the plot of log hazards ratio vs. the variable was applied in model building process. The proportional hazards assumption was evaluated by testing the significance of an interaction term of the factor with the log of time. Due to the large number of candidate risk factors, proportional hazards assumption were only checked for variables chosen by the preliminary model selection process. The c-index was calculated for each final model to evaluate the ability of the model to discriminate between those with and without a sudden death.

The variation explained by each model was expressed using generalized R^2 values.[11] This method forces the values of quantification to range between 0 and 1. The ratio of the variable R^2 to the R^2 for the overall model [(model R^2 of the full model minus the model R^2 with the factor of interest excluded)/the model R^2 from the full model] is used as an estimate of the amount of variation that the factor of interest explains from the total variation in outcome explained by the full model. For example, consider a hypothetical model X which includes heart rate (HR), LVEF, and prior atrial fibrillation plus 10 other variables. If the full model $R^2 = 0.15$ but the R^2 for this same model excluding HR was 0.135, then the measure for the amount of total variation in model X explained by HR would be $(0.15 - 0.135)/0.15$ or $0.015/0.15 = 10\%$.

Results

Patient population

The baseline characteristics of the study population according to outcome are shown in *Table 2*. Over 3 years of follow-up, the cumulative incidence of SCD was 8.6% ($n = 965$). Patients with SCD were older (median age 69 vs. 65 years, $P < 0.0001$) and were more likely to have a history of diabetes (29 vs. 22%, $P < 0.0001$) and prior MI (44 vs. 27%, $P < 0.0001$) than patients without SCD. Patients with SCD had a higher median baseline HR (78 vs. 75 b.p.m., $P < 0.0001$). As expected, patients with resuscitated cardiac arrest and SCD had a lower LVEF than patients without SCD. However, even in this post-MI HF population, one in five patients with SCD had relatively preserved baseline LV function (LVEF $\geq$40%). From a therapeutic standpoint, patients with SCD were less likely to have undergone percutaneous revascularization (11 vs. 23%, $P < .0001$) after randomization.

Factors associated with sudden cardiac death at different time points after myocardial infarction

In order to determine if predictors of SCD change with time, we performed analyses within landmark periods with Cox proportional hazards modelling using four different periods of follow-up (*Figure 1*). Our strategy was to identify predictors associated with survival free from SCD until the next critical follow-up period. *Tables 3–6* detail the clinical variables associated with SCD during the immediate post-MI time period (in-hospital), post-discharge (discharge to 30 days), short-term (30 days to 6 months), and long-term follow-up (6 months to 3 years). The c-indices for each model were as follows: in-hospital period c-index = 0.730, discharge to 30 days c-index = 0.793, 30 day to 6 month follow-up c-index = 0.747, and 6 month to 3 year follow-up c-index = 0.763. Treatment with valsartan or combination therapy (valsartan and captopril) relative to captopril monotherapy was not associated with an incremental reduction in SCD at any time point.

Lower creatinine clearance and higher HRs were strong predictors of SCD prior to discharge (*Table 3*). In the first 30 days of follow-up, higher baseline HR, a lower baseline LVEF in those patients with an LVEF <40%, and atrial fibrillation post-MI were strongly associated with the occurrence of SCD (*Table 4*).

Creatinine clearance at randomization was an important predictor of freedom from SCD at discharge, 30 days, and 6 months, but not during longer-term follow-up (6 months to 3 years). On the other hand, the occurrence of atrial fibrillation post-MI was associated with an increased risk of SCD during the initial hospitalization [HR 2.03 (95% CI 1.30–3.16), $P = 0.0017$] that persisted throughout the entire follow-up period, out to 3 years after MI [HR 1.65 (95% CI 1.23–2.19), $P = 0.0007$]. Neither of these factors was

Table 2 Baseline characteristics according to study outcome[a]

	None (n = 10 291)	Resuscitated cardiac arrest only (n = 267)	SCD only (n = 623)	Both (n = 75)	P-Value[a]
Age, years	65.0 (55, 73)	67.5 (58, 74)	68.7 (60, 75)	65.9 (59, 73)	<0.0001
Female	30.2	30.0	32.7	25.3	0.4435
Race					0.0057
White	93.4	90.3	94.5	89.3	
Black	3.0	6.7	3.4	5.3	
Asian	0.7	0	0.3	2.7	
Other	2.9	3.0	1.8	2.7	
Heart rate, b.p.m.	75 (68, 84)	78 (68, 89)	78 (68, 85)	78 (68, 88)	<0.0001
Systolic BP, mm Hg	120 (110, 130)	120 (110, 130)	120 (110, 136)	120 (110, 131)	0.0001
Killip classification					<0.0001
I	33.2	29.7	23.0	22.7	
II	46.3	38.7	46.4	42.7	
III	14.8	19.2	23.0	20.0	
IV	5.8	12.4	7.7	14.7	
LV function					
LVEF	35 (30, 40)	32 (26, 36)	32 (26, 35)	30 (25, 33)	<0.0001
LVEF ≥40	27.6	22.1	19.7	10.7	<0.0001
Past medical history					
Diabetes	22.4	37.1	29.1	40.0	<0.0001
Hypertension	55.0	56.6	64.8	62.7	<0.0001
Prior MI	26.8	39.0	43.7	48.0	<0.0001
Stroke	5.6	8.6	8.8	12.0	0.0002
Heart failure	13.1	22.1	27.6	32.0	<0.0001
PCI	7.9	9.0	5.8	17.3	0.0037
CABG	6.9	14.2	9.1	12.0	<0.0001
History of smoking					0.7144
Never	36.0	37.5	39.0	34.7	
Current	32.2	30.7	32.3	30.7	
Past	31.7	31.8	28.7	34.7	
Medication use					
ACE inhibitor	42.4	46.8	49.6	58.7	<0.0001
GP IIb/IIa inhibitor	15.6	13.9	7.2	9.3	<0.0001
ARB	1.3	1.1	1.1	1.3	0.9876
Beta-blocker	62.1	53.6	54.9	54.7	<0.0001
Post-randomization					
Angina	20.8	23.0	18.2	17.6	0.2963
Heart failure	56.2	64.0	65.8	68.9	<0.0001
Diabetes	23.6	38.2	30.8	40.0	<0.0001
CABG	2.7	1.9	1.3	1.3	0.1335
PCI	23.2	16.1	10.5	21.3	<0.0001

Continuous variables are expressed as median (25th, 75th). Categorical variables are expressed as percentages.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; b.p.m., beats per minute; CABG, coronary artery bypass grafting; EF, ejection fraction; GP, glycoprotein; LV, left ventricular; MI, myocardial infarction; PCI, percutaneous coronary intervention; SCD, sudden cardiac death.
[a]P-values shown are for any association.

recorded during the follow-up period, so we could not estimate the relative association of changes in creatinine clearance or new onset atrial fibrillation after discharge with SCD.

Recurrent clinical events

In addition to the baseline variables noted above, the presence of HF [HR 2.19 (95% CI 1.34–3.59)], recurrent MI [HR 3.52 (95% CI 1.73–

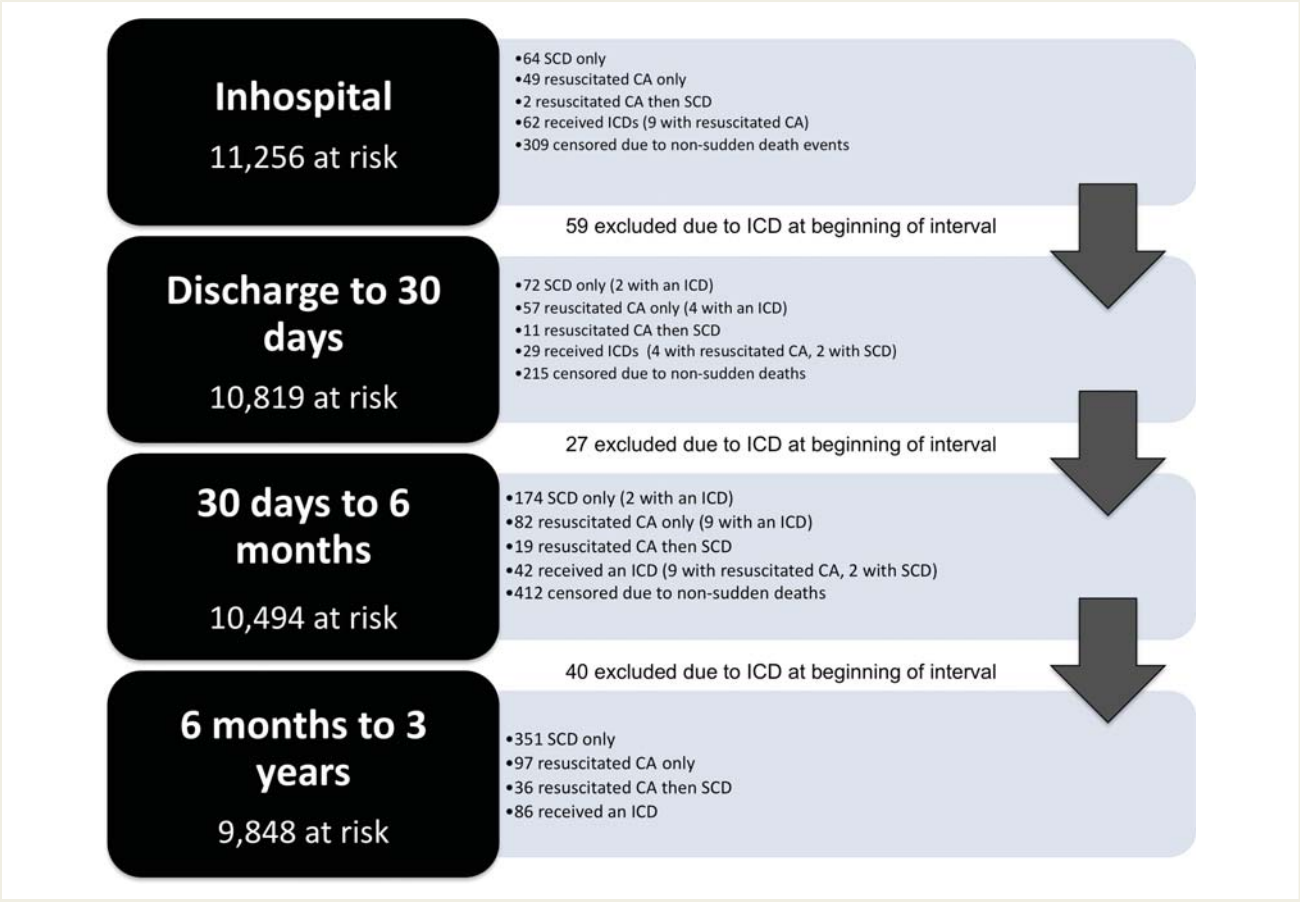

Figure 1 Study algorithm. Four serial Cox proportional hazards models using landmark analysis were developed to examine survival free from sudden cardiac death during initial hospitalization, discharge to 30 days, 30 days to 6 months, and 6 months to 3 years after myocardial infarction. Patients with an implantable cardioverter defibrillator were censored at the beginning of each landmark period. The number at risk for each interval represents the population included in the survival analysis after excluding those with an ICD at baseline.

7.19)], and rehospitalization for any reason [HR 2.48 (95% CI 1.52–4.06)] in the first 30 days of follow-up were significantly associated with the occurrence of SCD. Recurrent clinical events and higher HR in follow-up were persistently associated with SCD between 6 months and 3 years (*Table 6*). Revascularization during follow-up, including primary PCI for the qualifying MI, PCI during follow-up, and coronary artery bypass grafting, was associated with a decreased risk of SCD. However, in the first 30 days after MI, coronary artery bypass grafting was paradoxically associated with an increased risk of SCD [HR 2.30 (95% CI 1.05–5.05)].

Left ventricular ejection fraction

Higher LVEF in patients with LVEF <40% (e.g. 50 vs. 45) was not associated with survival free from SCD at any time point. However, higher LVEF in those patients with LVEF <40% (e.g. 35 vs. 30) was associated with a decreased risk of SCD. As shown in *Table 7*, this protective association with baseline systolic function at the time of initial hospitalization remained strong during long-term follow-up (6 months to 3 years) with an HR of 0.67 (0.57–0.77).

Prior myocardial infarction and myocardial necrosis

In long-term follow-up, a prior history of MI (in addition to the index MI) was strongly associated with the occurrence of SCD [HR 1.70 (95% CI 1.16–2.49)]. The degree of myocardial necrosis, as reflected by the peak CK, was not associated with SCD at any time point ($P \geq 0.5$ for all models). Accordingly, this variable was dropped from the final landmark period analyses.

Contribution of individual risk factors changes with time

In order to evaluate and compare the relative contribution of each clinical variable within each of the four landmark periods, the correlation coefficient for each variable was plotted as a percentage of the total model variance (defined as the global R^2 for each landmark period model). Some of the significant predictors of SCD and their contribution at each time point are provided in *Figure 2*. By definition, rehospitalization and interval development of HF were unavailable for the in-hospital period. For example, baseline creatinine clearance accounted for 20% of the predictive power of the in-hospital model, but less than 2% of the model

Table 3 Predictors of sudden cardiac death during the initial hospitalization

Variable	Wald Chi-Square	HR	95% CI	*P*-value
Randomized treatment				
Valsartan	0.54	0.84	0.53–1.33	0.4613
Valsartan, captopril	0.02	1.03	0.67–1.59	0.8818
Enrolment in East Europe	4.89	0.57	0.35–0.94	0.0271
History and physical examination				
Age (units of 10)	4.71	0.78	0.62–0.98	0.03
Weight (units of 10)	4.17	1.16	1.01–1.33	0.041
SBP (units of 10)	5.95	0.85	0.75–0.97	0.0147
Heart rate (units of 10)	11.38	1.20	1.06–1.37	0.0049
Current smoker	3.91	1.53	1.00–2.32	0.0481
Prior stroke	5.98	2.03	1.15–3.59	0.0145
CrCl (units of 10)	13.16	0.82	0.74–0.91	0.0003
LVEF increase per 10% (when LVEF ≥40%)	1.14	0.76	0.46–1.26	0.2866
LVEF increase per 10% (when LVEF <40%)	4.52	0.74	0.56–0.98	0.0336
Baseline medications				
Aspirin	1.17	0.74	0.44–1.27	0.2795
Beta-blocker	2.69	0.72	0.49–1.07	0.1009
Statin	1.11	0.80	0.52–1.22	0.2914
Post-qualifying MI				
Atrial fibrillation	9.80	2.03	1.30–3.16	0.0017
Catheterization	4.02	0.63	0.41–0.99	0.045

C-index = 0.730. Overall $R^2 = 0.043$.
CI, confidence interval; CrCl, creatinine clearance; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SBP, systolic blood pressure.

of the last period (19.6%→3.7%→2.2%→0.5%). Similarly, the predictive contribution of atrial fibrillation after MI also waned with time (12.5%→6.0%→2.2%→2.9%). On the other hand, the relative contribution of baseline LV function (LVEF <40%) to the models remained stable over time (6.3%→6.1%→8.1%→6.8%).

Discussion

We investigated the time-dependence of factors associated with SCD in over 11 000 patients with MI complicated by HF or LV dysfunction. While there are many predictive models for SCD following MI, the models presented here are time-updated with data available 'at the bedside' during follow-up visits. There were four main findings in this study. First, predictors of SCD change with time after MI. Second, in addition to an LVEF <40%, higher HR, atrial fibrillation post-MI, and impaired creatinine clearance are significant predictors of SCD. Third, recurrent cardiovascular events, LVEF <40%, and prior MI explain the greater proportion of SCD risk in long-term follow-up. Finally, baseline clinical characteristics explain a limited amount of SCD risk in long-term follow-up (>6 months).

Time dependence of sudden cardiac death risk

The risk of SCD was previously shown to be the greatest in the 30 days after MI and to decline in the first year after MI.[4,12] Despite this, attempts to prevent SCD in early post-MI patients have not led to reductions in all-cause mortality.[5] This risk-benefit paradox may be explained by relative differences in the risk factors for SCD at different time points after MI.[13] In order to determine if risk factors for SCD vary as a function of time after MI, we investigated the factors associated with SCD in four landmark follow-up periods. The results of these serial Cox models show that the risk factors for SCD do change with time after MI in the strength of their association with SCD (*Figure 2*).

Factors strongly associated with SCD differed according to the follow-up period of interest. While HR and creatinine clearance measured at baseline were strongly associated with SCD during the in-hospital period, recurrent cardiovascular events (including HF, MI, and rehospitalization) and a baseline LVEF <40% were more strongly associated with the occurrence of SCD after discharge. However, when we examined the overall contribution of each factor relative to the other variables in the model (e.g. the amount of variance in the outcome explained by the variable as opposed to the strength of the statistical association), it became clear that the relative degree of variation explained by the baseline risk factors decreased with time. Baseline clinical variables accounted for very little of the model variance in the 6 month to 3 year follow-up period (*Figure 3*). These findings have important clinical implications, since current risk stratification systems for SCD are static and do not incorporate time elapsed after MI (other than excluding those patients within 40 days of their MI) or recurrent clinical events.[14]

It should be noted that we are not implying that changes in creatinine clearance or changes in LVEF become less important with time. These measures are not available for us to evaluate beyond baseline. However, it is clear that baseline variables do differ in their predictive capacity in follow-up, such that after a certain critical time window, their ability to predict clinical events may be substantially less.

Left ventricular ejection fraction

While the LVEF is the gold-standard for the risk-stratification of SCD, it does have several limitations as emphasized in a recent scientific statement from the American College of Cardiology/American Heart Association,[13] including limited sensitivity and poor specificity. While the cumulative incidence of SCD is greatest in post-MI patients with an LVEF ≤30%, we have shown that the incidence of SCD is greater in patients with an LVEF ≥40% in the first 30 days after MI when compared with patients with an LVEF ≤30% after 90 days.[4] In this analysis, the strength of the association between LVEF and survival free from SCD was greatest in long-term follow-up (>6 months), consistent with the results from randomized clinical trials.[5,15] Alternatively, HR and creatinine clearance explained more of the variation in SCD immediately post-MI. Finally, and perhaps most importantly, reduced LV function was only associated with SCD in those patients with an LVEF <40%. Therefore, improved risk stratification for SCD in

Table 4 Predictors of sudden cardiac death in the first 30 days after myocardial infarction

Variable	Wald Chi-square	HR	95% CI	*P*-value
Randomized treatment				
Valsartan	0.69	0.83	0.54–1.28	0.4054
Valsartan, captopril	1.32	1.26	0.85–1.88	0.2512
Enrolment in East Europe	6.26	1.71	1.12–2.60	0.0123
History and physical examination				
Heart rate (units of 10)	13.74	1.26	1.11–1.42	0.0002
LVEF increase per 10% (when LVEF ≥40%)	0.01	0.98	0.64–1.49	0.9117
LVEF increase per 10% (when LVEF <40%)	11.58	0.63	0.49–0.82	0.0007
CrCl (units of 10)	5.01	0.93	0.87–0.99	0.0252
Prior MI	10.67	1.77	1.26–2.50	0.0011
Medications				
Aspirin	0.59	0.84	0.54–1.31	0.4424
Beta-blocker	4.13	0.70	0.49–0.99	0.0421
Statin	0.04	0.96	0.64–1.43	0.8372
Post-qualifying MI				
Atrial fibrillation	10.92	1.92	1.30–2.82	0.0009
Catheterization	5.30	0.57	0.36–0.92	0.0213
Clinical events in follow-up (at 16 days)				
NYHA class II, III, or IV	6.70	1.76	1.15–2.70	0.0096
CABG	4.30	2.30	1.05–5.05	0.0382
Heart failure	9.66	2.19	1.34–3.59	0.0019
Recurrent MI	11.98	3.52	1.73–7.19	0.0005
Rehospitalization	13.11	2.48	1.52–4.06	0.0003
Unstable angina	4.01	1.76	1.01–3.07	0.0453

C-index = 0.793. Overall $R^2 = 0.082$.
CABG, coronary artery bypass grafting; CI, confidence interval; CrCl, creatinine clearance; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.

the first 30 days after MI will require moving beyond the EF. While the DINAMIT study[5] attempted to do this by using HR variability as an additional marker of SCD, as prior work has shown, impaired HR variability in patients with HF is more closely associated with all-cause mortality than SCD.[16]

Creatinine clearance

Several studies have suggested that impaired creatinine clearance is a strong predictor of increased mortality, cardiovascular death, and SCD.[17–19] In this post-MI population, preserved baseline creatinine clearance was associated with a decreased risk of SCD. Furthermore, creatinine clearance explained most of the correlation with SCD in the immediate post-MI period (>20% of the correlation with in-hospital SCD). The strength of this relationship decreased over time, such that in long-term follow-up (6 months to 3 years), the baseline creatinine clearance was not associated with the occurrence of SCD. While this may reflect the waning importance of baseline renal function with continued follow-up, it may also be a reflection of significant early mortality in this high risk group. Finally, creatinine clearance may have improved in some patients, such that the baseline measure may not have accurately reflected renal function during later periods. Clearly, the relationship between SCD and impaired renal function is an important one which requires further study.[20]

Improved risk stratification for sudden cardiac death

Several groups have developed risk stratification models for SCD in the post-MI setting.[21–23] These notable risk stratification tools, including models from the Multicenter Unsustained Tachycardia Trial (MUSTT)[21] and the Multicenter Automatic Defibrillator Implantation Trial (MADIT II),[22] relied on baseline clinical characteristics. Using follow-up data, we were able to incorporate subsequent clinical events and functional status. Therefore, a unique contribution of this landmark analysis is the identification of clinical factors at 30 days and 6 months which physicians can use to predict SCD risk at the bedside. While baseline variables, including creatinine clearance, are associated with early post-MI SCD, changes in clinical status are important factors associated with SCD at 6 months and 3 years. Patients who are hospitalized for

Table 5 Predictors of sudden cardiac death 30 days to 6 months after myocardial infarction

Variable	Wald Chi-square	HR	95% CI	*P*-value
Randomized treatment				
Valsartan	1.61	0.83	0.62–1.11	0.2040
Valsartan, captopril	0.57	0.90	0.67–1.19	0.4500
Enrolment in South America	5.89	1.84	1.12–3.00	0.0152
History and physical examination				
Clinical evidence of heart failure	6.43	1.49	1.10–2.03	0.0112
Killip class III/IV	12.56	1.58	1.21–2.06	0.0007
Current smoker	12.67	1.63	1.24–2.12	0.0004
Prior diabetes mellitus	16.13	1.69	1.31–2.17	<0.0001
Prior angina	10.94	1.51	1.18–1.93	0.0009
Prior TIA	4.48	1.76	1.04–2.99	0.0343
New LBBB	4.78	1.66	1.05–2.60	0.0288
LVEF increase per 10% (when LVEF ≥40%)	0.47	0.91	0.69–1.20	0.4916
LVEF increase per 10% (when LVEF <40%)	17.72	0.67	0.56–0.81	<0.0001
CrCl (units of 10)	4.43	0.95	0.91–1.00	0.0354
Medications				
Aspirin	0.24	0.93	0.69–1.25	0.6244
Beta-blocker	0.03	1.02	0.78–1.34	0.866
Statin	3.84	0.76	0.58–1.00	0.498
Post-qualifying MI				
Primary PCI	5.99	0.58	0.38–0.90	0.0144
Atrial fibrillation	4.44	1.40	1.02–1.91	0.0351
Angina	4.33	0.72	0.52–0.98	0.0374
Clinical events in follow-up (at 45 days)				
NYHA class II, III, or IV	4.74	1.36	1.03–1.79	0.0295
Heart rate (units of 10)	4.38	1.10	1.01–1.21	0.0363
Rehospitalization	7.08	1.57	1.13–2.19	0.0078
Heart failure	4.20	1.64	1.02–2.62	0.0404

C-index = 0.747. Overall $R^2 = 0.051$.
CI, confidence interval; CrCl, creatinine clearance; HR, hazard ratio; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

HF develop further functional limitation or recurrent MI have an increased risk of SCD, independent of other clinical data.

Sudden cardiac death risk stratification in clinical practice must be adaptive and iterative in order to prevent SCD in patients who have been previously characterized as low risk. The results of this analysis show that risk factors for SCD change with time after MI, and that in many cases recurrent clinical events and updated clinical data explain a greater proportion of risk. The temporal variation in these associations must be kept in mind when devising risk stratification algorithms and designing prospective trials for improved SCD prevention. Finally, these models also help identify potentially modifiable risk factors, including increased HR (beta-blockers), worsening HF (cardiac resynchronization therapy and aldosterone blockade), and recurrent MI (statin therapy and revascularization).[14] Ideally, risk stratification for SCD should become a dynamic process, guided by time-updated predictions which can be relayed to physicians in real time.

Limitations

Our study was a *post hoc* analysis with a pre-specified and centrally adjudicated outcome. There are several limitations that should be kept in mind when considering the results. First, our study population was a high-risk ACS trial population with either LV dysfunction or symptomatic HF. While we controlled for differences in demographics and other clinical characteristics, including Killip classification, we cannot exclude the possibility that our results have been influenced by selection bias or confounding. Of note, we were not able to account for the severity of coronary artery disease. Additionally, while our models were inclusive, it is possible (and likely) that unobserved and unrecorded factors were also associated with SCD.

Our analysis was further limited by the lack of several variables in follow-up, including repeated measures of LVEF, creatinine clearance, and cardiac rhythm. Left ventricular function and creatinine clearance were only measured during the initial hospitalization at

Table 6 Predictors of sudden cardiac death from 6 months to 3 years after myocardial infarction

Variable	Wald Chi-square	HR	95% CI	*P*-value
Randomized treatment				
Valsartan	0.02	0.98	0.78–1.24	0.8906
Valsartan, Captopril	0.08	1.03	0.82–1.30	0.7824
Enrolment in East Europe	16.09	1.60	1.27–2.00	<0.0001
History and physical examination				
Age (units of 10)	4.58	1.14	1.01–1.28	0.0323
Clinical evidence of heart failure	3.09	1.21	0.98–1.50	0.0786
Current smoker	5.04	1.30	1.03–1.63	0.0247
Prior heart failure	7.66	1.40	1.10–1.75	0.0056
Prior MI	26.05	1.71	1.39–2.10	<0.0001
Prior diabetes mellitus	13.89	1.48	1.20–1.82	0.0002
Q-wave MI on ECG	8.14	0.75	0.61–0.91	0.0043
LVEF increase per 10% (when LVEF ≥40%)	0.003	1.01	0.82–1.24	0.9573
LVEF increase per 10% (when LVEF <40%)	26.21	0.67	0.58–0.78	<0.0001
CrCl (units of 10)	1.77	0.97	0.93–1.01	0.1830
Medications				
Aspirin	0.18	0.95	0.75–1.20	0.6705
Beta-blocker	5.34	0.79	0.65–0.97	0.209
Statin	2.01	0.85	0.69–1.06	0.1564
Post-qualifying MI				
Atrial fibrillation	11.45	1.65	1.23–2.19	0.0007
PCI	13.06	0.56	0.41–0.77	0.0003
Clinical events in follow-up (at 198 days)				
Heart rate (units of 10)	4.92	1.10	1.01–1.19	0.0266
CABG	8.52	0.30	0.13–0.67	0.0035
Heart failure	5.04	1.45	1.05–1.99	0.0248
Recurrent MI	7.45	1.70	1.16–2.49	0.0064
Rehospitalization	10.49	1.47	1.17–1.86	0.0012

C-index = 0.763. Overall $R^2 = 0.068$.
CABG, coronary artery bypass grafting; CI, confidence interval; CrCl, creatinine clearance; ECG, electrocardiogram; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 7 Hazard ratios for sudden cardiac death change with time

Variable	Initial hospitalization		Discharge to 30 days[a]		30 days to 6 months		6 months to 3 years	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Heart rate in units of 10 at baseline and follow-up[a]	1.20	1.06–1.37	1.26	1.11–1.42	1.10	1.01–1.21	1.10	1.01–1.19
CrCl per 10 cc/min	0.82	0.74–0.91	0.93	0.87–0.99	0.95	0.91–1.00	0.97	0.93–1.01
LVEF per 10% (when LVEF <40%)	0.74	0.56–0.98	0.63	0.49–0.82	0.67	0.56–0.81	0.67	0.58–0.78
AF post-MI	2.03	1.30–3.16	1.92	1.30–2.82	1.40	1.02–1.91	1.65	1.23–2.19
Rehospitalization			2.48	1.52–4.06	1.57	1.13–2.19	1.47	1.17–1.86
Interval heart failure			2.19	1.34–3.59	1.64	1.02–2.62	1.45	1.05–1.99

[a]Index HR used for this model.
AF, atrial fibrillation; CI, confidence interval; CrCl, creatinine clearance; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

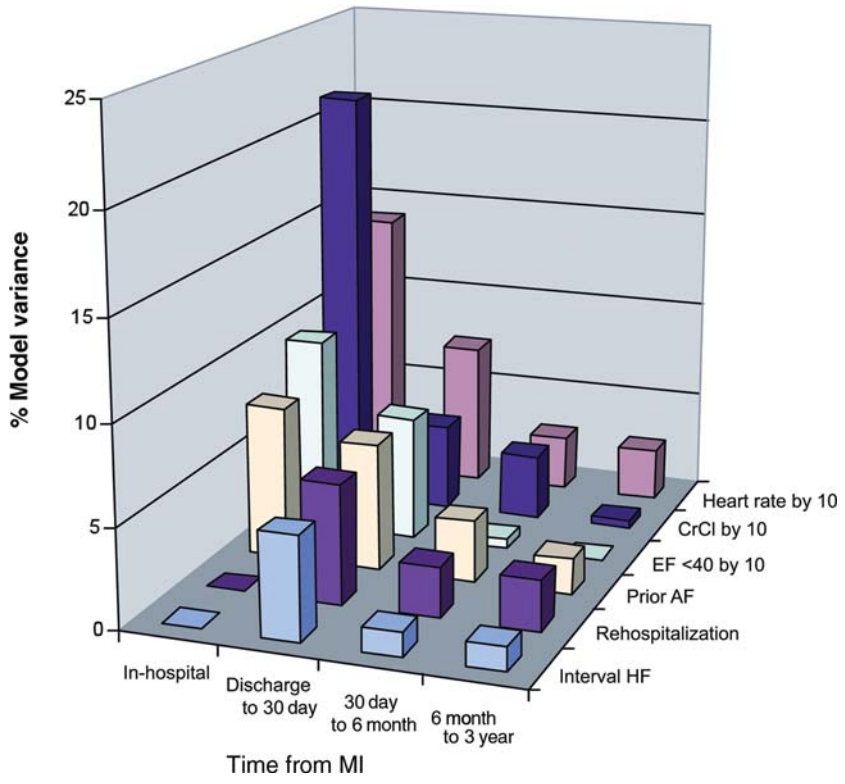

Figure 2 Correlation coefficients of factors associated with sudden cardiac death change with time after myocardial infarction. Each column represents the percent increase in the generalized R^2 with the addition of the variable of interest. Each column represents the percent increase in generalized R^2 from the full model to the model excluding the variable of interest.

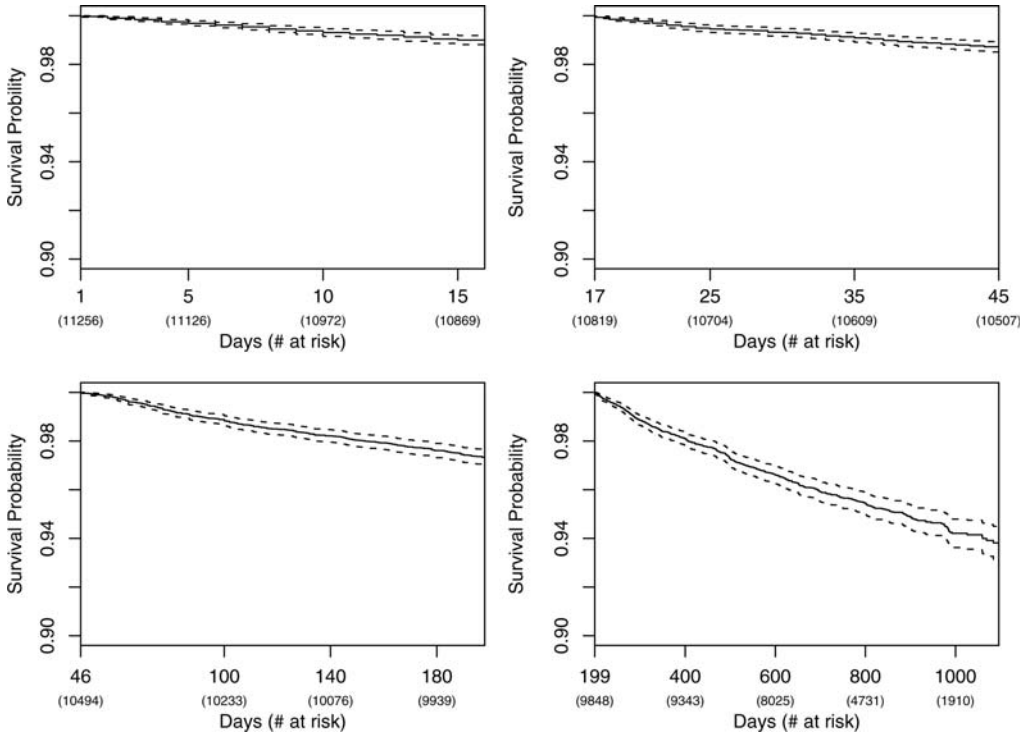

Figure 3 Survival free from sudden cardiac death. Shown here is the survival free from sudden cardiac death during the (*A*) initial hospitalization, (*B*) discharge to 30 days, (*C*) 30 days to 6 months, and (*D*) 6 months to 3 years after myocardial infarction.

randomization. Given the strong association between these factors and the risk of SCD in short-term follow-up, these factors may have been important predictors of SCD in later follow-up.

We chose a landmark analysis strategy because we were interested in identifying how risk factors for SCD change with time after MI. By examining outcomes across restricted follow-up periods, we identified factors most closely associated with SCD at these particular follow-up points. Our goal was to provide clinically meaningful risk factors to the practicing physician who encounters a patient in follow-up. An alternative analysis strategy aimed at identifying global (or overall) risk factors for SCD might have produced different results.

We addressed the problem of competing risks by including all patients in our analysis at baseline and then censoring patients who experienced non-sudden death. In other words, we chose to address competing risks by analysing the predictors of SCD in the presence of all other hazards. By censoring patients at the time of non-sudden death, the risk factors we identified predict, in the presence of all other causes of death, the risk of dying from SCD instead of other causes among those who are still alive. This method does not address the risk of SCD following alternative outcomes; however, it does avoid the inherent probability assumptions when examining simultaneous competing risks.[24] While our analysis was limited to observed events only, this reflects clinical practice.

Conclusions

Both the incidence and predictors of SCD change with time after MI. Over time, baseline clinical characteristics have less and less predictive value and time-updated information is more important. Moving forward, future studies of risk stratification for SCD should account for interval clinical events and time after MI.

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