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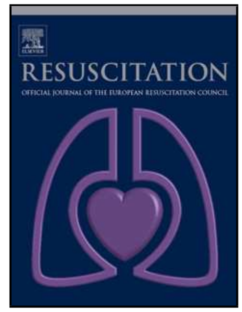

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Title: A user-friendly risk-score for predicting in-hospital cardiac arrest among patients admitted with suspected non ST-elevation acute coronary syndrome – the SAFER-score

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Abstract

Aim: To develop a simple risk-score model for predicting in-hospital cardiac arrest (CA) among patients hospitalized with suspected non-ST elevation acute coronary syndrome (NSTE-ACS). **Methods:** Using the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART), we identified patients (n=242 303) admitted with suspected NSTE-ACS between 2008 and 2014. Logistic regression was used to assess the association between 26 candidate variables and in-hospital CA. A risk-score model was developed and validated using a temporal cohort (n=126 073) comprising patients from SWEDEHEART between 2005 and 2007 and an external cohort (n=276 109) comprising patients from the Myocardial Ischaemia National Audit Project (MINAP) between 2008 and 2013. **Results:** The incidence of in-hospital CA for NSTE-ACS and non-ACS was lower in the SWEDEHEART-derivation cohort than in MINAP (1.3% and 0.5% vs. 2.3% and 2.3%). A seven point, five variable risk score (age ≥60 years (1 point), ST-T abnormalities (2 points), Killip Class >1 (1 point), heart rate <50 or ≥100 bpm (1 point), and systolic blood pressure <100 mmHg (2 points) was developed. Model discrimination was good in the derivation cohort (c-statistic 0.72) and temporal validation cohort (c-statistic 0.74), and calibration was reasonable with a tendency towards overestimation of risk with a higher sum of score points. External validation showed moderate discrimination (c-statistic 0.65) and calibration showed a general underestimation of predicted risk. **Conclusions:** A simple points score containing five variables readily available on admission predicts in-hospital CA for patients with suspected NSTE-ACS.

Key Words: In-Hospital Cardiac Arrest; Acute Coronary Syndrome; Non-ST Elevation Acute Coronary Syndrome; Risk Score; Risk Stratification

Introduction

In-hospital cardiac arrest (CA) is an infrequent, but life-threatening complication of a non-ST elevation acute coronary syndrome (NSTE-ACS). The cause of in-hospital CA is usually ventricular tachycardia (VT) or ventricular fibrillation (VF), reported to occur in 1.5-2.1% of patients[1, 2]. Although less common, patients are also at risk of non-VT/VF CA[3]. There are no contemporary clinical risk scores available to estimate the risk of hospital CA using data obtained at the time of admission among patients with suspected NSTE-ACS.

Recommendations for continuous ECG-monitoring of patients admitted to hospital with suspected NSTE-ACS differ, but guidelines emphasize the importance of early risk stratification to reduce adverse clinical outcomes[4, 5]. The current American Heart Association / American College of Cardiology guidelines for the management of patients with NSTE-ACS suggest several clinical factors predictive of VT/VF including signs of heart failure at presentation, hypotension, tachycardia, cardiogenic shock and poor TIMI flow[4]. The latest European guidelines on the management of NSTE-ACS recommend ECG-monitoring until non-ST elevation myocardial infarction is ruled out or when the diagnosis is established, in low-risk patients until revascularization or ≤24 hours, or prolonged monitoring only if intermediate/high-risk features are present (e.g. hemodynamic instability, major arrhythmias, left ventricular ejection fraction <40%, failed reperfusion and the presence of critical stenosis or complications related to percutaneous coronary intervention (PCI)[5].

The aim of this study was to develop an easy-to-use clinical risk-score that may help the physician assess the risk of in-hospital CA and hence the need for cardiac rhythm monitoring and level of surveillance in patients admitted with suspected NSTE-ACS. For this purpose, we identified predictors of CA present at hospital admission and developed and validated a risk-score model for in-hospital CA in the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). We externally validated the risk score in the United Kingdom Myocardial Ischaemia National Audit Project (MINAP).

Methods

Study population

The study comprised all patients admitted to a coronary care unit (CCU) with suspected or confirmed ACS and registered in SWEDEHEART. Data on clinical variables at admission, current medication, treatment and procedures during hospitalization, and final diagnoses are recorded as part of the registry. SWEDEHEART has been described in detail previously[6]. All patients are informed about collection of data in the registry and are allowed to opt-out. SWEDEHEART is cross-linked with the Swedish National Patient Registry, to enrich data on previous medical history, and with the Swedish Population registry to obtain date of death. The protocol of this study was approved by the regional ethics committee in Stockholm, Sweden and was conducted complying with the Declaration of Helsinki.

Derivation cohort

All patients at least 18 years old registered in SWEDEHEART between January 1 2008 and December 31 2014 were eligible (n=353 140). Patients could be eligible for entry more than once. Exclusion criteria included ST-elevation myocardial infarction (n=40 798), CA prior to admission (n=4200), and missing data regarding CA prior to admission (n=54 864) or in-hospital CA (n=13 281). In total, 242 303 cases (187 662 unique patients) remained in the study population for analyses (figure 1).

Definition of CA

In-hospital CA requiring defibrillation or cardiopulmonary resuscitation is recorded prospectively as part of SWEDEHEART. This variable is categorized as “VT/VF”, “other causes of CA”, or “no CA”. Given that there may be overlap between the first two categories all analyses were conducted using a dichotomized variable defined as in-hospital CA “yes” or “no”.

Statistical analyses

Baseline characteristics for continuous data are presented as median (interquartile range) or as numbers and proportions for categorical data.

Risk score derivation

Logistic regression was used to assess the association between in-hospital CA and baseline patient characteristics. Candidate variables were incorporated based on findings from prior studies, current NSTE-ACS guideline recommendations, clinical relevance, and availability at admission [1, 2, 4, 5, 7]. Continuous variables were divided into deciles and the most appropriate cut-offs were chosen, without testing for non-linear relationships or interactions. Backward selection was performed using a 0.05 significance level. In the final model, all included variables were dichotomized.

The following 26 variables were tested in the logistic regression models: age, gender, weight, smoking status (dichotomized as current smoker yes/no); prior diseases including hypertension, diabetes, chronic obstructive pulmonary disease, heart failure, myocardial infarction, stroke, and peripheral vascular disease; prior coronary interventions including PCI and coronary artery bypass graft (CABG) surgery; current pharmacological treatment including beta blockers, calcium antagonists, digoxin, aspirin, angiotensin-converting enzyme (ACE) inhibitors / angiotensin receptor blockers (ARB), and statins; clinical findings at presentation including Killip class, heart rate, systolic blood pressure, and electrocardiographic ST-T-changes; laboratory findings at presentation including glucose, hemoglobin, and estimated glomerular filtration rate (eGFR) based on the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula[8]. Given that only peak values are reported in SWEDEHEART and therefore on admission assay results were not available in the dataset , the cardiac troponin concentration was not included.

A risk-score model was developed using the points system described by Sullivan et al[9]. Briefly, as dichotomous variables were included in the model, each risk factor could take on the values 0 or $ß_i$, where $ß_i$ represented the respective estimate of the regression coefficient of the multiple logistic-regression model. The regression coefficient of one of the variables was defined as the constant, B, which corresponded to one point in the point score. Each risk factor was assigned points by dividing $ß_i$ by B, rounded to the nearest integer. The estimated risk was determined by adding the intercept of the estimate, $ß_{0,}$ to the point total multiplied by the constant B and then transforming the sum using the logistic function. Model discrimination was assessed using the c-statistic and calibration by comparing observed to predicted risk in calibration plots.

Missing data

Complete data on all candidate variables (26) was available in 159 693 (65.9%) cases. The most frequently missed variable, glucose, had 19.6% missing. Data was assumed to be missing at random. To account for missing data, multiple imputation by chained equations (MICE) was performed generating 20 imputed data sets. All candidate variables and the outcome variable were used as predictors for missing variables. For the two variables glucose and eGFR, two additional, auxiliary variables, insulin and oral diabetes medication were also used. For the final risk score model, complete data on all included variables was available in 227 912 (94.1%) cases. The main results were compared for the imputed and complete case cohorts. Patients excluded solely due to missing data regarding in-hospital CA, pre-hospital CA, or CA at admission were compared to patients included in the cohort in respect of baseline characteristics, in-hospital mortality and mortality at 30 days.

Internal validation

Since the number of events (n= 2077) was large relative to the number of predictors included in the final model, the risk of overfitting was considered to be negligible and bootstrapping of the sample not performed. This was further supported by using the heuristic shrinkage estimator of van Houewelingen and le Cessie with a computed estimated shrinkage factor of 0.997[10].

Temporal validation

A temporal validation was performed using data from SWEDEHEART between January 1 2005 and December 31 2007. This cohort (n=126 073, 102 762 unique patients) was selected using the same inclusion and exclusion criteria as for the derivation cohort. To adjust for missing data multiple imputation (20 imputed data sets) was performed in the same manner as for the original cohort.

External validation

External validation was undertaken using anonymised data from the Myocardial Ischaemia National Audit Project (MINAP) between January 1 2008 and December 31 2013. MINAP has been described in depth elsewhere[11]. In-hospital CA requiring defibrillation or cardiopulmonary resuscitation is recorded prospectively as part of MINAP. All analyses were conducted using a dichotomized variable defined as in-hospital CA “yes” or “no”. The same inclusion and exclusion criteria as for the derivation cohort were used (supplementary figure

1). The cohort comprised 276 109 cases. Missing data for Killip class, one of the variables in the final risk score model, was 72.0%. For the remaining variables included in the final risk score model, data missingness ranged from 0.1% to 8.7%. Multiple imputation was performed (10 imputed datasets) according to methods previously described for MINAP[12]. To adjust for differences in underlying risk between the development and external cohorts, a model with $ß_0$ calculated from MINAP was included. The National Institute for Cardiovascular Outcomes Research (NICOR) which includes the MINAP database (Ref: NIGB: ECC 1-06 (d)/2011) had support under section 251 of the National Health Service (NHS) Act 2006 to use patient information for medical research without consent.

Statistical analyses were performed with Stata version 13 (StataCorp, College station, Texas, USA) and R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Derivation cohort

In total, 2077 (0.9%) cases of in-hospital CA were recorded in patients admitted to a hospital with suspected or confirmed NSTE-ACS in the derivation cohort (n=242 303). Patients with in-hospital CA were more likely to be older, have electrocardiographic ST-T-abnormalities, previous history of heart failure, and diabetes, lower systolic blood pressure, hemoglobin, and lower renal function (eGFR), higher heart rate and blood glucose level, and higher Killip class (table 1).

Among patients with a final diagnosis of NSTE-ACS (n=102 650), there were 1.3% (n=1365) cases of in-hospital CA (supplementary figure 2). For patients with NSTE-ACS, invasive coronary treatment (PCI or CABG surgery) during index hospitalization was recorded for 581 (42.6%) cases with in-hospital CA and 53 063 (52.4%) cases without in-hospital CA. The majority of patients who were not diagnosed with ACS (n=139 653) had a final diagnosis of stable angina pectoris or non-cardiac chest pain (supplementary figure 3). Among patients without ACS there were 0.5% (n=712) cases of in-hospital CA.

Derivation of the risk score

Five variables independently predicting in-hospital CA were included in the final risk score model. We developed a points score with a maximal sum of seven points whereby the included variables were: age ≥60 years (1 point), electrocardiographic ST-T abnormalities (2 points), Killip Class >1 (1 point), heart rate <50 or ≥100 bpm (1 point), and systolic blood pressure <100 mmHg (2 points) (table 2). For simplicity, two variables, glucose >10 mmol/L and eGFR <30 mL/min per 1.73 m^2, were omitted and did not substantially alter the model performance. The observed proportions of in-hospital CA by sum of points in the derivation cohort, in total, ranged between 0.17% and 8.53 % (figure 2a and supplementary table 1a). The majority of patients had a point score sum between 1 and 3 points (supplementary table 1b). Discrimination was good (c-statistic 0.72 [95% CI, 0.71-0.73]) and the calibration plot showed reasonable agreement, but with a tendency towards overestimation of risk with a higher sum of score points (figure 3a). A higher risk score was associated with higher in-hospital mortality in the complete case cohort, ranging from 0.06% to 28.2% for patients without in-hospital CA vs. 20.5% to 50.0% for patients experiencing in-hospital CA. Analyses restricted to first-time admissions (n=187 662) showed similar results regarding discrimination (c-statistic 0.73 [95% CI, 0.72-0.74]) and calibration (data not shown).

Sensitivity analyses

For the five variables included in the points score model, there was 5.9% missing data in the derivation cohort. Complete case analyses demonstrated similar results regarding model performance as for the main analyses (supplementary figure 4). Patients excluded due to missing data for in-hospital CA (n=13 281) resembled patients without in-hospital CA in the cohort regarding baseline characteristics and had comparable though slightly lower in-hospital and 30-day mortality rates. Patients excluded due to missing data for cardiopulmonary resuscitation prior to admission (n=54 221) were of similar age, slightly more likely to be female and had a lower burden of prior disease compared with patients without in-hospital CA in the cohort. Presentation characteristics were not comparable because of missing data (about 80%) (supplementary table 2). In-hospital and 30-day mortality was comparable to the cohort in total.

Temporal validation

A temporal validation from SWEDEHEART 2005-2007 was performed and showed good agreement in respect of discrimination (c-statistic 0.74 [95% CI, 0.73-0.76]) and calibration (figure 3b). Analyses restricted to first-time admissions (n=102 762) showed similar results regarding discrimination (c-statistic 0.75 [95% CI, 0.74-0.77]) and calibration (data not shown).

External validation

There were 6388 (2.3%) cases of in-hospital CA recorded in the MINAP cohort (n=276 109). The vast majority of patients in the cohort (87%) had a final diagnosis of NSTE-ACS. The cumulative incidence of in-hospital CA was 2.3% in patients with NSTE-ACS and no ACS alike. Patients with in-hospital CA in the MINAP cohort compared with the SWEDEHEART derivation cohort were older (median 80 years vs. 75 years), but comparable with regards to a lower systolic blood pressure, lower hemoglobin level, and lower renal function, higher heart rate, and higher blood glucose level compared to those without in-hospital CA (supplementary table 3). The yearly incidence of in-hospital CA was higher for both NSTE-ACS and non-ACS than in SWEDEHEART (supplementary figure 2). Patients with a low sum of risk score points had a comparable risk of in-hospital CA regardless of a final diagnosis of NSTE-ACS or not. However, for patients with a sum of risk score points in the upper range, those without ACS were much higher risk (figure 2c and supplementary table 1a).

Discrimination was moderate (c-statistic 0.65 [95% CI, 0.65-0.66]) and the calibration plot showed a general underestimation of predicted risk (figure 3c). A sensitivity analysis including only complete cases regarding Killip class, but with imputed data regarding the remaining variables in the risk score model showed similar discrimination (c-statistic 0.67

[95% CI, 0.66-0.68] and had a similar calibration plot (supplementary figure 5). When adjusting for the underlying risk in the MINAP cohort by replacing $ß_0$, calibration was good in the lower range of sum of points, but with an increasing sum of points, a general overestimation of risk was observed (supplementary figure 6). Additional data on the MINAP cohort with complete cases only regarding Killip class is found in the supplementary material (supplementary tables 4-6 and supplementary figure 7).

Discussion

Our study confirms that CA is a rare, yet not negligible complication following hospitalization for NSTE-ACS, affecting 1.3-2.3% of patients. For patients admitted with suspected NSTE-ACS, this study shows that the risk of in-hospital CA may be estimated using the SAFER score, consisting of five clinical findings (systolic blood pressure, age, heart rate, ECG changes, and heart failure signs) readily available on admission to hospital. Discrimination of CA was good in the development and internal validation cohorts, though less so in the external validation cohort.

The CCU was introduced in the early 1960s, enabling patients with ACS to have continuous ECG monitoring where life-threating arrhythmias could be swiftly detected and treated by trained personnel[13]. With the development and improvement of care and outcomes for patients with ACS, questions have been raised about the need and cost effectiveness for low-risk patients to be admitted to the CCU[14]. Current guidelines recommend that patients with non-ST elevation myocardial infarction and low risk for arrhythmias could be initially monitored in a CCU or an intermediate care unit likewise[5]. van Diepen and colleagues reported that in a population based cohort of nearly 8000 patients with stable NSTE-ACS, the majority of patients (65%) were admitted to a CCU but had no differences in clinical outcomes compared with those hospitalized in a cardiology telemetry ward (35%)[15]. The SAFER score could help the clinician select higher-risk patients that may benefit from monitoring in a CCU and lower-risk patients where monitoring in a cardiology telemetry ward may be sufficient.

The usefulness of this point score for excluding patients without need for rhythm monitoring is probably limited. In the SWEDEHEART cohort the risk of in-hospital CA rarely fell below 0.5% and in the MINAP cohort, patients with 1 risk score point had more than 1% risk of in-hospital CA. However, equipment for heart rhythm monitoring is a scarce resource in many low- and middle-income countries[16]. In a limited resource setting, our point score could help decide who should be monitored. However, for any risk score model, it is important to consider the population under investigation and the underlying risk; application of the SAFER score to a different population would require an evaluation of underlying risk and external validation of the score.

We have not been able to evaluate the effect of the duration of cardiac monitoring, as the date and time of in-hospital CA was not recorded. However, in a study from Piccini and colleagues, patients with NSTE-ACS were as likely to have VT/VF after as before 48 hours and 38% had VT/VF after revascularization[2]. Therefore, a high-risk patient probably would benefit from extended monitoring and also here the SAFER score might aid in targeting patients.

Our findings are in concordance with a study by Goldman et al from 1996, which evaluated patients admitted with chest pain and the risk of in-hospital CA. Similar to our study, they found that five factors on admission (ST-segment elevation or Q-waves on initial ECG, ST-segment depression or T-wave inversion on initial ECG, systolic blood pressure below 110 mm Hg, pulmonary rales above the bases, and worsening of known ischemic heart disease) were predictive of major in-hospital complications including CA[17].

Although our study was based on a nationwide cohort of patients admitted with suspected NSTE-ACS, it has limitations. We were unable to differentiate between VT, VF and asystole/ pulseless electrical activity resulting in CA. There were missing data for in-hospital CA and CA prior to admission and for MINAP, Killip class was missing in a large proportion of patients, which could have decreased model discrimination. Data on timing of in-hospital CA were not available and the temporal relationship to revascularization could not be assessed. Notably, all study patients were admitted to a CCU because of suspected or confirmed NSTE-ACS and, therefore, patients with a final diagnosis of non-ACS cannot be compared to patients with undifferentiated chest patient in the emergency ward. This was particularly clear for the MINAP cohort, for whom non-ACS patients had an incidence of in-hospital CA equal to patients with NSTE-ACS.

Conclusion

We have shown that a simple risk score model, developed and validated in large national cohorts, including five easily accessible variables, predicts the risk of in-hospital CA for patients admitted with suspected NSTE-ACS and may help the clinician to choose proper level of surveillance.

Conflicts of interest

None

Acknowledgements

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FIGURE LEGENDS

Figure 1. Flow chart: Exclusion and inclusion criteria in the SWEDEHEART derivation cohort. One patient could have more than one exclusion criterion. STEMI, ST-elevation myocardial infarction; NSTE-ACS, non-ST elevation acute coronary syndrome; CA, cardiac arrest.

Figure 2a. Estimated risk, observed proportions of in-hospital cardiac arrest (CA) and distribution of patients per sum of risk score points in the SWEDEHEART derivation cohort. Total (n=242 303). No ACS (n=139 653). NSTE-ACS (n=102 650). CA, cardiac arrest; NSTE-ACS, non-ST elevation acute coronary syndrome.

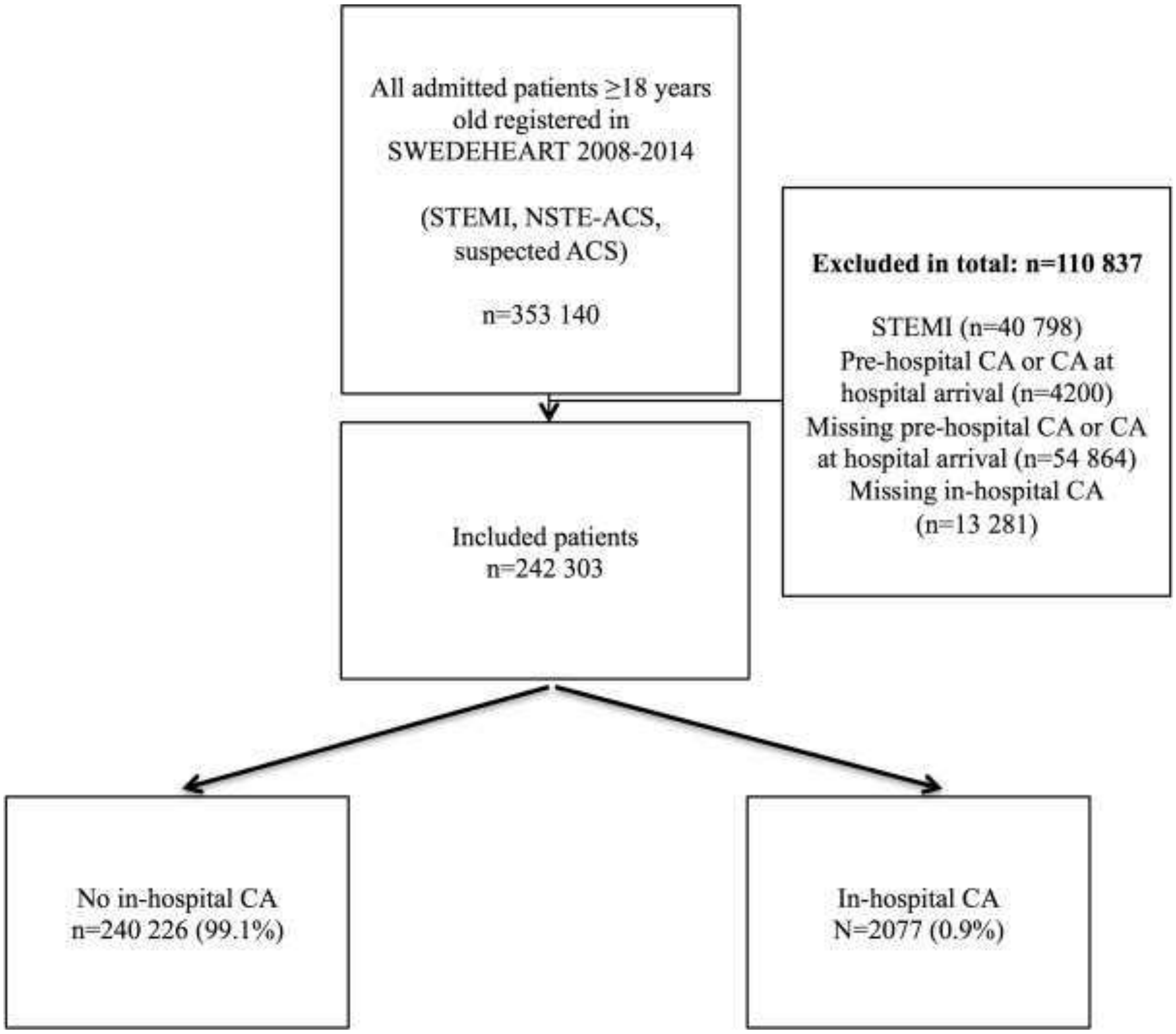
Figure 2b. Estimated risk, observed proportions of in-hospital cardiac arrest (CA) and distribution of patients per sum of risk score points in the SWEDEHEART temporal validation cohort. Total (n=126 073). No ACS (n=82 221). NSTE-ACS (n=43 852).

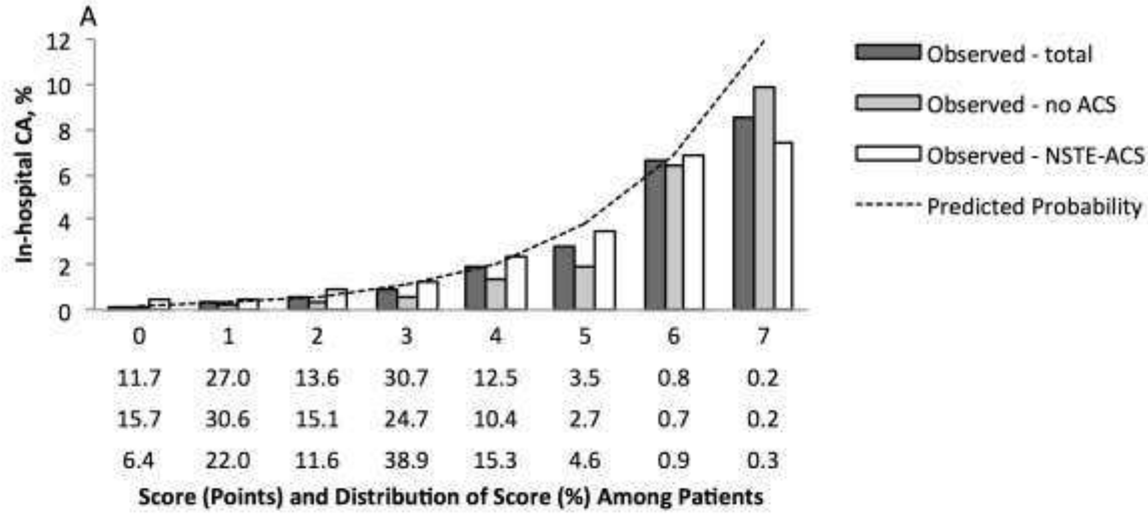
Figure 2c. Estimated risk, observed proportions of in-hospital cardiac arrest (CA) and distribution of patients per sum of risk score points in the MINAP validation cohort. Total (n=276 109). No ACS (n=36 131). NSTE-ACS (n=239 978).

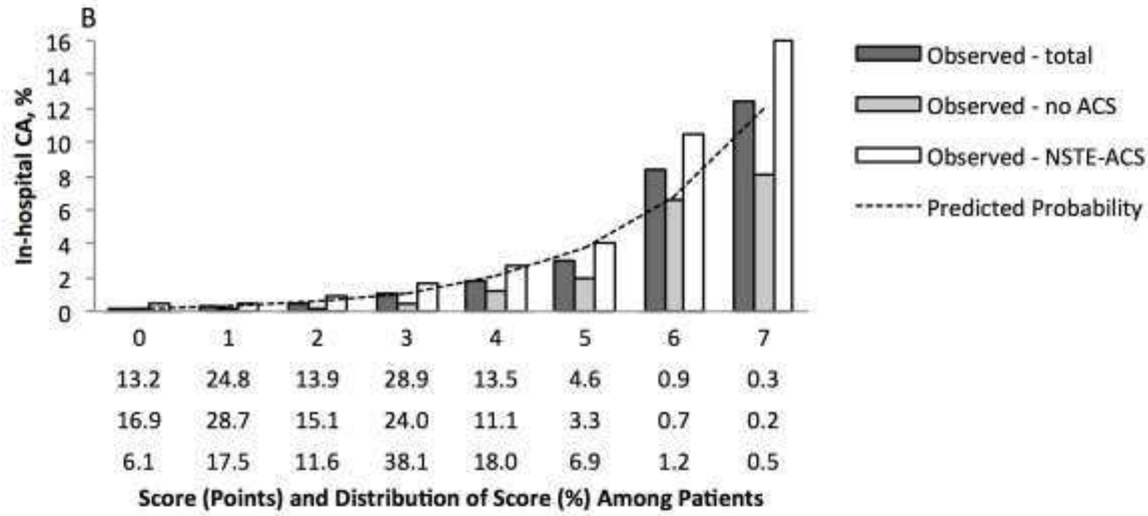
Figure 3a. Calibration plot and calculation of c-statistic for the SWEDEHEART derivation cohort 2008-2014. C-statistic over imputed data = 0.72 (95% CI 0.71-0.73).). CA, cardiac arrest.

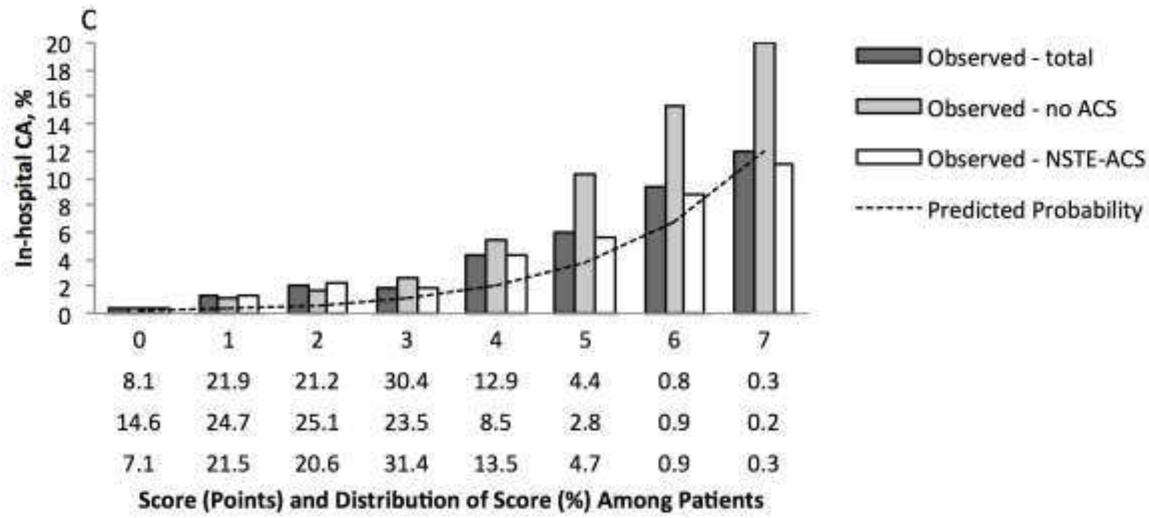
Figure 3b. Calibration plot and calculation of c-statistic for the SWEDEHEART temporal validation cohort 2005-2007. c-statistic over imputed data = 0.74 (95% CI 0.73-0.76)

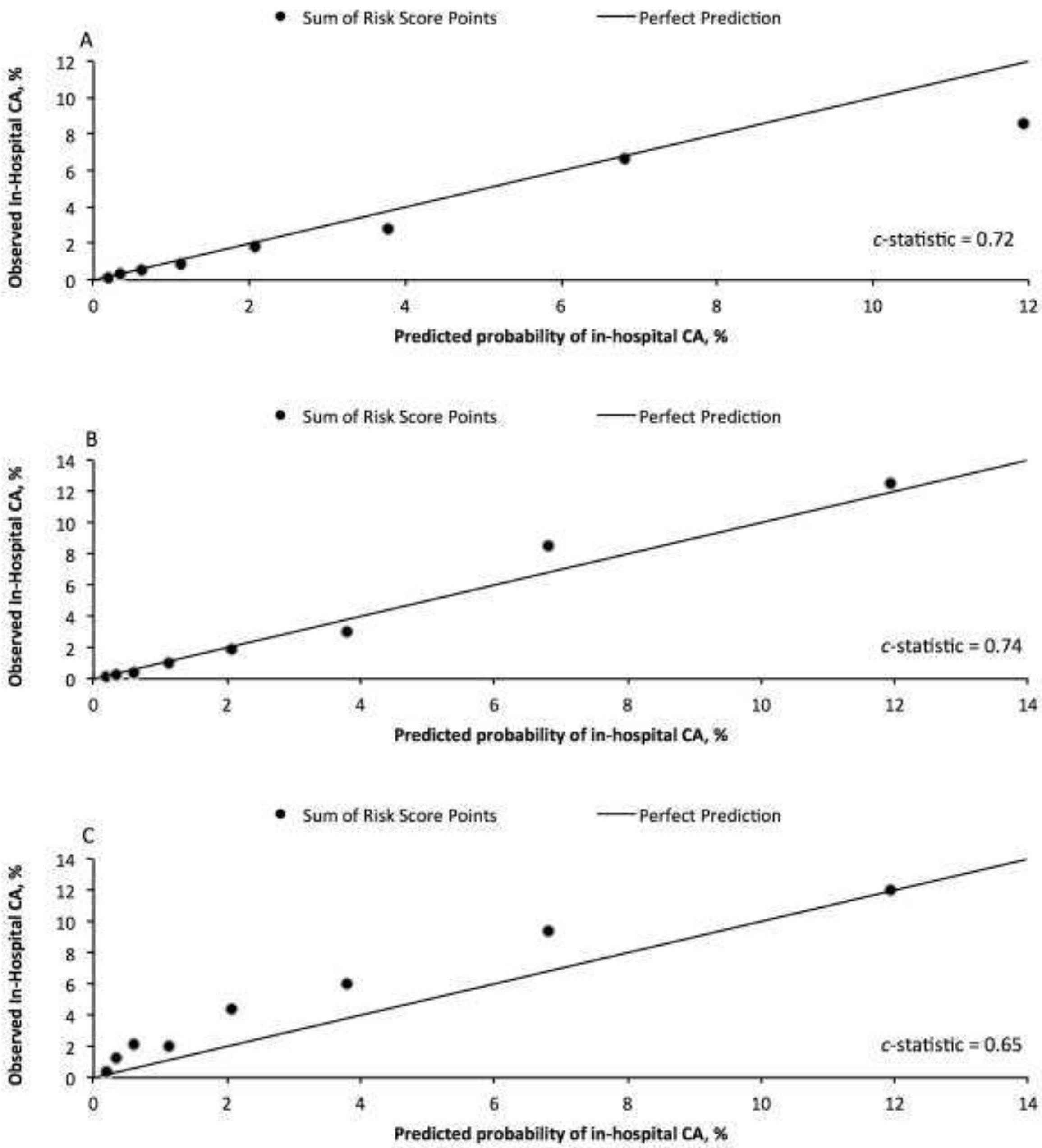
Figure 3c. Calibration plot and calculation of c-statistic for the MINAP validation cohort 2008-2013. c-statistic over imputed data = 0.65 (95% CI 0.65-0.66)


All admitted patients ≥18 years old registered in SWEDEHEART 2008-2014
(STEMI, NSTE-ACS, suspected ACS)
n=353 140
Excluded in total: n=110 837
STEMI (n=40 798)
Pre-hospital CA or CA at hospital arrival (n=4200)
Missing pre-hospital CA or CA at hospital arrival (n=54 864)
Missing in-hospital CA (n=13 281)
Included patients n=242 303
No in-hospital CA n=240 226 (99.1%)
In-hospital CA N=2077 (0.9%)


A
In-hospital CA, %
12
10
8
6
4
2
0
Observed - total
Observed - no ACS
Observed - NSTE-ACS
Predicted Probability
0 1 2 3 4 5 6 7
11.7 27.0 13.6 30.7 12.5 3.5 0.8 0.2
15.7 30.6 15.1 24.7 10.4 2.7 0.7 0.2
6.4 22.0 11.6 38.9 15.3 4.6 0.9 0.3
Score (Points) and Distribution of Score (%) Among Patients


B
In-hospital CA, %
16
14
12
10
8
6
4
2
0
Observed - total
Observed - no ACS
Observed - NSTE-ACS
Predicted Probability
0 1 2 3 4 5 6 7
13.2 24.8 13.9 28.9 13.5 4.6 0.9 0.3
16.9 28.7 15.1 24.0 11.1 3.3 0.7 0.2
6.1 17.5 11.6 38.1 18.0 6.9 1.2 0.5
Score (Points) and Distribution of Score (%) Among Patients


C
In-hospital CA, %
20
18
16
14
12
10
8
6
4
2
0
Observed - total
Observed - no ACS
Observed - NSTE-ACS
Predicted Probability
0 1 2 3 4 5 6 7
8.1 21.9 21.2 30.4 12.9 4.4 0.8 0.3
14.6 24.7 25.1 23.5 8.5 2.8 0.9 0.2
7.1 21.5 20.6 31.4 13.5 4.7 0.9 0.3
Score (Points) and Distribution of Score (%) Among Patients



Sum of Risk Score Points
Perfect Prediction
A
Observed In-Hospital CA, %
Predicted probability of in-hospital CA, %
c-statistic = 0.72
B
Observed In-Hospital CA, %
Predicted probability of in-hospital CA, %
c-statistic = 0.74
C
Observed In-Hospital CA, %
Predicted probability of in-hospital CA, %
c-statistic = 0.65

Table 1. Baseline characteristics for the SWEDEHEART derivation cohort

Characteristic	No cardiac arrest (n=240 226)	Cardiac arrest (n=2077)	Total (n=242 303)	Missing n (%)
Demographics				
Age, median (iqr), years	70 (60-79)	75 (66-82)	70 (60-79)	0 (0)
Men, n (%)	144 259 (60.1)	1337 (64.4)	145 596 (60.1)	0 (0)
Weight, median (iqr), kg	79 (68-90)	79 (68-90)	79 (68-90)	16 322 (6.7)
Presentation characteristics				
Systolic blood pressure, median (iqr), mmHg	147 (130-165)	130 (110-151)	147 (130-165)	5925 (2.4)
Diastolic blood pressure, median (iqr), mmHg	81 (71-92)	78 (65-90)	81 (71-92)	10 026 (4.1)
Heart rate, median (iqr), bpm	76 (65-91)	87 (70-110)	76 (65-91)	3030 (1.3)
Killip class > I, n (%)	24 389 (10.4)	526 (26.3)	24 915 (10.5)	5556 (2.3)
ST-T abnormalities, n (%)	125 254 (53.5)	1597 (79.8)	126 851 (53.7)	5985 (2.5)
eGFR, CKD-EPI, median (iqr), mL/min per 1.73 m^2	76.4 (56.8-90.9)	56.6 (37.9-79.0)	76.3 (56.7-90.9)	18 477 (7.6)
Glucose, median (iqr), mmol/L	6.5 (5.6-8.1)	8.3 (6.5-11.3)	6.5 (5.6-8.2)	47 516 (19.6)
Hemoglobin, median (iqr), g/L	138 (126-148)	131 (118-144)	137 (126-148)	24 011 (9.9)
Medical history				
Current smoker, n (%)	36 457 (16.4)	299 (17.2)	36 756 (16.4)	18 333 (7.6)
Hypertension, n (%)	143 352 (59.7)	1351 (65.0)	144 703 (59.7)	0 (0)
Diabetes mellitus, n (%)	58 025 (24.2)	682 (32.8)	58 707 (24.2)	0 (0)
Prior heart failure, n (%)	40 849 (17.0)	561 (27.0)	4141 (2.0)	0 (0)
Prior myocardial infarction, n (%)	87 414 (36.4)	890 (42.9)	88 304 (36.4)	0 (0)
Prior PCI, n (%)	60 671 (25.3)	464 (22.3)	61 135 (25.2)	0 (0)
Prior CABG, n (%)	29 854 (12.4)	362 (17.4)	30 216 (12.5)	0 (0)
Prior stroke, n (%)	29 977 (12.5)	362 (17.4)	30 339 (12.5)	0 (0)
Prior peripheral vascular disease, n (%)	15 487 (6.4)	220 (10.6)	15 707 (6.5)	0 (0)
Prior chronic obstructive pulmonary disease, n (%)	20 144 (8.4)	227 (10.9)	20 371 (8.4)	0 (0)
Medication at admission				
Aspirin, n (%)	114 357 (47.8)	1019 (49.8)	115 376 (47.8)	975 (0.4)
Beta-blocker, n (%)	119 014 (49.8)	1137 (55.7)	120 151 (49.8)	1127 (0.5)
ACE-inhibitor or ARB, n (%)	103 367 (43.2)	980 (48.0)	104 347 (43.2)	1018 (0.4)
Calcium antagonist, n (%)	47 657 (19.9)	468 (22.9)	48 125 (20.0)	1142 (0.5)
Statin, n (%)	100 189 (41.9)	863 (42.2)	101 052 (41.9)	1026 (0.4)
Oral antidiabetic, n (%)	27 912 (11.7)	282 (13.8)	28 194 (11.7)	867 (0.4)
Insulin, n (%)	25 843 (10.8)	344 (16.8)	26 187 (10.8)	882 (0.4)
Variables in the risk score				
Systolic blood pressure < 100 mmHg, n (%)	5658 (2.4)	235 (12.0)	5893 (2.5)	5925 (2.4)

Age ≥60 years, n (%)	182 943 (76.2)	1851 (89.1)	184 794 (76.3)	0 (0)
Frequency of heart rate <50 or ≥100 bpm, n (%)	48 420 (20.4)	864 (42.5)	49 284 (20.6)	3030 (1.3)
Ecg, changes (ST-T abnormalities) n (%)	125 254 (53.5)	1597 (79.8)	126 851 (53.7)	5985 (2.5)
Rales (Killip >1), n (%)	24 389 (10.4)	526 (26.3)	24 915 (10.5)	5556 (2.3)

Bpm: beats per minute; Iqr: interquartile range; eGFR: estimated Glomerular Filtration Rate; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery By-Pass Grafting; ACE: Angiotensin Converting Enzyme. ARB: Angiotensin II Receptor Blocker.

Table 2. Variables included in the final risk score model

	Predictor	$ß_i$**	Points***	Point total	Estimate of risk****
Intercept ($ß_0$)		-6.32761		0	0.18
Systolic	Systolic BP <100 mmHg	1.29782	2	1	0.33
Age*	Age ≥60	0.61853	1	2	0.61
Frequency	Heart rate <50 or ≥100 bmp	0.73144	1	3	1.13
Ecg	ST-T abnormalities	0.97011	2	4	2.08
Rales	Killip class >1	0.60985	1	5	3.79
				6	6.81
				7	11.94

*defined as constant B; **estimated regression coefficient; ***Points= $ß_i$ / B rounded to the nearest integer; **** sum of ($ß_0$ + point total x B) transformed with the logistic function