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ABSTRACT

Background: Early risk stratification is important in the management of patients with acute coronary syndromes (ACS).

Objective: To develop a rapidly available risk stratification tool for use in all ACS.

Design and methods: Application of modern data mining and machine learning algorithms to a derivation cohort of 7520 ACS patients included in the AMIS (Acute Myocardial Infarction in Switzerland)-Plus registry between 2001 and 2005; prospective model testing in two validation cohorts.

Results: The most accurate prediction of in-hospital mortality was achieved with the "Averaged One-Dependence Estimators" (AODE) algorithm, with input of seven variables available at first patient contact: age, Killip class, systolic blood pressure, heart rate, pre-hospital cardiopulmonary resuscitation, history of heart failure, history of cerebrovascular disease. The c-statistic for the derivation cohort (0.875) was essentially maintained in important subgroups, and calibration over five risk categories, ranging from <1% to >30% predicted mortality, was accurate. Results were validated prospectively against an independent AMIS-Plus cohort (n = 2854, c-statistic 0.868) and the Krakow-Region ACS Registry (n = 2635, c-statistic 0.842). The AMIS model significantly outperformed established "point-of-care" risk-prediction tools in both validation cohorts. In comparison to a logistic regression-based model, the AODE-based model proved to be more robust when tested on the Krakow validation cohort (c-statistic 0.842 vs 0.746). Accuracy of the AMIS model prediction was maintained at 12-month follow-up in an independent cohort (n = 1972, c-statistic 0.877).

Conclusions: The AMIS model is a reproducibly accurate point-of-care risk stratification tool for the complete range of ACS, based on variables available at first patient contact.

The risk of short-term death for patients with acute coronary syndromes (ACS) is widely heterogeneous. Reliable risk stratification remains an essential part of their care,[1] especially with regard to the time point of revascularisation, use of antithrombotic therapies and to the length and level of their specialised care and monitoring. For this goal, a number of risk-prediction models have been developed,[2–13] and among these, models developed from randomised controlled trials and later validated in large registries have reached broad acceptance.[11 14 15]

None the less, questions have arisen concerning the performance of these scores in patients treated according to current standards. First, some of these scores were developed in an era before the introduction of potent antiplatelet/antithrombotic agents and the establishment of percutaneous coronary intervention (PCI) as the treatment of choice for most patients with ACS, and the impact of these changes in treatment strategy on the accuracy of risk scores remains unclear. Second, many high-risk patients were excluded from the trials from which the scores were developed, including patients with cardiogenic shock or pre-hospital resuscitation, patients with a history of cerebrovascular disease und coagulation disorders, and patients with ST-elevation myocardial infarction (STEMI) presenting too late for fibrinolytic treatment.[6 7 9 11] Third, these scores were all applicable selectively to patients with either STEMI or non-ST-elevation ACS (non-STE-ACS).[6–9 11–13]

Recently, the Global Registry of Acute Coronary Events (GRACE) investigators reported a prediction score valid over the complete spectrum of ACS.[16] This score has undergone extensive validation and has reached broad acceptance. Treatment guidelines of the European Society of Cardiology for non-STE-ACS recommend use of the GRACE score as the preferred risk stratification tool in routine practice.[1] However, in contrast to the TIMI risk scores for STEMI,[7 9] but in line with the TIMI risk score for non-STE-ACS,[8] this score requires the input of blood test results, thus delaying the availability of the prediction result.

With these questions in mind, this study aimed to develop a rapidly applicable model for use in all kinds of ACS, based on outcomes in unselected, contemporary patients. An additional goal of this study was to evaluate the use of modern data mining/machine learning techniques for model development. Most established risk scores have been developed using traditional statistical methods such as logistic regression techniques. We hoped that more advanced, partially non-linear algorithms, which have only rarely been applied in medical science, would prove useful in optimising model accuracy.

METHODS

Patient cohorts

Derivation cohort

The AMIS (Acute Myocardial Infarction in Switzerland) registry was initiated in 1997 and prospectively collects data from ACS patients admitted to 67 Swiss hospitals.[17] While initially only patients with myocardial infarction were included, the database was extended in 2001 to include patients with the complete spectrum of ACS (hence called "AMIS-Plus"). Collection and analysis of data in the AMIS-Plus registry have been approved by the regional ethics committees of

Table 1 Admission characteristics of patients from the AMIS-Plus registry used in model development and validation

	Derivation cohort (n = 7520)	Validation cohort (n = 2854)
	Oct 2001–May 2005	June 2005–July 2006
Age (years)	65.9 (13.4)	66.1 (13.4)
Male	5415 (72.0%)	2062 (72.2%)
Systolic BP (mm Hg)	134 (27)	136 (28)
Heart rate (beats/min)	79 (20)	79 (21)
Killip ⩾ II	1858 (25.3%)	503 (17.6%)
Resuscitation before admission	341 (4.5%)	87 (3.0%)
Previous MI, angina or PCI	2560 (34.0%)	1117 (39.0%)
History of heart failure	341 (4.5%)	121 (4.2%)
History of stroke/TIA	422 (5.6%)	168 (5.9%)
Atrial fibrillation	376 (5.0%)	140 (4.9%)
Hypertension	4075 (54.2%)	1680 (58.9%)
Hypercholesterolaemia	4169 (55.4%)	1419 (49.7%)
Current smoker	2836 (37.7%)	947 (33.2%)
Diabetes mellitus	1506 (20.0%)	542 (19.0%)
STEMI	4571 (60.8%)	1597 (56.0%)
Non-STE-ACS	2949 (39.2%)	1257 (44.0%)
ECG at presentation		
ST elevation	4300 (57.2%)	1491 (52.2%)
Q wave	1228 (16.3%)	283 (9.9%)
ST depression	2264 (30.1%)	800 (28.0%)
T wave changes	2120 (28.2%)	704 (24.7%)
LBBB	372 (5.0%)	129 (4.5%)
RBBB	428 (5.7%)	121 (4.2%)

Values are number (%) or mean (SD).
BP, blood pressure; ECG, electrocardiogram; LBBB, left bundle branch block; MI, myocardial infarction; Non-STE-ACS, non-ST-elevation acute coronary syndromes; PCI, percutaneous coronary intervention; RBBB, right bundle branch block; STEMI, ST-elevation myocardial infarction; TIA, transient ischaemic attack.

all participating hospitals. The derivation cohort for model development consisted of patients included in this registry between October 2001 and May 2005. After exclusion of 185 datasets with missing (or nonsensical) values for age (>120 years), systolic blood pressure (<30 or >300 mm Hg) or heart rate (<15 or >300/min) 7520 sufficiently complete datasets remained.

AMIS validation cohort

All patients included in the AMIS-Plus database between June 2005 and July 2006 (n = 2854) represented the independent validation dataset for the model. No patients were excluded from the AMIS validation dataset.

External validation cohort

The Krakow Region (Malopolska State) ACS registry selectively included patients treated with a non-invasive strategy in 29 hospitals without on-site PCI facilities in Malopolska State, Poland between 2002 and 2006 (n = 2635).[18 19] No patients were excluded.

Model development

The development of the AMIS model followed typical machine learning methodology.[20] After establishing the variable to be predicted—in-hospital death—the data were pre-processed into a format suitable for algorithm consumption. In a second step a variety of algorithms were tested regarding their predictive performance. Software packages used for data preparation were SPSS Clementine 10.0, and for model development the open source software Weka 3.4.7 (available at http://www.cs.waikato.ac.nz/~ml/weka/index.html).

Of the information collected in the AMIS-Plus registry 86 variables are assessed at admission. From these, variable selection was performed using the J48 decision-tree learner (a variant of C4.5 provided by Weka),[20] combined with a sequential backward deletion process, which starts by learning a model with all variables and then repeatedly tests which variable can be discarded without decreasing the overall model prediction quality.[21] Since some machine-learning algorithms are limited to categorical variables, the data were pre-processed either by applying categories or by using the fixed-bin discretisation algorithm provided by Weka. We used 10-fold cross-validation to establish the predictive power of the model, as assessed using the c-statistic (that is, the area under the curve, range 0–1) of the model's receiver operating characteristic (ROC).[22]

To determine the best suitable prediction algorithm we compared the performance with respect to the c-statistic and computational complexity of 30 data-mining algorithms from the Weka data-mining toolkit using 10-fold cross-validation and the variables determined by the sequential backward deletion process.

Comparisons with other ACS risk scores

Model performance of the AMIS model was compared with the TIMI risk score for STEMI and the simple risk index.[7 9] These two risk-prediction scores were chosen for comparison with the AMIS model because of their similar applicability at first patient contact, without input of blood test results. The GRACE risk model could not be directly compared to the AMIS model owing to absence of the variables "elevated cardiac enzyme levels at admission" and "initial serum creatinine level" in the AMIS-Plus database.[16] The c-statistics achieved with the different

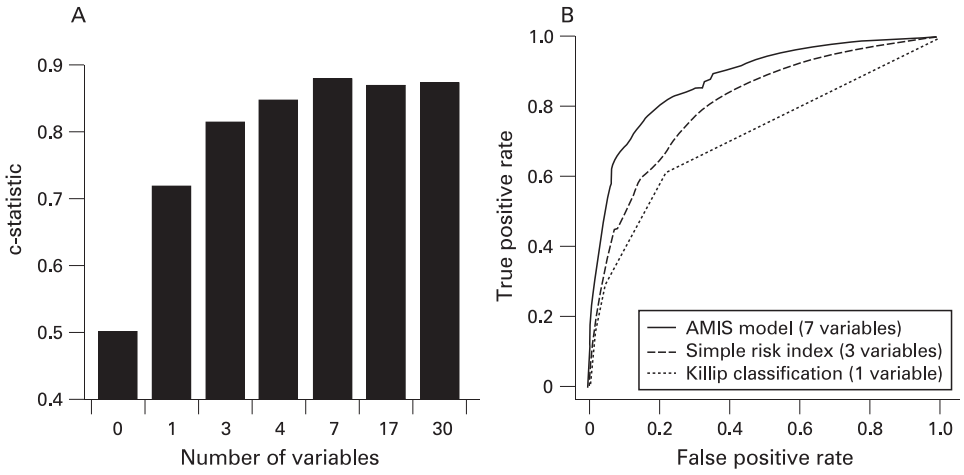

Figure 1 Critical mass of prognostic information for model optimisation. (A) Bar chart depicting discriminative performance (c-statistic) in relation to the number of variables included in the model. (B) Receiver operator characteristic curves for the AMIS model (seven variables), the simple risk index (three variables) and the Killip classification when used as a single variable in the derivation dataset.

models were compared according to the non-parametric method described by DeLong.[23]

RESULTS

Patient characteristics

The derivation cohort consisted of 7520 entries to the AMIS-Plus registry between October 2001 and May 2005. The presenting characteristics of these patients are summarised in table 1. Hospital mortality for this cohort was 7.5%.

Model characteristics

Selection of input variables was performed according to data analysis algorithms as described in the Methods section. We found that a critical mass of prognostic information was achieved using seven key variables. The c-statistic did not improve, but rather tended to decrease when additional input variables were included in the model (fig 1). The combination of input variables found to provide the best discriminative performance were (1) age, (2) Killip class, (3) systolic blood pressure, (4) heart rate, (5) pre-hospital cardiopulmonary resuscitation, (6) history of heart failure and (7) history of cerebrovascular disease. Notably, all seven variables are available at first patient contact at the bedside. Model output was an estimate of in-hospital mortality risk for each patient. The best performing—in terms of accuracy and robustness—of the 30 machine-learning algorithms tested was the "Averaged One-Dependence Estimators" (AODE) algorithm, an extension of the naive Bayes algorithm first reported in 2002.[24 25] This provided the basis for the final model, which we named the "AMIS model". The AODE algorithm also has the advantage of delivering a computationally highly efficient model with a complexity of the order (2×7^2) for classification, allowing its implementation on a variety of devices including hand-held computers or mobile telephones.

Performance of the AMIS model

Using the AMIS model, the c-statistic for the derivation cohort was 0.875 (95% CI 0.86 to 0.89). As shown in figure 2A, the discriminatory capacity of the AMIS model compared favourably to the TIMI risk score, which delivered a c-statistic of 0.803 (95% CI 0.79 to 0.82). Similarly, the AMIS score clearly outperformed the simple risk index, which thanks to its simplicity can be considered to be a pre-hospital, bedside point-of-care risk-prediction tool (c-statistic 0.813, 95% CI 0.79 to 0.83). The AMIS model performed significantly better than both other scores ($p<0.0001$ for both comparisons), while the performance of the TIMI risk index and the simple risk index were similar ($p = 0.24$). Since differences exist between patient characteristics of the AMIS model development cohort (registry of complete ACS spectrum) and the other scores (thrombolysis trials), subgroup analysis was performed in STEMI vs non-STE-ACS patients, younger and older patients and patients treated by thrombolysis vs primary PCI or a primary conservative strategy (table 2). This demonstrated a consistently superior performance of the AMIS model in all subgroups. Interestingly, when tested on our derivation cohort, similar performance for patients with and without STEMI could also be observed for the TIMI score and the simple risk index, despite the fact that these models were developed and validated on STEMI cohorts.

Calibration of predictions was tested by dividing the cohort into five categories based on increasing predicted risk, as shown in figure 2B. Calibration of the model proved to be excellent, delivering close matches between mean predicted and effective hospital mortality rates for each category.

Validation of the AMIS model

Prospective validation of the AMIS model was performed on an independent cohort of 2854 patients subsequently included in the AMIS-Plus registry—with no exclusions—between June 2005 and July 2006, with an overall in-hospital mortality rate of 5.5%. The c-statistic of the AMIS model for this validation cohort was 0.868 (95% CI 0.84 to 0.90). The performance of the AMIS model on the whole cohort (fig 2C) and in the subgroup analyses (table 2) basically mirrored the results achieved for the derivation cohort, also in comparison to the TIMI score (0.835, 95% CI 0.81 to 0.86) and simple risk index (0.817, 95% CI 0.78 to 0.85). Again, the AMIS model significantly outperformed both other scores ($p = 0.004$ compared to the TIMI risk score, $p = 0.0002$ compared to the simple risk index). Importantly, the ROC curve of the AMIS model was positioned above the curves of the other models, with no crossover points, during their whole course, indicating its superiority over the complete range of risks (fig 2C). We attributed the similar accuracy of the AMIS model in both its derivation cohort and independent validation

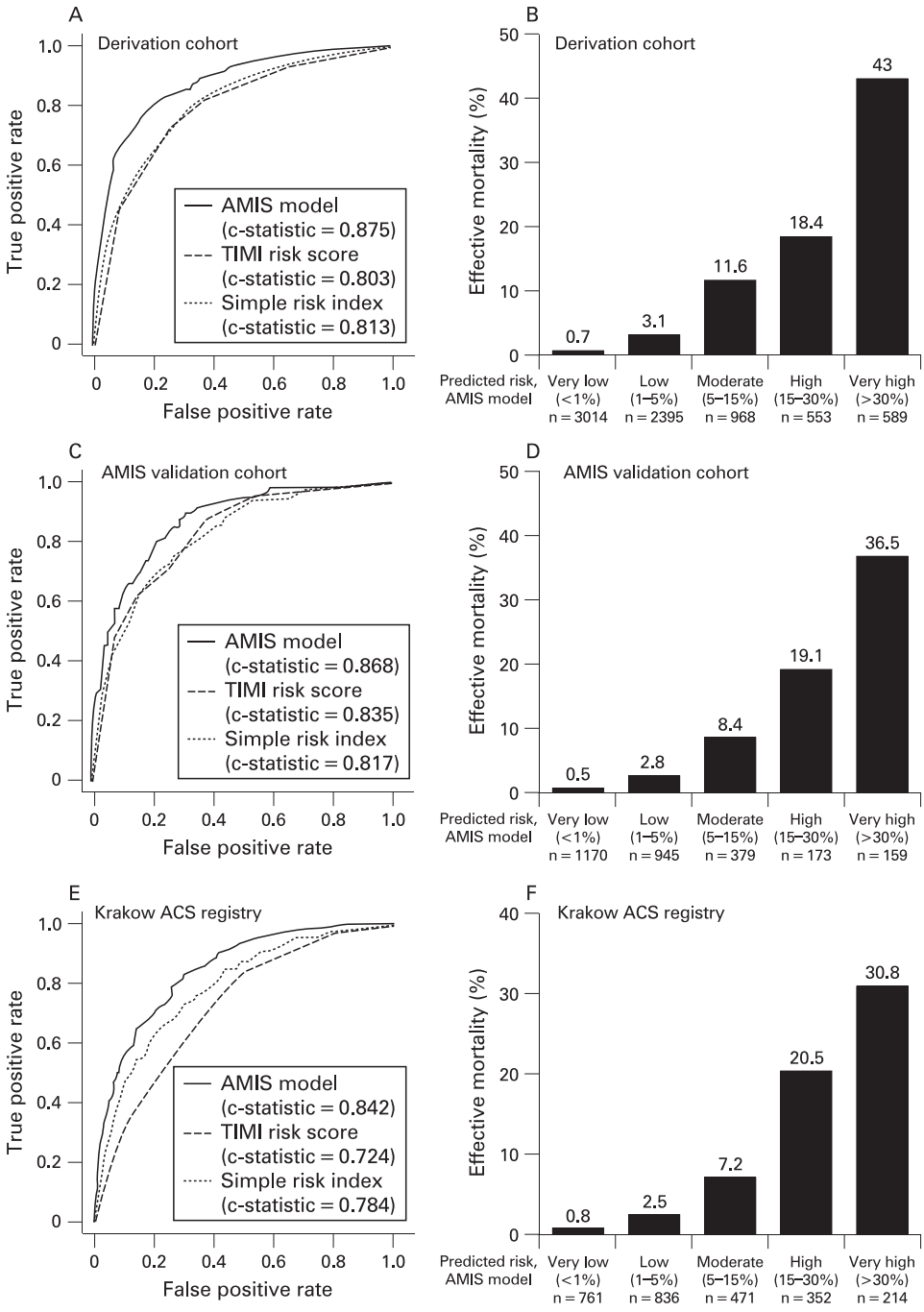

Figure 2 Performance of the AMIS model in comparison to established risk-prediction tools. (A, C, E) Receiver operating characteristic curves and c-statistic of the AMIS model, the TIMI risk score, and the simple risk index. (B, D, E) Risk calibration of the AMIS model, depicting effective mortality of patients discreditised into five categories of increasing predicted risk. (A) and (B) depict results from the derivation dataset, (C) and (D) from the independent AMIS-Plus validation dataset, (E) and (F) from the Krakow Region (Malopolska) ACS registry.

dataset to the fact that 10-fold cross-validation had already been used as in internal validation technique while developing the model in the derivation dataset.

Since the AMIS model was developed and validated on a Swiss dataset in which the majority of patients were treated by primary PCI, we sought further validation of the model on an external cohort treated with a more conservative strategy. The Krakow Region (Malopolska) ACS registry selectively included patients treated with a non-invasive strategy in 29 hospitals in the greater Krakow area (Poland) between 2002 and 2006.[18 19] Among the 2635 patients included in this registry (57% male, mean age 68.2 (11.5) years, 31% STEMI) hospital mortality was 7.6%. The c-statistic using the AMIS model for this cohort was 0.842 (95% CI 0.82 to 0.87), compared to 0.724 (95% CI 0.69 to 0.76) for the TIMI risk score and 0.784 (95% CI 0.75 to 0.82) for the Simple Risk Index (fig 2E). In this heterogeneous cohort, the AMIS model was significantly more accurate than both other scores ($p<0.0001$ for both comparisons). Risk calibration was maintained with the AMIS model over the complete range of risks (fig 2F). Subgroup analysis for the performance of the three risk-prediction models in this cohort is listed in table 2.

Table 2 Discriminative capacity of different risk-prediction models in subgroup analyses

	Derivation cohort				Validation cohort				Krakow cohort			
	No	AMIS	TIMI	SRI	No	AMIS	TIMI	SRI	No	AMIS	TIMI	SRI
Whole cohort	7520	0.875	0.803	0.813	2854	0.868	0.835	0.817	2635	0.842	0.724	0.784
STEMI vs non-STE-ACS												
STEMI	4571	0.879	0.816	0.812	1597	0.879	0.827	0.815	818	0.760	0.592	0.746
Non-STE-ACS	2949	0.868	0.794	0.821	1257	0.851	0.839	0.831	1817	0.859	0.773	0.815
Age												
Age ⩾65 years	4013	0.805	0.712	0.731	1589	0.798	0.750	0.751	1766	0.783	0.719	0.758
Age <65 years	3507	0.886	0.844	0.829	1265	0.879	0.844	0.814	869	0.802	0.662	0.791
Primary treatment strategy												
Primary PCI	4453	0.884	0.783	0.808	2138	0.891	0.802	0.815	NA	NA	NA	NA
Thrombolysis	980	0.853	0.833	0.781	68	0.855	0.873	0.784				
No revasc Tx	2087	0.788	0.673	0.707	648	0.742	0.684	0.695				

Values represent the number of patients in each subgroup and the c-statistic for the corresponding cohort, model and subgroup.
AMIS, AMIS model; NA, not applicable; No revasc Tx, no primary revascularisation therapy; Non-STE-ACS, non-ST-elevation acute coronary syndrome; SRI, simple risk index; STEMI, ST-elevation myocardial infarction; TIMI, TIMI risk score.

Prediction of late mortality

Although developed and validated for the prediction of in-hospital mortality, we also tested the predictive accuracy of the AMIS model on mortality of ACS patients at 12 months. The AMIS-Plus study group began enrolling patients in a registry to assess post-discharge mortality in July 2006. Up until August 2008 post-discharge mortality during the first year was 3.8%, so that 1-year total mortality—including hospital mortality—came to 8.9% for this cohort of 1972 patients with ACS. The c-statistic for the AMIS model in predicting 12-month mortality in this cohort was 0.877 (95% CI 0.86 to 0.90).

Comparison of machine-learning algorithms

A pre-specified goal of this study was to evaluate the use of modern machine-learning techniques for model development in comparison to more traditional statistical methods such as logistic regression. When using the same seven variables, models based on the AODE algorithm (the AMIS model) or logistic regression performed similarly well in the derivation cohort (c-statistic 0.875, 95% CI 0.86 to 0.89, and 0.874, 95% CI 0.86 to 0.89, respectively, p = ns). However, when these two models, both developed on the same derivation cohort, were tested on the more heterogeneous Krakow validation cohort, the AODE-based model proved to be much more robust and clearly outperformed the logistic regression-based model (c-statistic 0.842, 95% CI 0.82 to 0.87, vs 0.746, 95% CI 0.70 to 0.79, p<0.0001).

DISCUSSION

In this paper we report the development and validation of a novel risk-prediction model for ACS. The AMIS model had excellent predictive performance both in the derivation cohort and in two independent validation cohorts, which differed from each other in important aspects. The model performed well both with regard to discriminative precision (c-statistic) and risk calibration.

Since a number of risk-prediction scores for patients with myocardial infarction or ACS are already established, the specific advantages of the new AMIS model will be recapitulated here. First, the AMIS model is applicable to the complete range of ACS. We could show similar discriminative capacity for different subgroups, such as patients with STEMI or non-STE-ACS, for younger and more elderly patients, and for patients managed with different treatment strategies (table 2). Furthermore, the model was developed on patients from a contemporary nationwide Swiss registry, which included all subsets of patients not traditionally represented in the databases of randomised controlled trials. This is reflected by the inclusion of the variables "pre-hospital mechanical resuscitation" and "history of cerebrovascular disease" in the model. These variables have not been included in most previously reported risk-prediction tools.

Second, all seven variables required for risk calculation with the AMIS model (table 2) are rapidly available at first patient contact in the pre-hospital phase. Once a brief clinical assessment has been made, risk-prediction can be calculated without the input of blood test results. Since a major goal of a risk-prediction model is to optimise early patient management, this early availability appears advantageous. The absence of ECG or blood test variables from the AMIS model may seem counter-intuitive. However, during model development we found that many variables known to be independent predictors of risk did not improve discriminative precision with the AODE algorithm. These included STEMI versus non-STE-ACS, time from symptom onset to revascularisation therapy, the presence of atrial fibrillation at admission or a history of diabetes.

Third, the AMIS model is very easy to use. The mortality risk is available directly upon entering the seven variables into an appropriate calculator. This could be the online calculator publicly available at the AMIS-Plus website (www.amis-plus.ch) or, for use by ambulance personnel or during house visits, the model could be loaded onto a handheld computer or even a mobile telephone, digital aids which are currently widely available.

A prespecified goal of this study was to apply advanced data-mining/machine-learning techniques for model derivation, an approach which proved to be most valuable. A main strength of the AMIS model lies less in the choice of variables, but rather in the way in which variable information is processed by the model—based on the AODE algorithm[24 25]—to calculate predicted risk. This became evident in the manner in which the AODE-based model clearly outperformed a conventional logistic regression model in the Krakow validation cohort, although both models were derived from the same cohort using the same variables (see results section).

In medical science, logistic regression has been the mainstay of model generation. An alternative approach in machine-learning is the naive Bayes algorithm. Numerous approaches have been proposed to improve the classification accuracy of naive Bayes by weakening the attribute independence assumption. To

maintain the simple structure and low computational cost, research has focused on the one-dependence estimator, an approach chosen by the "averaged one-dependence estimator" (AODE) algorithm, initially described by Webb *et al* in 2002.[24] The strength of this dynamic algorithm is the ability to alter the coefficient of each variable used in the model in dependence of the value of the previous variable in the decision tree. Thus, for example, the coefficient assigned to systolic blood pressure of an individual will vary according to his age. We are unaware of other prediction tools used in medical science applying the AODE algorithm.

Up until now the only model which estimated risk based on bedside clinical variables alone was the simple risk index, using age, systolic blood pressure and heart rate. Although modelled and validated for patients with STEMI, it was noteworthy that when tested on our cohort—a contemporary, broad ACS population—the simple risk index performed similarly in STEMI and non-STE-ACS (table 2). This is consistent with a previous report on the discriminative capacity of the simple risk index (c-statistic 0.73) in a large non-STE-ACS database.[26] In our independent and external validation datasets the c-statistics of the simple risk index remained inferior to the AMIS model.

The AMIS model, as any other risk stratification tool, estimates risk for patients treated according to current standards, and does not represent the natural course of ACS. It should therefore be emphasised that the model should not be used to delay hospital admission or withhold treatment from patients estimated to be at low risk of short-term mortality. That being said, there is evidence to support the concept that patients with increased baseline risk have the largest benefit from early and aggressive therapy.[27] Despite this, data from the CRUSADE quality improvement initiative and the GRACE registry clearly showed that high-risk ACS patients are being treated less aggressively than their low-risk counterparts, and that this undertreatment was associated with increased risk-adjusted in-hospital mortality.[28 29] One might hope that more widespread use of simple, point-of-care risk-prediction tools such as the AMIS model might improve this "risk-treatment paradox".

Limitations

The Global Registry of Acute Coronary Events (GRACE) score,[16] a robust and well validated model which was recently developed on the basis of a large international ACS registry, is recommended for risk-prediction across the entire spectrum of ACS.[1] The fact that we were not able to compare its performance directly with the AMIS model, because of the absence of two required variables in our datasets ("elevated cardiac enzyme levels at admission" and "initial serum creatinine levels"), is a limitation of this study. In its original publication,[16] c-statistics of the GRACE model in its derivation (0.83) and validation datasets (0.85 in a subsequent, independent GRACE registry cohort, and 0.79 in the external GUSTO IIb cohort) were comparable to those achieved by the AMIS model in its corresponding independent validation cohorts, suggesting similar levels of predictive accuracy.

Like the GRACE score, the AMIS model includes the variable "pre-hospital resuscitation". This may appear of questionable value to the everyday clinical use of the model in decision-making, since these patients, who accounted for 4.5% of the derivation cohort and 3.0% of the validation cohort, evidently need to be managed on a "high-risk" basis. Similarly, the "high-risk" variables "history of heart failure" and "history of stroke" were present in all cohorts at a frequency of below 6% (see table 1). When these three variables were omitted from the model, the c-statistic declined only moderately from 0.879 to 0.845 with an AODE-based model in the derivation cohort (fig 1A). This underscores the limited value of additional variables beyond age and baseline parameters of haemodynamic status (Killip class, systolic blood pressure and heart rate) for the prediction of early ACS mortality. However, we thought that the added accuracy warranted the inclusion of these three easily assessed and clinically important variables, especially with regard to use of the model in population-based analyses, such as risk-adjusted benchmarking or quality control.

CONCLUSION

The AMIS model reproducibly provides risk-prediction of sufficient quality for daily clinical practice for patients with the entire spectrum of acute coronary syndromes at a very early stage of patient care, enabling optimisation of management decisions.

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Contributors and guarantor: DJKurz, AB and OB devised the study. KH performed the model development and statistical analyses together with AB and DJK. DR, PE and ZS participated in collection and maintenance of the respective patient registries. DJK wrote the first draft of the manuscript. All authors contributed to the final version of the manuscript. DJK takes overall responsibility for the manuscript.

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