**Machine learning-based prediction of adverse events following an acute coronary syndrome (PRAISE): a modelling study of pooled datasets**

# Machine learning-based prediction of adverse events following an acute coronary syndrome (PRAISE): a modelling study of pooled dataset

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**Summary**

**Background**

The accuracy of current prediction tools for ischaemic and bleeding events after an acute coronary syndrome (ACS) remains insufficient for individualised patient management strategies. We developed a machine learning-based risk stratification model to predict all-cause death, recurrent acute myocardial infarction, and major bleeding after ACS.

**Methods**

Different machine learning models for the prediction of 1-year post-discharge all-cause death, myocardial infarction, and major bleeding (defined as Bleeding Academic Research Consortium type 3 or 5) were trained on a cohort of 19 826 adult patients with ACS (split into a training cohort [80%] and internal validation cohort [20%]) from the BleeMACS and RENAMI registries, which included patients across several continents. 25 clinical features routinely assessed at discharge were used to inform the models. The best-performing model for each study outcome (the PRAISE score) was tested in an external validation cohort of 3444 patients with ACS pooled from a randomised controlled trial and three prospective registries. Model performance was assessed according to a range of learning metrics including area under the receiver operating characteristic curve (AUC).

**Findings**

The PRAISE score showed an AUC of 0·82 (95% CI 0·78–0·85) in the internal validation cohort and 0·92 (0·90–0·93) in the external validation cohort for 1-year all-cause death; an AUC of 0·74 (0·70–0·78) in the internal validation cohort and 0·81 (0·76–0·85) in the external validation cohort for 1-year myocardial infarction; and an AUC of 0·70 (0·66–0·75) in the internal validation cohort and 0·86 (0·82–0·89) in the external validation cohort for 1-year major bleeding.

**Interpretation**

A machine learning-based approach for the identification of predictors of events after an ACS is feasible and effective. The PRAISE score showed accurate discriminative capabilities for the prediction of all-cause death, myocardial infarction, and major bleeding, and might be useful to guide clinical decision making.

**Funding**
None.

***Research in context***

**Evidence before this study**

Prediction of all-cause death in patients with acute coronary syndrome (ACS) has relevant implication on post-discharge follow-up and treatment approaches. Similarly, ischaemic and bleeding events after an ACS can also severely affect patient prognosis. We searched PubMed on July 30, 2020, without language or date restrictions for publications about risk scores validated to predict mortality along with bleeding and thrombotic risks in patients with ACS. We used the search terms “acute coronary syndrome”, “percutaneous coronary intervention”, “risk score”, “mortality risk score”, “bleeding risk score”, “thrombotic risk score”, and “antiplatelet therapy”. We excluded articles reporting only multivariate predictors without prediction score, papers referring only to antithrombotic management for patients with a concomitant indication to oral anticoagulation, risk prediction models for only in-hospital outcomes, and those without a validation cohort. Currently available scores conceived and validated to predict patients' mortality after all types of ACS (ie, the GRACE and TIMI risk scores) were mostly derived on cohorts of patients not treated with contemporary standards of care. Current guidelines support the use of dedicated scores (ie, PRECISE-DAPT and DAPT scores) to tailor the intensity and duration of dual antiplatelet therapy (DAPT) strategy according to the offsetting risk of ischaemia and bleeding. Nonetheless, such scores were derived from unselected cohorts of patients mostly treated with clopidogrel after percutaneous revascularisation both for stable coronary artery disease and ACS, thus limiting their accuracy in external cohorts and their applicability in clinical practice. Furthermore, all of these scores are based on linear models applied to variables frequently based on a-priori assumption. The feasibility and the effectiveness of a machine learning-based prognostic risk assessment in this setting has never been explored before.

**Added value of this study**

We developed and externally tested the PRAISE score, a machine learning-based model to predict the risk of 1-year post-ACS all-cause death, recurrent myocardial infarction, and major bleeding. The model was derived from a contemporary cohort of patients treated with percutaneous coronary intervention for ACS and treated according to current guidelines recommendation on DAPT. The PRAISE score showed excellent predictive abilities for all the explored endpoints both in the derivation and external validation cohort. To highlight the clinical implication of the risk estimated by the model, we suggested a stratification into three classes (low, intermediate, and high) entailing a clinically significant increase in the risk of event occurrence. According to such classification, the PRAISE scores would classify almost 10% of patients as being at high risk of 1-year post-discharge ischaemic and bleeding events, thus being candidates for a tighter follow-up. Furthermore, patients deemed at high ischaemic risk according to the PRAISE score showed a consistent prevailing ischaemic risk, regardless of their bleeding risk class, which could potentially be used to identify patients who would benefit most from an extended DAPT strategy. By contrast, patients with intermediate-to-high bleeding risk and a low ischaemic risk would benefit from a shortened DAPT strategy.

**Implications of all the available evidence**

In the setting of risk assessment, the machine learning approach offers a way to overcome the shortcomings of existing methods by applying computer algorithms to large datasets and capturing non-linear relationships between clinical variables. The PRAISE score is a bedside risk assessment tool that could be easily implemented in everyday clinical practice to predict patients' prognosis after ACS, along with their risk of ischaemic and bleeding events. This instrument has the potential to support clinical decision making with respect to antithrombotic treatments and follow-up planning, thus addressing the unmet need for tailored care after percutaneous coronary intervention.

## *Introduction*

Patients with acute coronary syndrome (ACS) are at high risk for ischaemic and bleeding events, with both being drivers of adverse prognosis.[1] Careful evaluation of these risks plays a fundamental role in the clinical management of each patient, with important implications regarding the choice of optimal medical therapy for secondary prevention.[2-6]

To this aim, several predictive tools have been developed to estimate ischaemic and bleeding risks following an ACS, some of which have potential to support clinical decision making around the optimal duration of dual antiplatelet therapy (DAPT).[7-11] However, the overall accuracy of these scores, along with their generalisability to external cohorts, remains modest, representing an unmet need for individualised patient management strategies.[12,13]

From a clinical standpoint, the poor performance of existing risk scores among patients with ACS might be related to their derivation from unselected percutaneous coronary intervention populations encompassing patients with stable presentation. Moreover, machine learning methods might be able to overcome some of the limitations of current analytical approaches to risk prediction by applying computer algorithms to large datasets with numerous, multidimensional variables, capturing high-dimensional, non-linear relationships among clinical features to make data-driven outcome predictions.[14] The effectiveness of this approach has been shown in several cardiovascular applications, where machine learning was superior to validated traditional risk stratification tools, including prediction of death among patients with suspected coronary artery disease or of heart failure in candidates for cardiac resynchronisation therapy.[15,16] Thus, we sought to develop a machine learning-based risk stratification model integrating clinical, anatomical, and procedural features to predict ischaemic and bleeding events after an ACS, by pooling several large international cohorts of patients to inform model development and validation.

## *Methods*

### Datasets

To develop the machine learning models, we used a derivation cohort of 19 826 adult patients (≥18 years) with ACS with 1 year of follow-up. These patients were obtained from two registries: the BleeMACS registry (NCT02466854) and the RENAMI registry.[17] The BleeMACS registry included 15 401 consecutive patients with ACS who were admitted between Jan 1, 2003, and Dec 31, 2014, at 15 tertiary hospitals in North and South America, Europe, and Asia and treated with either clopidogrel, ticagrelor, or prasugrel. The RENAMI registry included 4425 consecutive patients admitted between Jan 1, 2012, and Dec 31, 2016, at 12 European hospitals and treated with prasugrel or ticagrelor.

To assess the performance of the models, we used an external validation cohort that included 3444 adult patients admitted to hospital with ACS with 2 years of follow-up from four prospectively collected sources: 442 patients with ACS who were enrolled from July, 2009, to July, 2014, in the European SECURITY randomised controlled trial with a follow-up of 1 and 2 years;[18] 1465 patients from two prospective registries from the University of Ferrara, Italy (402 patients from the FRASER study [NCT02386124][19] and 1063 patients from the Prospective Registry of Acute Coronary Syndromes in Ferrara [NCT02438085]), both enrolling patients from January, 2014, to January, 2016, with a follow-up of 2 years; and 1537 consecutive patients who were prospectively enrolled in the Clinical Governance in Patients with ACS project of the Fondazione IRCSS Policlinico S Matteo (Pavia, Italy; NCT04255537), from Sept 1, 2015, to Dec 31, 2019, with follow-up of 1 and 2 years. Full inclusion and exclusion criteria for all included cohorts have been published previously[17-19] and can be found on ClinicalTrials.gov.

**Outcomes**

Four machine learning models using different classifiers were developed to predict the occurrence of each of three outcomes: all-cause death, recurrent acute myocardial infarction, and major bleeding 1 year after discharge. Myocardial infarction was defined according to each study definition,[3,17-19] and major bleeding was defined according to the Bleeding Academic Research Consortium (BARC) definition as type 3 or 5 BARC bleeding.[20] The predictive ability of the models for the 2-year outcome occurrence was also evaluated in the external validation cohort.

**Feature selection and data preprocessing**

The structured dataset included 25 variables: 16 clinical variables (age, sex, diabetes, hypertension, hyperlipidaemia, peripheral artery disease, estimated glomerular filtration rate [EGFR; using the Modification of Diet in Renal Disease study formula[21]], previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass graft, previous stroke, previous bleeding, malignancy, ST-segment elevation myocardial infarction [STEMI] presentation, haemoglobin, and left ventricular ejection fraction [LVEF]), five therapeutic variables (treatment with β blockers, angiotensin- converting enzyme inhibitors or angiotensin-receptor blockers, statins, oral anticoagulation, and proton-pump inhibitors), two angiographic variables (multivessel disease and complete revascularisation), and two procedural variables (vascular access and percutaneous coronary intervention with drug-eluting stent). The definition of each variable is detailed in the appendix (p 17)).

**Model development and validation**

The derivation cohort was randomly split into two datasets: a training (80%) cohort, which was used to train the four machine learning models and tune their parameters, and an internal validation (20%) cohort, which was used to test the developed models on unseen data and to fine-tune the hyperparameters (appendix pp 4–5).
Trials of four machine learning classifiers—adaptive boosting, naive Bayes, K-nearest neighbours, and random forest—were employed to generate four models for the prediction of each study outcome.[22,23] Model performance was assessed according to a range of learning metrics (F2 score, mean area under the receiver operating characteristic curve [AUC], and calibration plots), and the best-performing model for each study outcome was selected; these three models are referred to as the PRAISE models, whose output is a risk score for each study outcome based on the 25 included variables. The final PRAISE models use the adaptive boosting classifier and were validated on the external validation cohort (appendix pp 5–6). Additionally, we performed a further analysis by merging the cohorts into a single pooled dataset of 23 270 patients, which was randomly split into a training cohort (70% of patients) and a test cohort (30% of patients). A calculator for the PRAISE risk score for each outcome is available online.

**Feature importance**

To determine the major predictors of each study outcome in our patient population, the importance of each permutation feature was measured from the final model. Permutation feature importance computes the value of each feature included in the model by calculating the increase in the model's prediction error after permuting its values. A feature is considered important if permuting its values decreases the model's discriminative capability, as the model relies heavily on that feature for the prediction. In the case of adaptive boosting (ie, the PRAISE models), the importance of a variable is determined by three main factors: whether the variable was selected or not during the training process to split the data in a tree node, how much the squared error improved as a result, and the

weight of the trees. Intuitively, if a variable is found in most of the high-weighted trees and produces high-purity splits, it will have a higher relative importance value (appendix pp 7–9). Since the relative importance is not a fixed-scale value, the results are presented in terms of scaled importance, which means that the relative importance of a variable is scaled with respect to the feature with the highest relative importance value in order to obtain easy-to-read and comparable plots. Moreover, we did distinct subgroup analyses to appraise the relevance of evaluated predictors according to STEMI versus non-STEMI presentation (appendix pp 12–16).
We computed a simplified risk score for each study outcome with a model whose input was the eight variables with the highest importance weight for that outcome, which provided roughly 60% of the overall importance weight.

**Classes of risk**

For each PRAISE score (death, myocardial infarction, and major bleeding), the 23 270 patients of the pooled dataset (ie, combining the derivation and external validation datasets) were divided into estimated risk deciles and then grouped into levels of low, intermediate, and high risk with thresholds reflecting clinically meaningful gradients in risk from one group to the next. The observed risk for each risk score class was then calculated.
Cross-classification of the pooled cohorts with myocardial infarction and major bleeding risk scores was determined (ie, classes were established by combining the risk categories of the myocardial infarction and major bleeding PRAISE scores).
The hypothetical trade-off between ischaemic and bleeding risks for each patient was assessed by plotting the absolute observed risk difference (along with its 95% CI) between myocardial infarction and major bleeding in each of the nine risk classes against the predicted myocardial infarction and major bleeding risk in each class (appendix p 21).

**Statistical analysis**

Categorical variables are reported as count (%) and continuous variables as mean (SD) or median (IQR). The presence of normal distribution was verified by Kolmogorov-Smirnoff test. We used the *t* test to assess differences between parametric continuous variables, the Mann-Whitney *U* test for non-parametric variables, the $\chi^2$ test for categorical variables, and the Fisher exact test for 2 × 2 tables. No correction for multiple testing was done. A two-sided $p<0{\cdot}05$ was considered statistically significant. All analyses were done with SPSS version 24.0.

**Role of the funding source**

This study was investigator initiated and no sponsor had any role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data and had final responsibility for the decision to submit for publication.

***Results***

Clinical and therapeutic characteristics of the study population are shown in table 1, and are shown stratified by each outcome occurrence in the appendix (pp 17–19).
In the derivation cohort, death occurred in 662 (3·3%) patients, myocardial infarction in 609 (3·1%) patients, and major bleeding in 562 (2·8%) patients, within 1-year follow-up (table 2). In the external validation cohort, death occurred in 58 (1·7%) patients within 1 year and 301 (8·7%) within 2 years, myocardial infarction in 58 (1·7%) patients within 1 year and 130 (3·8%) within 2 years, and major bleeding in 27 (0·8%) patients within 1 year and 162 (4·7%) within 2 years.

Leading predictors varied by study outcomes (figure 1). LVEF, age, haemoglobin level, and statin therapy at discharge were the most important features to predict all-cause death, whereas haemoglobin level, age, LVEF, and EGFR emerged as important features for the prediction of both myocardial infarction and major bleeding events, although with different relative importance (figure 1). The relevance of these variables was consistent for patients both presenting with STEMI and non-STEMI (appendix pp 12–16).

The discriminative performance of the PRAISE models for the study outcomes as expressed by the receiver operating characteristic curves in the training, internal validation, and external validation cohorts are shown in figure 2. AUCs of the PRAISE model for 1-year death were 0·91 (95% CI 0·90–0·92) in the training cohort and 0·82 (0·78–0·85) in the internal validation cohort. When applied to the external validation cohort, the model yielded an AUC of 0·92 (0·90–0·93).

AUCs for 1-year myocardial infarction were 0·88 (95% CI 0·86–0·89) in the training cohort and 0·74 (0·70–0·78) in the internal validation cohort. When applied to the external validation cohort, the model yielded an AUC of 0·81 (0·76–0·85).

AUCs for 1-year major bleeding were 0·87 (95% CI 0·85–0·88) in the training cohort and 0·70 (0·66–0·75) in the internal validation cohort. When applied to the external validation cohort, the model yielded an AUC of 0·86 (0·82–0·89).

When the PRAISE models were tested for 2-year outcome prediction on the external validation cohort, AUCs were similar (0·93 [95% CI 0·91–0·95] for death, 0·84 [0·81–0·88] for myocardial infarction, and 0·88 [0·85–0·91] for major bleeding).

The performance of the model for the pooled dataset is described in the appendix (p 16)).

AUCs for the simplified PRAISE score with eight variables for the training, internal validation, and external validation cohorts are reported in the appendix (p 12)), ranging from 0·93 (95% CI 0·92–0·94) to 0·78 (0·74–0·81) for death, from 0·90 (0·89–0·91) to 0·68 (0·64–0·72) for myocardial infarction, and from 0·90 (0·89–0·91) to 0·62 (0·59–0·67) for major bleeding.

When considering the distribution of observed death, myocardial infarction, and major bleeding events in the whole study cohort, stratified by deciles of event probability according to the relating PRAISE score, similar patterns of event distribution were observed for the three risk scores (figure 3). This resulted in the same stratification of risk deciles for all three outcomes (low risk: first to sixth deciles; intermediate risk: seventh to ninth deciles; and high risk: tenth decile). A gradual and progressive increase in absolute event rates was observed across risk classes for all the PRAISE scores (death: 0·5% [75/13 962] low risk *vs* 2·9% [205/6981] intermediate risk *vs* 29·4% [683/2327] high risk; myocardial infarction: 0·7% [94/13 962] *vs* 2·8% [193/6981] *vs* 19·4% [452/2327]; and major bleeding: 0·6% [88/13 962] *vs* 2·6% [179/6981] *vs* 19·6% [457/2327]). Compared with low risk, being categorised as being at intermediate risk and high risk was associated with increased ($p<0·0001$) event occurrence for all the PRAISE scores, with a 5·8-times increase in death, 4·0-times increase in myocardial infarction, and 4·5-times increase in major bleeding events for participants categorised as being at intermediate risk, and a 58·8-times increase in death, 27·7-times increase in myocardial infarction, and 32·7-times increase in major bleeding events for participants categorised as being at high risk.

Cross-classification of the entire cohort according to the PRAISE myocardial infarction and major bleeding risk score categories resulted in nine classes (figure 4). From the low to high risk classes for major bleeding, a graded increase in the relative frequency of patients belonging to higher risk classes for myocardial infarction was observed. Among the 2327 patients at high risk of major bleeding, 1667 (71·6%) showed a low-to-moderate risk of myocardial infarction. Among the 2327 patients at high risk of myocardial infarction, 1667 (71·6%) showed a low-to-moderate risk of major bleeding.

Among patients classified as being at high risk of myocardial infarction, the absolute observed risk difference between myocardial infarction and major bleeding events supported a consistent prevailing ischaemic risk regardless of the major bleeding PRAISE risk class, with the exception of the highest PRAISE bleeding risk decile, where the 95% CI contained the null (ie, no difference in

risk; figure 4). For patients classified as being at low risk of myocardial infarction, their risk of major bleeding exceeded their risk of myocardial infarction once they were classified as being at intermediate-to-high risk of major bleeding.

***Discussion***

In this study, we used data on 23 270 patients who were discharged after an ACS to develop and test machine learning-based risk scores to predict the risk for all-cause death, myocardial infarction, and major bleeding 1 year after discharge. We found that the PRAISE scores presented excellent discriminative abilities for the prediction of 1-year all-cause death, myocardial infarction, and major bleeding following an ACS, also when externally validated. Clinically meaningful risk cutoffs for all-cause death, myocardial infarction, and major bleeding PRAISE scores would classify 60% of patients with ACS as being at low risk (<1% probability) of post-discharge ischaemic and bleeding events 1 year after discharge, and 10% of patients with ACS as being at high risk (>19%) of these events. Finally, robust hypothetical trade-offs in the occurrence of ischaemic and bleeding events are observed for each patient according to their myocardical infarction and major bleeding score classes. Specifically, the risk of myocardial infarction is always greater than the risk of major bleeding among patients classified by the PRAISE score as being at high risk of myocardial infarction (with the exception of the highest PRAISE major bleeding risk decile, where only a numerical trend is observed), whereas risk of major bleeding overtakes risk of myocardial infarction among patients classified by PRAISE as being at intermediate-to-high risk of major bleeding and low risk of myocardial infarction.

Accurate prediction of death after an ACS still represents an unmet need. Thrombolysis in Myocardial Infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) scores, although also validated on contemporary cohorts, were derived from patients not treated with current standard therapies.[24] For example, in the derivation cohort of GRACE, less than a third of patients underwent percutaneous coronary intervention, while statins at discharge were prescribed for less than two thirds of them.[25] Our score offers very high accuracy in detecting the risk of all-cause death after an ACS in a population treated with current standard therapies.

Regarding ischaemic versus bleeding risks, the growing evidence that DAPT can prevent the onset of non-stent-related ischaemic events, along with the advent of new and safer drug-eluting stents able to reduce stent-related adverse outcomes (eg, stent thrombosis),[26,27] has led to a paradigm shift in the way DAPT is conceived in clinical practice. The ability to identify patients who might benefit from intensive antithrombotic strategies requires a personalised evaluation of offsetting risks of ischaemia and bleeding according to each patient's characteristics.

Research efforts in investigating the predictors of ischaemic and bleedings events have led to the development of several scores to estimate patients' risk after percutaneous revascularisation. Large real-life registries have shown that the perceived risk often does not correspond to the real patient risk and that this mismatch leads to low accuracy in the prescription of potent P2Y12 inhibitors and lower quality of care after percutaneous coronary intervention.

Machine learning algorithms, exploring high-dimensional and non-linear relations among features, could represent a novel approach to the compelling requirement of a personalised risk assessment. Indeed, PRAISE risk scores, derived from a machine learning process, appear to overperform compared with existing ischaemic and bleeding risk scores. Notably, commonly recommended scores such as PRECISE-DAPT and PARIS[7,8] were derived from cohorts of patients admitted for both stable coronary artery disease and ACS. However, these two scenarios are associated with different risks, both in terms of ischaemic and bleeding occurrence. Accordingly, clinical presentation is the first element to be considered in choosing the individualised DAPT regimen (ie, potent P2Y12 inhibitors for 6–12 months in patients with ACS *vs* clopidogrel for 3–6 months in stable patients). Moreover, the studies used derivation cohorts in which most patients were on clopidogrel, thus limiting their applicability to the current practice. In this context, the PRAISE scores, derived from a

large contemporary cohort of patients, all admitted for ACS and treated following current recommendations on antithrombotic therapy, have the potential to overcome the shortcomings of existing scores.

The PRAISE scores we propose stem from the exploration of 25 variables, most of them routinely assessed during the management of patients admitted for ACS. Notably, although a predictive scale usually underperforms when applied in an external cohort, our model was validated in an independent, external dataset and maintained a good level of discrimination for all the explored outcomes, including all-cause death.

Although the increase in risk of events was progressive and gradual throughout the PRAISE scores, we proposed categorising patients into three classes of risk (ie, low, intermediate, and high) for each outcome. Such stratification is meant to highlight the clinical implication of each risk value computed by the model. According to such stratification, a tenth of patients (the highest decile) would be classified at discharge as being at high risk of either death, recurrent myocardial infarction, or major bleeding, thus being candidates for a tighter follow-up.

Despite our study not being specifically designed to address the issue of optimal DAPT regimen and duration, we hypothesise that this could be one of the most important implications of the PRAISE scores. Stratification of patients into three classes of ischaemic and bleeding risk might contribute to rational planning of an antiplatelet strategy that avoids a one-size-fits-all approach. The combination of both ischaemic and bleeding risk scores could be very useful. Unlike the PARIS and PRECISE-DAPT classifications, we found that patients deemed at high ischaemic risk according to their PRAISE score showed a consistent prevailing ischaemic risk, regardless of their bleeding risk classification, albeit more modestly when classified as high risk of bleeding. Bleeding risk was found to offset ischaemic risk among patients in the intermediate-to-high bleeding risk classes and with low ischaemic risk. The inclusion of only patients with ACS in PRAISE and the different analytic model adopted are both likely to contribute to this difference. The approach of jointly considering ischaemic and bleeding outcomes to quantify risk was first suggested by the DAPT study investigators.[29] It can be argued that such an approach implicitly assumes a comparable weighting of both ischaemic and bleeding events on subsequent morbidity and mortality. This concern certainly applies to the DAPT score,[29] which only includes myocardial infarction and stent thrombosis as ischaemic endpoints, but can also be applied to a minor extent to the PRAISE scores, which included hard endpoints such as all-cause death, allowing clinicians to obtain a more definite picture of individual patient risk. Furthermore, the DAPT score was proposed for patients who tolerated 12 months of DAPT to select those eligible for prolongation. However, earlier decisions (ie, at discharge) as explored with the PRAISE scores are more meaningful to appropriately plan DAPT intensity and duration.

This study has several limitations. The first is the observational retrospective design of the two registries composing the derivation cohort. However, good discrimination was confirmed in the external validation cohort, including patients enrolled in one randomised trial and three prospective registries. The values of AUC actually tended to be higher in the external validation cohort, possibly due to the lower percentage of missing data among the prospectively enrolled patients. In the analysis on the pooled dataset, the AUC of the test cohort was modestly lower than in the external validation cohort (appendix p 16). A further possible limitation of our approach can be identified in the slight underestimation of the adaptive boosting classifier among high-risk patients. As seen in figure 3, our model generally mirrors the observed risk in the first nine deciles quite accurately, but slightly underestimates risk for patients in the tenth decile. Naive Bayes, on the other hand, markedly overestimates the high-risk class (appendix pp 7–9). This has a negative effect on its general predictive capabilities. Future refinements might consider possible routes to mitigate these underestimation issues—for example, by penalising false negatives during the training phase or choosing a different threshold for the classification. An interesting approach for risk prediction is the Dynamic-DeepHit,[30] a deep learning-based algorithm for dynamic survival analysis with competing risks based on longitudinal data. Dynamic-DeepHit learns the time-to-event distributions without the need to make assumptions about the underlying stochastic models for the longitudinal and the time-

to-event processes. Dynamic-DeepHit is focused on survival analysis. The PRAISE scores, however, do not include time as a variable as it is created to be used with a fixed time lapse (eg, 1-year follow-up).

Unfortunately, the available clinical data prevented us from computing the PARIS (insufficient data about current smoking) and the PRECISE-DAPT (insufficient data on white blood cell counts) scores. Despite this, the lower 95% CI of the PRAISE AUCs was still higher than the AUCs reported in the external validation cohorts of PRECISE-DAPT and GRACE scores.[7,24] We could only include variables collected within the RENAMI and BLEEMACS registries. For instance, some procedural and angiographical features such as the burden of coronary disease, the number of implanted stents, and the interventional techniques adopted for complex lesions could have improved the model discrimination. However, previous reports have shown that while a combination of clinical and procedural features might be related to early adverse ischaemic outcomes, clinical variables alone can be predictive of long-term prognosis.[31] The usefulness of the PRAISE scores to support clinical decision on the optimal DAPT duration should be regarded as hypothesis generating at this stage, and dedicated randomised trials should be carried out to evaluate the validity of this potential application of the model.

In conclusion, we have developed and tested the PRAISE risk scores, a machine learning-based tool to predict the risk for all-cause death, myocardial infarction, and major bleeding after discharge for ACS. This study showed that a machine learning-based approach in this setting is feasible and effective with potentially important implications on the optimisation of the quality of care.

**Contributors**

FD, ODF, GG, MI, and GMDF conceived and designed the study. GM, MAD, UM, and MA did the machine learning-based analysis. AA-S, JMH, CL, SM-F, GQ, TK, GC, JPSH, AD-R, GP, SR-R, and EA-A drafted the manuscript. All authors revised and approved the final version of the manuscript. FD and ODF had direct access to and verified the data.

**Declaration of interests**

We declare no competing interests.

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**Table 1.** Baseline features of included cohorts

| Empty Cell | Empty Cell | **Derivation cohort (n=19 826)** | **External validation cohort (n=3444)** |
|---|---|---|---|
| Median age, years | | 64 (54–73) | 68 (58–76) |
| Sex | | | |
| | Female | 4363 (22·0%) | 953 (27·7%) |
| | Male | 15 463 (78·0%) | 2491 (72·3%) |
| Diabetes | | 4920/19 817 (24·8%) | 839 (24·4%) |
| Hypertension | | 11 086/19 824 (55·9%) | 1307 (38·0%) |
| Dyslipidaemia | | 10 106/19 701 (51·3%) | 1622 (47·1%) |
| EGFR <60 mL/min | | 2490/15 810 (15·7%) | 166/3434 (4·8%) |
| Renal clearance, mL/min per 1·72 $m^2$ | | 83 (49–117) | 75 (43–123) |
| Median ejection fraction | | 55% (39–61) | 50% (40–60) |
| Previous myocardial infarction | | 2498/19 815 (12·6%) | 778 (22·6%) |
| Previous coronary artery bypass graft | | 526/19 823 (2·7%) | 228 (6·6%) |
| Previous percutaneous coronary intervention | | 2515/19 701 (12·8%) | 597 (17·3%) |
| Peripheral artery disease | | 983/17 543 (5·6%) | 608/3434 (17·7%) |
| Previous stroke or transient ischaemic attack | | 1116/19 385 (5·8%) | 173/3442 (5·0%) |
| Previous bleedings | | 873/17 749 (4·9%) | 72/3435 (2·1%) |
| STEMI | | 11 216/19 820 (56·6%) | 1419 (41·2%) |
| Unstable angina or non-STEMI | | 8039/18 345 (43·8%) | 2027/3438 (59·0%) |
| Haemoglobin at admission, mg/dL | | 14 (12–17) | 15 (11–16) |
| Multivessel disease | | 8772/15 061 (58·2%) | 1138/3423 (33·2%) |
| Complete revascularisation | | 7290/12 669 (57·5%) | 857/3413 (25·1%) |
| Percutaneous coronary intervention with drug-eluting stent implantation | | 11 579/19 435 (59·6%) | 2628/3442 (76·4%) |
| Medical therapy at discharge | | | |
| | Clopidogrel | 13 561/19 824 (68·4%) | 435 (12·6%) |
| | Prasugrel | 2347/19 467 (12·1%) | 1215/3443 (35·3%) |
| | Ticagrelor | 3349/19 467 (17·2%) | 1626/3443 (47·2%) |

| Empty Cell | Empty Cell | **Derivation cohort (n=19 826)** | **External validation cohort (n=3444)** |
|---|---|---|---|
| | Statin | 15 937/17 125 (93·1%) | 2647/3432 (77·1%) |
| | β blockers | 13 552/16 603 (81·6%) | 2318/3430 (67·6%) |
| | ACE inhibitors or ARBs | 12 582/16 596 (81·6%) | 2020/3430 (58·9%) |
| | Proton-pump inhibitors | 6451/18 607 (34·7%) | 1378/3400 (40·5%) |
| | Oral anticoagulation | 827/18 019 (4·6%) | 245/3401 (7·2%) |

Data are n (%), n/N (%), or median (IQR). EGFR=estimated glomerular filtration rate. STEMI=ST-segment elevation myocardial infarction. ACE=angiotensin-converting enzyme. ARBs=angiotensin-II receptor blockers.

**Table 2.** Study outcomes

| Empty Cell | **Derivation cohort (n=19 826)** | **External validation cohort (n=3444)** |
|---|---|---|
| **All-cause mortality** | | |
| 1-year follow-up | 662 (3·3%) | 58 (1·7%) |
| 2-year follow-up | .. | 301 (8·7%) |
| **Recurrent acute myocardial infarction** | | |
| 1-year follow-up | 609 (3·1%) | 58 (1·7%) |
| 2-year follow-up | .. | 130 (3·8%) |
| **BARC type 3 or 5 bleeding** | | |
| 1-year follow-up | 562 (2·8%) | 27 (0·8%) |
| 2-year follow-up | .. | 162 (4·7%) |

BARC=Bleeding Academic Research Consortium.

**Figure 1.** Radar plot for the eight most important predictors of death, myocardial infarction, and major bleeding
ACE=angiotensin-converting enzyme. ARBs=angiotensin-II receptor blockers.
EGFR=estimated glomerular filtration rate. LVEF=left ventricular ejection fraction.

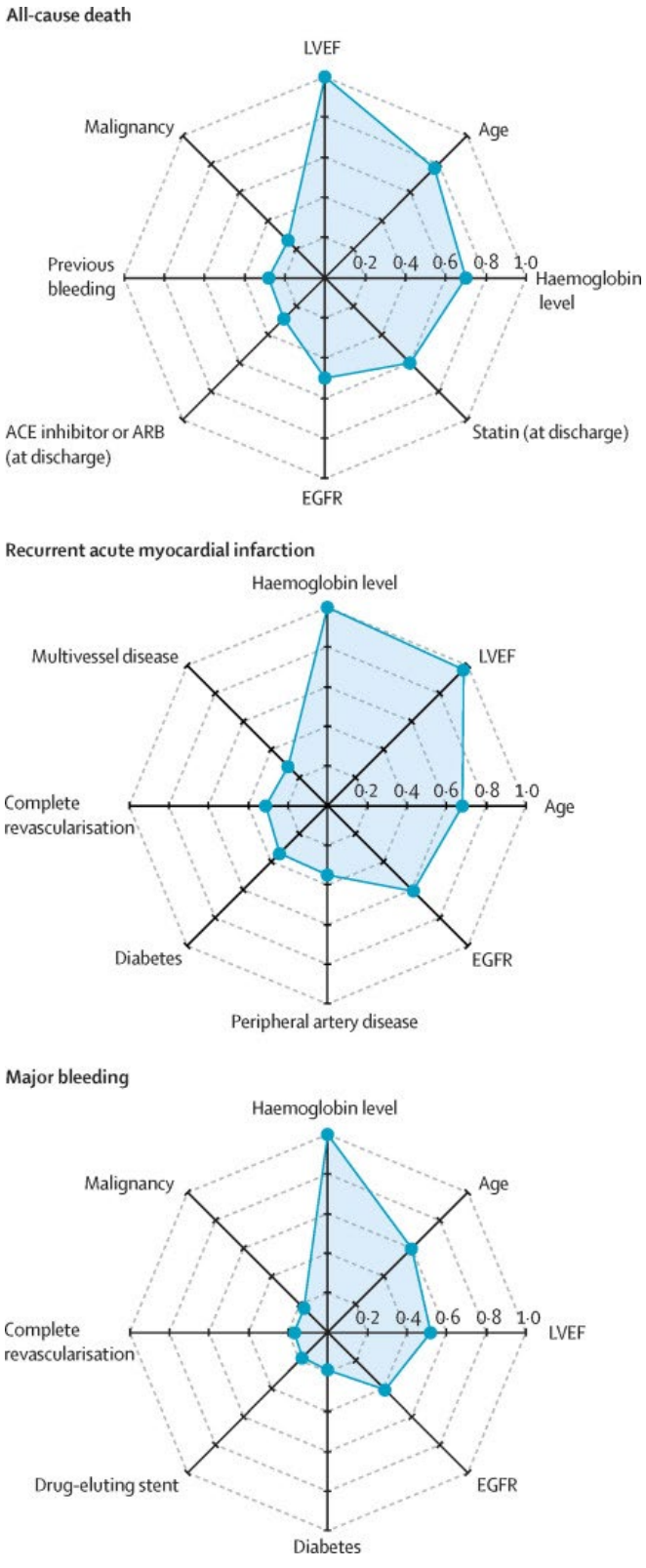

**Figure 2.** AUCs for death, myocardial infarction, and major bleeding for the training, internal validation, and external validation datasets at 1-year follow-up

AUC=area under the receiver operating characteristic curve.

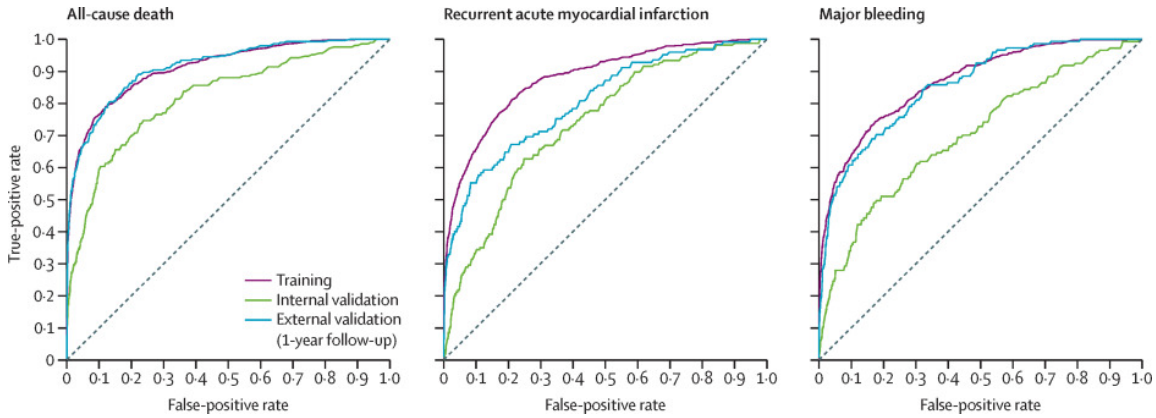


**Figure 3.** Risk of observed death, myocardial infarction, and major bleeding according to deciles of event probability based on PRAISE scores

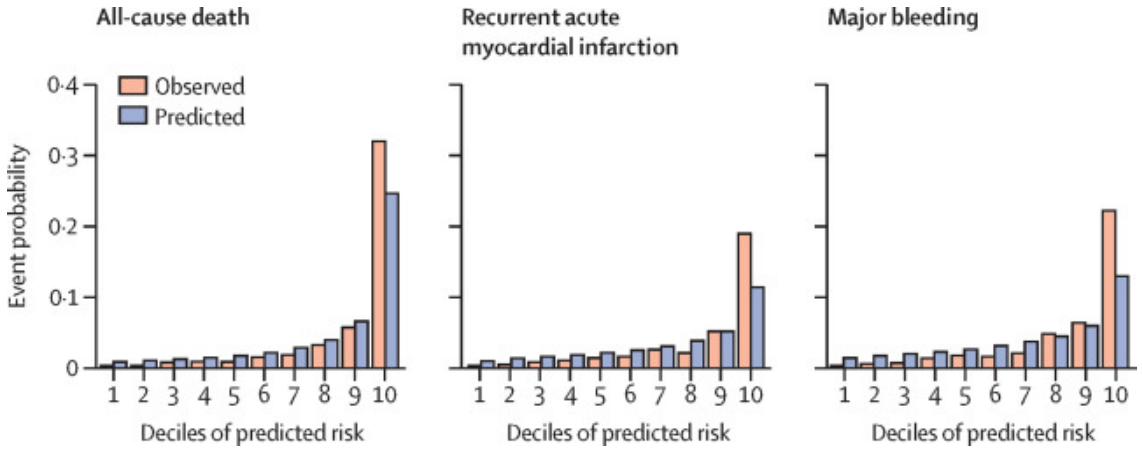

**Figure 4.** Cross-classification of myocardial infarction and major bleeding risk classes (A) and illustration of the hypothetical trade-off between the two types of risk (B)
In panel B, a positive risk difference indicates greater observed risk of myocardial infarction than major bleeding and a negative risk difference indicates greater observed risk of major bleeding than myocardial infarction. Each line is fitted to the observed mean risk difference according to major bleeding risk deciles and myocardial infarction risk categories, with shaded areas representing 95% CIs for mean risk difference. Of note, the first six deciles of major bleeding risk denote low risk, the seventh to ninth deciles denote intermediate risk, and the tenth decile denotes high risk.