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Predictors of one-year mortality at hospital discharge after acute coronary syndromes: A new risk score from the EPICOR (long-term follow up of antithrombotic management patterns in acute CORonary syndrome patients) study

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Abstract
Aims: A reliable prediction tool is needed to identify acute coronary syndrome (ACS) patients with high mortality risk after their initial hospitalization.
Methods: EPICOR (long-term follow up of antithrombotic management patterns in acute CORonary syndrome patients: NCT01171404) is a prospective cohort study of 10,568 consecutive hospital survivors after an ACS event (4943 ST-segment elevation myocardial infarction (STEMI) and 5625 non-ST-elevation ACS (NSTEMI)). Of these cases, 65.1% underwent percutaneous coronary intervention (PCI) and 2.5% coronary artery bypass graft (CABG). Post-discharge mortality was recorded for up to two years. From over 50 potential predictor variables a new risk score for one-year mortality was developed using forward stepwise Cox regression, and examined for goodness-of-fit, discriminatory power, and external validation.
Results: A total of 407 patients (3.9%) died within one year of discharge. We identified 12 highly significant independent predictors of mortality (in order of predictive strength): age, lower ejection fraction, poorer EQ-5D quality of life, elevated serum creatinine, in-hospital cardiac complications, chronic obstructive pulmonary disease, elevated blood glucose, male gender, no PCI/CABG after NSTE-ACS, low hemoglobin, peripheral artery disease, on diuretics at discharge. When combined into a new risk score excellent discrimination was achieved (c-statistic=0.81) and this was also validated on a large similar cohort (9907 patients) in Asia (c=0.78). For both STEMI and NSTE-ACS there was a steep gradient in one-year mortality ranging from 0.5% in the lowest quintile to 18.2% in the highest decile. NSTE-ACS contributes over twice as many high-risk patients as STEMI.
Conclusions: Post-discharge mortality for ACS patients remains of concern. Our new user-friendly risk score available on www.acsrisk.org can readily identify who is at high risk.

Keywords
Acute coronary syndrome, hospital discharge, mortality, prognostic model, risk score

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Introduction

Secondary prevention following an acute coronary syndrome (ACS) event is key as further ischemic events are common following the index event. Risk prediction tools have identified a number of factors which impact on risk of death and myocardial infarction (MI) following an ACS event. However, patient prognosis at hospital discharge continues to vary markedly, and post-discharge mortality remains a concern. Most risk scores include hospital mortality in their estimations. There are no tools for risk calculation of one-year mortality in hospital survivors. It is usually at the time of discharge that patients are asking about their prognosis. Therefore, there is a need for a reliable prediction tool to identify patients with high mortality risk, which may ultimately allow tailored treatment decisions and improve prognosis. For instance, patients identified as at high risk may receive more frequent follow-up visits to facilitate their optimal care.

For patients experiencing an acute coronary event, a crucial time to assess their prognosis and future management is at discharge from hospital. Hence, there is merit in developing a risk model that utilizes all the patient data on demographics, medical history, and patient status at, and during, admission, and at discharge. From a large representative international cohort study of consecutive patients with ACS who survived to discharge, we have related such detailed patient records to their subsequent follow-up for one year, expressing prognosis in terms of one-year mortality.

While ST segment elevation myocardial infarction (STEMI) and non-ST-elevation ACS (NSTE-ACS) patients have very different management and prognosis patterns during the in-hospital phase, from the moment of hospital discharge there is sufficient common ground and similarity of the key risk factors to combine both sets of patients into a single overall risk model.

There is an extensive literature on risk scores in ACS, and their use is advocated by the European Society of Cardiology (ESC) guidelines for the management of NSTE-ACS. However, relatively little attention has been paid to risk assessment at hospital discharge, with just one previous risk score to date regarding six-month mortality post discharge. This is a valuable opportunity to quantify individual patient risk of mortality to one year after discharge following an acute coronary event hospitalization.

Methods

EPICOR (long-tErm follow uP of antithrombotic management patterns In acute CORonary syndrome patients) is a prospective, international, observational, real-world practice, cohort study (NCT01171404) comprising consecutive patients, hospitalized for ACS within 24 h of symptom onset, who survived to hospital discharge.

In total, 10,568 patients with non-fatal ACS who survived until hospital discharge were enrolled between September 2010–March 2011 from 555 hospitals in 20 countries across Europe and Latin America. A detailed account of the methodology of the study is described elsewhere.

For external validation of our risk model, we used data from the EPICOR-Asia study (NCT01361386) which enrolled 12,993 patients from eight Asian countries from June 2011–April 2012. This Asian study has followed an almost identical protocol and case record forms as in our EPICOR study.

Statistical methods

We identified over 50 candidate variables for prediction (patient history, at admission, during admission, and at discharge), and these are listed in Appendix 1. From these a new risk score for one-year mortality post discharge was developed using Cox proportional hazard models. The statistical approach for model building was forward stepwise variable selection, with a criterion of $p<0.01$ for variable inclusion. For continuous predictors, checks were undertaken for non-linearity and, if found appropriate, remodelling of such variables was conducted e.g. either using a binary cut-off (e.g. hemoglobin, blood glucose) or by expressing as a linear trend above a certain level (e.g. serum creatinine). In combining predictors for patients with STEMI and with NSTE-ACS it is important to explore evidence of statistical interactions with other predictors. On the whole, most variables selected showed a similar magnitude of risk prediction for both STEMI and NSTE-ACS patients. The one exception was that the increased risk of not receiving coronary revascularization during hospitalization was more marked in NSTE-ACS patients.

Some prognostic variables were missing in a small minority of patients. To overcome this problem, thereby enabling all patients’ available data to be validly used, a multiple imputation method was used based on a recently developed extension of the chained equations approach.

Most predictor variables identified (see Table 1) are well understood, but the novel use of the EuroQoL EQ-5D requires explanation. This questionnaire evaluates five issues: patient mobility, self-care, usual activities, pain/discomfort and anxiety/depression. For each there is specific wording to elicit whether the patient has no, moderate, or severe limitation. For each we have scored 0, 1 or 2 points respectively, and adding up these scores yields a simple overall score ranging from 0 points up to a maximum of 10 points. While there do exist more complex weighted schemes for handling the EQ-5D, we feel that for practical use in our context of user-friendly risk prediction this required the adoption of such simple scoring.

The multiple imputations were performed using Stata 12.0 while all other analyses used SAS version 9.2.
Results

The study cohort comprises 10,568 consecutive hospital survivors after an ACS event (4943 STEMI and 5625 NSTE-ACS). Four hundred and seven patients (3.9%) died within one year of discharge while 242 (2.3%) were lost to follow-up.

From all of the candidate variables available, a Cox proportional hazard model was used with forward stepwise variable selection to identify 12 highly significant independent predictors of one-year mortality. These are described in Table 1 along with geographic region.

Table 2 presents the multivariable predictive model which simultaneously uses all 12 risk variables to produce
Variables in Table 2 are listed in order of their statistical significance (age is the strongest predictor) and each hazard ratio is adjusted for all the other variables. One statistical interaction was identified: for NSTE-ACS patients only, those who received percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) during this admission had a lower mortality than those on medication only. For continuous variables, potential non-linearity in the prediction of survival was explored. Hence the increasing impact of serum creatinine on mortality was confined to values above 1.2 mg/dl while for blood glucose and hemoglobin binary cut-offs of ≥160 mg/dl and <13 g/dl were respectively used.

Figure 1 displays the independent impact of each predictor on mortality risk. In addition, there remain substantial regional differences in one-year mortality not explained by these predictors: Eastern Europe and Latin American have adjusted hazard ratios of 2.15 and 2.10, respectively, compared with Western Europe (North).

From the risk coefficients in Table 2, the multivariable risk score is readily calculated for each patient and its distribution (×10) is shown in Figure 2. The curve in Figure 2 relates a patient’s score to the probability of dying within one year of discharge. Good discrimination is achieved with c-statistic=0.81.

Figure 3 shows the cumulative mortality over one year for patients classified into six risk groups. Groups 1–4 comprise the bottom four quintiles of risk while groups 5 and 6 are the top two deciles of risk. While all six groups are clearly separated, the absolute magnitude of differences between risk groups is much more marked for the top two deciles, with 6.3% and 18.2% one-year mortality, respectively. This contrasts with 0.5% one-year mortality in the lowest quintile.

Regarding model goodness-of-fit, Figure 4(a) compares observed and model-predicted one-year mortality risk across the six risk groups.

Table 3 shows two separate models for STEMI and NSTE-ACS patients. For nearly all predictors, the strength of mortality association is similar in both subgroups. However, the lower risk if coronary revascularization occurred during admission is more notable in NSTE-ACS patients, and this statistical interaction is captured in the main predictive model in Table 2.

For STEMI patients we investigated the impact of rapid time to admission (or time to reperfusion) on reducing mortality after discharge. There were 697 STEMI patients (14%) admitted within one hour of symptom onset: hazard ratio 0.44 (p=0.026) compared to other STEMI patients. Also, 1316 STEMI patients (27%) had reperfusion within two hours of symptom onset: hazard ratio 0.64 (p=0.053) compared to other STEMI patients. These findings were of borderline statistical significance so these two variables were not included in the main predictive model.

In order to validate our main model on an external cohort, we used the 9907 patients in the EPICOR Asia registry who had complete data on all variables listed in Table 2, of whom 3.1% died within one year of hospital discharge. Figure 4(b) compares the observed and model-predicted one-year mortality risk across the six risk groups (from lowest quintile to top decile). The model fit and extent of risk discrimination is very similar to what was found in our original cohort. The c-statistic in EPICOR Asia patients is 0.784, only slightly less than the c=0.81 achieved in model development.

| Variable | All patients |
|----------|--------------|
| Coefficient | HR | 95% CI | p-value |
| Age (per 10 years) | 0.43 | 1.54 | 1.40–1.70 | <0.00001 |
| Ejection fraction <40%a | 0.62 | 1.87 | 1.42–2.46 | <0.0001 |
| Ejection fraction <30%a | 1.35 | 3.84 | 2.80–5.27 | <0.0001 |
| EQ-5D score (per unit) | 0.15 | 1.16 | 1.10–1.21 | <0.0001 |
| Serum creatinine (per unit ≥1.2 mg/dl)a | 0.22 | 1.25 | 1.13–1.38 | <0.0001 |
| Cardiac complication in hospital | 0.41 | 1.50 | 1.21–1.86 | 0.0002 |
| Blood glucose ≥160 mg/dla | 0.39 | 1.48 | 1.19–1.84 | 0.0004 |
| COPD | 0.52 | 1.68 | 1.26–2.24 | 0.0004 |
| Male gender | 0.40 | 1.49 | 1.18–1.89 | 0.0009 |
| NSTE-ACS with meds onlyb | 0.39 | 1.47 | 1.17–1.86 | 0.0012 |
| NSTE-ACS with PCI/CABGb | -0.22 | 0.80 | 0.61–1.05 | 0.1117 |
| Hemoglobin <13 g/dla | 0.35 | 1.42 | 1.13–1.80 | 0.0029 |
| Peripheral vascular disease | 0.45 | 1.57 | 1.17–2.10 | 0.0029 |
| On diuretics at discharge | 0.30 | 1.35 | 1.08–1.70 | 0.0095 |

CABG: coronary artery bypass graft; CI: confidence interval; COPD: chronic obstructive pulmonary disease; HR: hazard ratio; NSTE-ACS: non-ST-elevation ACS; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

aAt admission; bAs compared to STEMI.
Figure 1. Mortality hazard ratios for each variable in the predictive model. CABG: coronary artery bypass graft; CI: confidence interval; COPD: chronic obstructive pulmonary disease; NSTE-ACS: non-ST-elevation acute coronary syndrome; PCI: percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction.
Discussion

The findings we present are based on a large international prospective real-world cohort study comprising consecutive patients hospitalized from an ACS event within 24 h of symptoms onset who survived to hospital discharge. Such a representative population across Europe and Latin America is therefore uniquely well placed to quantify the independent determinants of mortality risk over one year post-discharge.

The 12 highly significant predictors we identified should all be readily available in routine clinical practice. To facilitate the quantification of individual risk we provide a web calculator www.acsrisk.org thus avoiding the burden of numerical calculations.

There is a marked identifiable variation in individual patient risk (see Figure 4). This means a sizeable proportion of patients can be classified as low risk, e.g. around half have a one-year mortality risk <1%. On the other hand 10% of patients have a high one-year mortality risk (see Figures 2 and 3). Knowing this fact, based on our risk model, should help in supporting appropriate patient management.

The contributions made by each specific predictor are worth noting. Not surprisingly, age has the most profound influence on mortality risk, followed by reduced ejection fraction. A more novel contributor to risk assessment is quality of life at discharge, using a simple score derived from the EuroQoL EQ-5D. Across five aspects (mobility, self-care, usual activities, pain/discomfort, anxiety/discomfort) we add one point for moderate impairment or two points for severe impairment. Patients scoring four points or more (11%) had more than double the mortality risk of patients with no impairment (45%), with a gradient of risk for patients in between these two extremes. Thus, a poor functional quality of life may be expressing some level of frailty and a mortality risk that is not captured by other predictors.

The 4943 STEMI patients had a lower one-year mortality after discharge compared to the 5625 NSTE-ACS patients: 3.1% vs 4.5% died, respectively. However, after adjustment for the other 11 risk factors, the hazard ratio became 1.00 (95% CI 0.80–1.24). This reflects that NSTE-ACS had a higher prevalence of other risk factors (see Table 1). Indeed, NSTE-ACS contributes over twice as many patients in the top decile of risk compared to STEMI. However, for NSTE-ACS patients only, one notable contributor to risk was not having PCI or CABG during hospital stay: hazard ratio 1.84 after adjustment for other risk factors. Thus, lack of coronary revascularization reflects an anticipated poorer prognosis post-discharge. This may be
explained by either the actual risk benefit of coronary revascularization or selection bias (i.e. poor risk patients are deemed not appropriate for intervention). From blood samples at admission, contributions to higher risk are represented by raised creatinine, raised glucose and lower hemoglobin. For disease history, both chronic obstructive pulmonary disease and peripheral vascular disease increased risk, indicating that conditions other than cardiac disease carry a mortality risk. Cardiac complications during the admission were associated with a 50% increase in mortality risk. Cardiac complications during the admission were associated with a 50% increase in mortality risk. Also, men had a 50% higher risk than women after all other risk factors were accounted for. In univariate analysis women have a higher one-year mortality than men (4.3% vs 3.7%). But women are more prone to having other risk factors (e.g. older age) so that in the multivariable model being female independently predicts a lower risk. Lastly, being on diuretics at discharge was an indicator of 35% higher mortality risk.

Confidence in the generalizability of any new risk model is much enhanced if it is validated on an external population. Here, the EPICOR Asia study has provided similar risk discrimination and goodness of fit (compare the two plots in Figure 4), as summarized by the c-statistic of 0.78 in Asian patients compared to 0.81 in the original cohort. Given that the two studies were from different geographic regions, this provides assurance that our risk model may well be of global applicability.

In external validation some reduction in c-statistic is always to be expected on statistical grounds i.e. risk coefficients in any model are optimized by the maximum likelihood principle of any model fit, so the true strength of prediction is inevitably slightly less in another independent data set. To further explore model fit in the Asian cohort we did another Cox regression model with the same 12 predictor variables: the hazard ratios of all but one variable were very similar to those reported in our original EPICOR model (Table 2). The one exception was peripheral vascular disease which was very uncommon in the Asian cohort so that its hazard ratio had a wide CI. This consistency of findings suggests that there is little effect of ethnic diversity on risk prediction.

While there exist several other risk scores for patients with ACS, most do not focus on risk from the time of hospital discharge and hence are not appropriate for comparison here. However, Eagle et al. have used the Global Registry of Acute Coronary Events (GRACE) registry to estimate mortality risk six months post discharge. Their risk calculator includes nine predictors: age, history of congestive heart failure, history of MI, increased heart rate at admission, lower systolic blood pressure at admission, elevated serum creatinine at admission, elevated cardiac enzymes, ST-segment depression, and no in-hospital PCI. This achieved a similar predictive strength to the current model (c-statistic = 0.81 at development, 0.75 at validation). However, the shorter time period could be a limiting factor. Their six-month mortality rate (4.8%) is higher than our one-year mortality rate (3.9%), perhaps reflecting the fact that their cohort is from around 10 years ago. Also, the mortality rate in EPICOR might not include high-risk patients transferred to other units for non-cardiac complications or needing longer-term care. It would be useful if the GRACE and EPICOR risk models were directly compared in an independent cohort of ACS patients followed from hospital discharge.

There are some limitations inherent to our risk model. Being a study on hospital survivors, blood pressure and

| Variable                                      | STEMI patients |                 | NSTE–ACS patients |                 |
|-----------------------------------------------|----------------|-----------------|-------------------|-----------------|
| Age (per 10 years)                            | 1.56           | 1.34–1.80       | 1.52              | 1.34–1.73       |
| Ejection fraction <40%                        | 1.42           | 0.89–2.27       | 2.29              | 1.62–3.24       |
| Ejection fraction <30%                        | 3.73           | 2.17–6.41       | 4.03              | 2.69–6.02       |
| EQ-5D score (per unit)                        | 1.18           | 1.09–1.28       | 1.14              | 1.07–1.22       |
| Serum creatinine (per unit ≥1.2 mg/dl)        | 1.27           | 1.04–1.55       | 1.23              | 1.09–1.38       |
| Cardiac complication in hospital              | 1.15           | 0.80–1.65       | 1.73              | 1.33–2.27       |
| Blood glucose ≥160 mg/dl                      | 1.29           | 0.91–1.84       | 1.64              | 1.24–2.16       |
| COPD                                          | 1.60           | 0.96–2.68       | 1.71              | 1.20–2.43       |
| Male gender                                   | 1.47           | 0.98–2.22       | 1.54              | 1.14–2.06       |
| PCI/CABG during admission                     | 0.73           | 0.52–1.04       | 0.52              | 0.40–0.69       |
| Hemoglobin <13 g/dl                           | 1.57           | 1.05–2.35       | 1.33              | 1.00–1.78       |
| Peripheral vascular disease                   | 1.47           | 0.76–2.86       | 1.55              | 1.10–2.18       |
| On diuretics at discharge                     | 1.43           | 0.97–2.11       | 1.29              | 0.97–1.73       |

CABG: coronary artery bypass graft; CI: confidence interval; COPD: chronic obstructive pulmonary disease; HR: hazard ratio; PCI: percutaneous coronary intervention. *At admission.
Conflict of interest

S Pocock has received research funding from AstraZeneca; H Bueno has received advisory/consulting fees from AstraZeneca, Bayer, BMS, Daichii-Sankyo, Eli-Lilly, Novartis, Pfizer, Sanofi, and Roche, and grants from AstraZeneca; M Licour, J Medina, and L Zhang are employees of AstraZeneca; L Annemans has received consulting and lecture fees from AstraZeneca; N Danchin has received consulting or speaking fees from AstraZeneca, BMS, Boehringer-Ingehelm, GSK, MSD-Schering Plough, Novartis, Pierre Fabre, Pfizer, Roche, Sanofi-Aventis, Servier, Takeda, and The Medicines Company; Y Huo has nothing to disclose; F Van de Werf has received consulting fees and research grants from Boehringer Ingelheim and Merck, and consulting fees from Roche, Sanofi-Aventis, AstraZeneca, and The Medicines Company.

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**Appendix 1. A list of candidate predictor variables**

| Demographics and medical history | Variables collected during admission |
|----------------------------------|------------------------------------|
| Gender                           | Time from symptom onset to admission |
| Age                              | Time from admission to reperfusion |
| Race                             | Time from symptom onset to reperfusion |
| Education level                  | Length of hospital stay |
| Professional status              | Killip class |
| Height                           | Diagnosis (STEMI, NSTEMI, unstable angina) |
| Weight                           | Left bundle branch block |
| Body mass index                  | Ejection fraction<sup>a</sup> |
| Hypertension                     | White blood count<sup>o</sup> |
| Hypercholesterolemia             | Creatinine<sup>a</sup> |
| Diabetes                         | Glucose<sup>a</sup> |
| Family history of CAD            | Hemoglobin<sup>a</sup> |
| Smoking                          | PCI during admission |
| Previous MI                      | CABG during admission |
| Prior PCI                        | Reperfusion (PCI at thrombolysis) |
| Prior CABG                       | No. of dilated vessels |
| Chronic angina                   | Any drug eluting stent |
| Prior heart failure              | No. of antiplatelets<sup>b</sup> |
| Prior atrial fibrillation        | Anticoagulant<sup>b</sup> |
| Prior transient ischemic attack/stroke | Beta blocker<sup>b</sup> |
| Prior peripheral vascular disease | Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker<sup>b</sup> |
| Chronic renal failure            | Diuretics<sup>b</sup> |
| COPD or other chronic lung disease | Aldosterone inhibitor<sup>b</sup> |
|                                 | Calcium-channel blocker<sup>b</sup> |
|                                 | Ischemic complications |
|                                 | Cardiogenic shock |
|                                 | Heart failure |
|                                 | Dyspnea |
|                                 | Arrhythmia |
|                                 | Dependence at discharge |
|                                 | EQ-5D overall health state at discharge |
|                                 | EQ-5D simple score at discharge |

<sup>COPD</sup>: chronic obstructive pulmonary disease;
<sup>a</sup>At admission; <sup>b</sup>at discharge.