ACHTUNG-Rule: a new and improved model for prognostic assessment in myocardial infarction

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Abstract

Background: Thrombolysis In Myocardial Infarction (TIMI), Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin (PURSUIT) and Global Registry of Acute Coronary Events (GRACE) scores have been developed for risk stratification in myocardial infarction (MI). The latter is the most validated score, yet active research is ongoing for improving prognostication in MI.

Aim: Derivation and validation of a new model for intrahospital, post-discharge and combined/total all-cause mortality prediction – ACHTUNG-Rule – and comparison with the GRACE algorithm.

Methods: 1091 patients admitted for MI (age 68.4 ± 13.5 , 63.2% males, 41.8% acute MI with ST-segment elevation (STEMI)) and followed for 19.7 ± 6.4 months were assigned to a derivation sample. 400 patients admitted at a later date at our institution (age 68.3 ± 13.4 , 62.7% males, 38.8% STEMI) and followed for a period of 7.2 ± 4.0 months were assigned to a validation sample. Three versions of the ACHTUNG-Rule were developed for the prediction of intrahospital, post-discharge and combined (intrahospital plus post-discharge) all-cause mortality prediction. All models were evaluated for their predictive performance using the area under the receiver operating characteristic (ROC) curve, calibration through the Hosmer–Lemeshow test and predictive utility within each individual patient through the Brier score. Comparison through ROC curve analysis and measures of risk reclassification – net reclassification improvement index (NRI) or Integrated Discrimination Improvement (IDI) – was performed between the ACHTUNG versions for intrahospital, post-discharge and combined mortality prediction and the equivalent GRACE score versions for intrahospital (GRACE-IH), post-discharge (GRACE-6PD) and post-admission 6-month mortality (GRACE-6).

Results: Assessment of calibration and overall performance of the ACHTUNG-Rule demonstrated a good fit (p value for the Hosmer–Lemeshow goodness-of-fit test of 0.258, 0.101 and 0.550 for ACHTUNG-IH, ACHTUNG-T and ACHTUNG-R, respectively) and high discriminatory power in the validation cohort for all the primary endpoints (intrahospital mortality: AUC ACHTUNG-IH 0.886 ± 0.035 vs. AUC GRACE-IH 0.906 ± 0.026 ; post-discharge mortality: AUC ACHTUNG-R 0.827 ± 0.036 vs. AUC GRACE-6PD 0.811 ± 0.034 ; combined/total mortality: AUC ACHTUNG-T 0.831 ± 0.028 vs. AUC GRACE-6 0.815 ± 0.033). Furthermore, all versions of the ACHTUNG-Rule accurately reclassified a significant number of patients in different, more appropriate, risk categories (NRI ACHTUNG-IH 17.1%, p (2-sided) = 0.0021; NRI ACHTUNG-R 22.0%, p = 0.0002; NRI ACHTUNG-T 18.6%, p = 0.0012). The prognostic performance of the ACHTUNG-Rule was similar in both derivation and validation samples.

Conclusions: All versions of the ACHTUNG-Rule have shown excellent discriminative power and good calibration for predicting intrahospital, post-discharge and combined in-hospital plus post-discharge mortality. The ACHTUNG version for intrahospital mortality prediction was not inferior to its equivalent GRACE model, and ACHTUNG versions for post-discharge and combined/total mortality demonstrated apparent superiority. External validation in wider, independent, preferably multicentre, registries is warranted before its potential clinical implementation.

Keywords

Myocardial infarction, prognosis, risk assessment, GRACE risk score

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Introduction

The 'Thrombolysis In Myocardial Infarction' (TIMI),^{1,2} 'Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin' (PURSUIT),^{3,4} 'Patient Refined Expectations for Deciding Invasive Cardiac Treatments' (PREDICT),⁵ 'Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries' (GUSTO)⁶ and 'Global Registry of Acute Coronary Events' (GRACE)⁷ algorithms have been developed for prognostication of patients with acute coronary syndromes (ACS). The GRACE model was a large multinational registry encompassing the full spectrum of acute coronary disease. Its population comprised 68,937 patients with a diagnosis of ACS and a prognostic model which predicted the risk of death (and combined death plus myocardial infarction (MI)) was established. Some investigators have shown the superior predictive accuracy of the GRACE score compared to TIMI or PURSUIT in the ACS population.^{8,9} Therefore, the GRACE algorithm is the most widely validated risk score for patients with ACS, with three versions for intrahospital, post-admission or post-discharge 6-month all-cause mortality prediction. Its ability for prognostic stratification beyond the 6-month mark has been clearly demonstrated in several studies.^{10,11}

Nevertheless, prognostic assessment of patients with an MI is still an area of ongoing research. Although the scores that have been developed are extremely useful for the prognostication of these patients and the validity of the GRACE score in particular is well established,^{12–14} better statistical approaches and scores more efficient in low- and high-risk patient stratification should be developed, considering early risk stratification plays a pivotal role in patients with MI. As these scores and approaches are developed, they need to be validated and tested for discrimination and calibration.

This study was performed for the derivation and preliminary validation of a new and improved algorithm for prognostication of patients with an MI – ACHTUNG-Rule, providing estimation of intrahospital (ACHTUNG-IH), post-discharge (ACHTUNG-R) and combined/total (ACHTUNG-T) [intrahospital plus post-discharge] all-cause mortality prediction. Subsequently, we aimed at establishing a comparison between the ACHTUNG-Rule and the most widely validated algorithm for prognostic evaluation of patients with an MI, the GRACE score.

Materials and methods

Study design

We included all patients admitted to the Acute Cardiac Care Unit of the Centro Hospitalar de Coimbra with a diagnosis of MI between 1 January 2007 and 31 December 2009. Using collected baseline data at the time of MI diagnosis

and outcome data from this cohort, we retrospectively assessed the GRACE score for intrahospital (GRACE-IH), 6-month post-admission (GRACE-6) and 6-month post-discharge (GRACE-6PD) mortality for all patients. We compared the ability of GRACE to predict primary and secondary endpoints to that of a new algorithm developed by multivariate analysis – ACHTUNG-Rule. For this purpose, three versions of ACHTUNG were developed:

1. ACHTUNG for intra-hospital all-cause mortality prediction (ACHTUNG-IH), which included the following predictors: Age, Creatinine clearance, C-reactive protein, Haemoglobin, Haemodynamics (blood pressure and heart rate at admission), Troponin I, Urea, NT-proBNP and Glycaemia (all analytical parameters were continuous and collected at admission);
2. ACHTUNG for post-discharge all-cause mortality prediction (ACHTUNG-R), which included the following predictors: Age, Creatinine clearance, C-reactive protein, Haemoglobin, Troponin I, Urea, NT-proBNP, Glycaemia and performance of a Revascularization procedure (all analytical parameters collected at admission, except for Troponin I, in which case the maximum achieved value was used);
3. ACHTUNG for combined/total all-cause mortality prediction (intrahospital plus post-discharge mortality) (ACHTUNG-T), comprising the same predictors included in ACHTUNG-IH.

All models were evaluated for their overall predictive performance, accuracy and calibration, and a comparison was performed between the ACHTUNG versions for IH, post-discharge and total mortality prediction and the equivalent GRACE score versions. These analyses were performed in the derivation cohort and in an independent patient sample using data from 400 patients admitted to the Centro Hospitalar de Coimbra for an MI between 1 August 2010 and 31 September 2011.

Patients and eligibility criteria

One-thousand and ninety-one patients consecutively admitted to the Acute Cardiac Care Unit of a tertiary referral hospital and university centre with an MI were included in the derivation sample, and 400 patients consecutively admitted at a later date were assigned to the validation cohort. Table 1 describes both study samples. Eligible patients were required to have a diagnosis of MI according to the Universal Definition of Myocardial Infarction.¹⁵ Patients were classified as having acute MI with ST-segment elevation (STEMI) or MI without ST-segment elevation (NSTEMI). Patients with previously known left bundle branch block or ventricular pacemaker rhythm were included in the NSTEMI group.

Table 1. Description of derivation and validation samples.

	Derivation sample	Validation sample
Age (years)	68.4 ± 13.5	68.3 ± 13.4
Male gender	64.7% (n = 706)	68.5% (n = 274)
Type of myocardial infarction	STEMI 41.8%; NSTEMI 58.2%	STEMI 38.8%; NSTEMI 61.2%
Diabetes mellitus	35.7% (n = 390)	28.5% (n = 114)
Previous hypertension	75.0% (n = 817)	74.8% (n = 299)
Hyperlipidaemia	56.5% (n = 615)	56.6% (n = 226)
Smoking habits	26.3% (n = 287)	28.5% (n = 114)
Previously known coronary disease	25.9% (n = 283)	29.0% (n = 116)
Atrial fibrillation at admission	13.5% (n = 147)	14.2% (n = 57)
Admission Killip class	1.38 ± 0.7	1.35 ± 0.7
Maximum Killip class	1.53 ± 0.9	1.46 ± 0.8
Average number of vessels with significant lesions	1.58 ± 0.99	1.56 ± 0.99
Without coronary disease (of those submitted to coronariography)	12.2% (n = 113)	11.0% (n = 44)
Glomerular filtration rate at admission	71.1 ± 38.3	79.6 ± 34.7
Submitted to revascularization procedures	60.4% (n = 659)	69.0% (n = 276)
Average GRACE score for intrahospital mortality	156.1 (P ₂₅ 112; P ₅₀ 143; P ₇₅ 174)	144.7 (P ₂₅ 112; P ₅₀ 143; P ₇₅ 174)
Average GRACE score for 6-month mortality	127.5 (P ₂₅ 92; P ₅₀ 119; P ₇₅ 146)	121.7 (P ₂₅ 92; P ₅₀ 119; P ₇₅ 146)
Average ACHTUNG score for intrahospital mortality	8.3 (P ₂₅ 3.2; P ₅₀ 5.2; P ₇₅ 9.7)	7.7 (P ₂₅ 2.5; P ₅₀ 4.7; P ₇₅ 8.2)
Average ACHTUNG score for post-discharge mortality	19.6 (P ₂₅ 3.8; P ₅₀ 11.1; P ₇₅ 27.2)	17.7 (P ₂₅ 3.0; P ₅₀ 8.0; P ₇₅ 22.4)
Average ACHTUNG score for combined mortality	24.4 (P ₂₅ 6.9; P ₅₀ 16.3; P ₇₅ 34.8)	22.3 (P ₂₅ 5.4; P ₅₀ 13.0; P ₇₅ 30.4)
Intrahospital mortality	7.7% (n = 84)	5.2% (n = 21)
Post-discharge mortality	16.5% (n = 165)	8.0% (n = 32)
	(Follow-up: 19.7 ± 6.4 months)	(Follow-up: 7.2 ± 4.0 months)

ACHTUNG: Age, Creatinine clearance, C-reactive protein, Haemoglobin, Haemodynamics, Troponin I, Urea, NT-proBNP, Glycaemia; GRACE: Global Registry of Acute Coronary Events; NSTEMI: MI without ST-segment elevation; STEMI: MI with ST-segment elevation.

Data collection

The following data were collected: demographic features, cardiovascular risk factors, analytical study at admission (including haemoglobin, glycaemia, NT-proBNP, C-reactive protein, creatinine, urea, troponin I, ionogram, prothrombin time), maximum troponin I levels, results of coronariography and revascularization procedures and pre-discharge transthoracic echocardiogram (when performed). Glomerular filtration rate (GFR – by Modification of Diet in Renal Disease (MDRD) formula) and the GRACE scores for intrahospital, 6-month post-admission and 6-month post-discharge mortality were calculated for all patients.

Study endpoints

The primary endpoints used to assess and compare the prognostic power of ACHTUNG-Rule and the GRACE score were intrahospital, post-discharge and combined (intrahospital plus post-discharge) all-cause mortality.

Patient follow-up

Patients assigned to the derivation cohort were followed for 19.7 ± 6.4 months after their discharge, whereas those in

the validation sample were followed for a mean period of 7.2 ± 3.0 months. Follow-up data were obtained from clinical records from outpatient clinic and hospital ward and emergency department admission(s), and through phone calls by the end of a 2-year period after discharge for patients not followed at our hospital.

Statistical analysis

Statistical analysis was done using SPSS, v.17.0. When needed, baseline characteristics are described with mean ± standard deviation for continuous data and counts and proportions for categorical data. Patients' baseline characteristics were used for determining their risk classification according to published criteria for GRACE:^{16,17}

1. For patients with non ST segment elevation MI (NSTEMI), a GRACE-IH score below 109 was considered low risk, whereas scores between 109 and 140 and above 140 were assigned to intermediate- and high-risk categories, respectively. GRACE-6 and GRACE-6PD scores below 89 were assigned as low risk, whereas scores between 89 and 118 and above 118 were considered intermediate and high risk, respectively.

2. For patients with ST elevation MI (STEMI), a GRACE-IH score below 126 was considered low risk, a score between 126 and 154 was assigned to the intermediate-risk category and above 154 to the high-risk group. GRACE-6 and GRACE-6PD scores below 100 were assigned to the low-risk category, with scores between 100 and 127 and above 127 the intermediate- and high-risk categories, respectively.

In the derivation sample, binary logistic regression multivariate analysis (method Enter) was performed to create models for intrahospital, post-discharge and combined mortality prediction (variables entered in the multivariate model analysis were those that predicted mortality in univariate analysis), named ACHTUNG-IH, ACHTUNG-R and ACHTUNG-T, respectively. Probabilities estimated by binary logistic regression were multiplied by 100 to create a new variable with the ACHTUNG score itself. Patients were divided into three risk categories:

1. ACHTUNG-IH: score below 4.3 – low risk; between 4.3 and 5.4 – intermediate risk; above 5.4 – high risk;
2. ACHTUNG-R: score below 5.2 – low risk; between 5.2 and 11.3 – intermediate risk; above 11.3 – high risk.
3. ACHTUNG-T: score below 11.0 – low risk; between 11.0 and 15.1 – intermediate risk; above 15.1 – high risk.

Regression coefficients obtained by multivariate analysis in the derivation cohort were then applied to the validation sample to calculate the predicted risks according to the ACHTUNG-Rule.

In both samples, we assessed the overall discriminatory power of each version of the ACHTUNG-Rule by calculating the area under each receiver operating characteristic curve (AUC). Discrimination, usually measured in terms of AUC, refers to the ability of a model to assign a higher probability to non-survivors than to survivors. The AUC, however, gives no indication of how close the predicted probabilities are to the true ones (estimated by the observed proportion of death). Calibration refers to this agreement between predicted and true probabilities and is most often measured by the Hosmer–Lemeshow goodness-of-fit statistics, which suggest good fit when the associated *p* values are greater than 0.05. Therefore, calibration of each model was evaluated using the Hosmer–Lemeshow goodness-of-fit test.

Accuracy of each version of the ACHTUNG-Rule was analyzed through the Brier score. Accuracy is a measure of the average distance (residual) between the observed outcome and its predicted probability for each individual patient. A popular accuracy measure is the Brier score, which is the squared mean of the residual values. The Brier

score is sensitive to both discrimination and calibration of the predicted probabilities, and describes how well a particular model predicts the likelihood of an outcome in an individual patient (a score of 0.0 implies perfect prediction, whereas a Brier close to 0.25 suggests lack of utility in end-point prediction).

ACHTUNG score versatility was tested by further assessing its discriminatory power according to the type of MI (NSTEMI and STEMI), gender, age, the presence of diabetes mellitus or renal dysfunction and the performance of a revascularization procedure.

Comparison through receiver operating characteristic (ROC) curve analysis and measures of risk reclassification (such as the net reclassification improvement index (NRI) or the integrated discrimination improvement index (IDI)) was performed between the ACHTUNG versions for intrahospital, post-discharge and combined mortality prediction and the equivalent GRACE score versions for intrahospital (GRACE-IH), post-discharge (GRACE-6PD) and combined post-admission 6-month mortality (GRACE-6). The NRI was calculated according to the method described by Pencina et al.¹⁸ to quantify these reclassifications. A positive and significant NRI translates a net overall successful reclassification of subjects into more appropriate risk categories (e.g. a patient who reaches the primary endpoint that is reclassified into higher risk groups with the new model or a subject who does not reach the primary endpoint that is reclassified into a lower risk category with the new model). The amount of overall reclassification is translated by the extent of the NRI (a per cent value). A positive NRI value represents an adequate reclassification into the correct risk category, whereas a negative NRI represents a worse reclassification with the new risk stratification scheme. The IDI, which may be seen as a continuous form of the NRI, assesses improvement in risk discrimination by estimating the change in the difference in the mean predicted probabilities of the outcome between those with and without the outcome in question.¹⁹

These analyses were performed in both derivation and validation samples.

Results

Baseline characteristics (GRACE vs. ACHTUNG derivation samples)

The GRACE score derivation sample included the full spectrum of ACS, of which 34% of patients had STEMI, 31% NSTEMI and 29% unstable angina.⁷ Our ACHTUNG derivation sample included patients with MI (41.8% with STEMI, 58.2% with NSTEMI), excluding those with unstable angina. Patients were of similar age in both cohorts and male gender was slightly less prevalent in our population sample. A higher prevalence of most comorbid illnesses and cardiovascular risk factors was reported in our study

(in particular, hypertension, diabetes mellitus and hyperlipidaemia were seen more often, whereas smoking habits were less prevalent). Patients included in our sample were more often submitted to cardiac catheterization (80.4% vs. 59.7%) and revascularization procedures (60.1% vs. 38.5%).

In our derivation cohort, intrahospital mortality rate was 7.7%, of which 56.5% were patients with STEMI. Mortality rate in the validation sample was slightly lower (5.2–76.2% with STEMI). Mortality during follow-up was 20.7% in the former (70.3% with NSTEMI) and significantly lower in the latter (10.0%, of which 75.9% with NSTEMI), a difference that is explained by the different lengths of follow-up.

The categorization of the 1491 patients assigned to the derivation and validation cohorts in the low-, intermediate- or high-risk subgroups according to the GRACE and ACHTUNG scores is illustrated in Table 2.

Derivation of the ACHTUNG-Rule

We derived our prediction models using binary logistic regression, technique Enter, with intrahospital, post-discharge and combined mortality as the outcomes, respectively. Variables included in the ACHTUNG-Rule were one demographic parameter (age), six analytical findings (haemoglobin, troponin I, urea, NT-proBNP, glycaemia and C-reactive protein) and four clinical variables (creatinine clearance by the MDRD formula, derived from serum creatinine concentration; haemodynamic parameters: systolic blood pressure and heart rate at admission; performance of

revascularization). Table 3 illustrates the weight of each factor in its respective predictive model.

Even though statistical significance was not reached for all variables (which was expected, considering logistic regression Enter method had been used), their combination allowed a more efficient prediction of mortality, as assessed by the AUC. The addition of further parameters did not improve the discriminatory performance of the predictive models. The *p* value for the Hosmer–Lemeshow goodness-of-fit test confirmed the good calibration of the three versions of the ACHTUNG-Rule (*p* = 0.258 for ACHTUNG-IH; *p* = 0.101 for ACHTUNG-T; *p* = 0.550 for ACHTUNG-R), indicating that the overall model fit was good.

ACHTUNG score for intrahospital mortality prediction – ACHTUNG-IH

Overall validation of ACHTUNG-IH

Derivation cohort. Using the predefined cutoff points, the ACHTUNG-IH score classified 36.2% of patients in the low-risk category and 20.9% and 42.9% in the intermediate and high-risk categories, respectively. Compared to GRACE-IH, a considerably higher proportion of patients was classified as low-risk by the ACHTUNG algorithm and a lower proportion was included in the high-risk group (Table 2). Incidence of the primary endpoint (intrahospital mortality) according to ACHTUNG-IH and GRACE-IH risk categories is reported in Table 4.

Table 2. Categorization of study sample patients in low-, intermediate- or high-risk subgroups according to the GRACE and ACHTUNG scores.

	Derivation cohort		
	Low risk	Intermediate risk	High risk
GRACE-IH	18.4% (<i>n</i> = 201)	24.8% (<i>n</i> = 270)	56.8% (<i>n</i> = 620)
GRACE-6 post-admission	18.9% (<i>n</i> = 206)	26.0% (<i>n</i> = 284)	55.1% (<i>n</i> = 601)
GRACE-6 post-discharge	13.9% (<i>n</i> = 139)	24.7% (<i>n</i> = 247)	61.4% (<i>n</i> = 613)
ACHTUNG-IH	36.2% (<i>n</i> = 395)	20.9% (<i>n</i> = 228)	42.9% (<i>n</i> = 468)
ACHTUNG-T	29.7% (<i>n</i> = 324)	20.3% (<i>n</i> = 221)	50.0% (<i>n</i> = 545)
ACHTUNG-R	31.6% (<i>n</i> = 316)	19.0% (<i>n</i> = 190)	49.3% (<i>n</i> = 493)
	Validation cohort		
	Low risk	Intermediate risk	High risk
GRACE-IH	26.9% (<i>n</i> = 107)	27.6% (<i>n</i> = 111)	45.5% (<i>n</i> = 182)
GRACE-6 post-admission	26.1% (<i>n</i> = 104)	28.4% (<i>n</i> = 114)	45.5% (<i>n</i> = 182)
GRACE-6 post-discharge	18.3% (<i>n</i> = 73)	28.8% (<i>n</i> = 115)	52.9% (<i>n</i> = 212)
ACHTUNG-IH	41.8% (<i>n</i> = 167)	23.3% (<i>n</i> = 93)	34.9% (<i>n</i> = 140)
ACHTUNG-T	36.9% (<i>n</i> = 148)	20.9% (<i>n</i> = 84)	42.2% (<i>n</i> = 168)
ACHTUNG-R	37.9% (<i>n</i> = 144)	19.7% (<i>n</i> = 74)	42.4% (<i>n</i> = 161)

GRACE: Global Registry of Acute Coronary Events; GRACE-IH: GRACE score for intrahospital mortality; GRACE-6: GRACE score for 6-month mortality; ACHTUNG: Age, Creatinine clearance, C-reactive protein, Haemoglobin, Troponin I, Urea, NT-proBNP, Glycaemia; ACHTUNG-IH: ACHTUNG score for intrahospital mortality; ACHTUNG-T: ACHTUNG score for combined mortality; ACHTUNG-R: ACHTUNG score for post-discharge mortality.

Table 3. ACHTUNG models for intrahospital (ACHTUNG-IH), post-discharge (ACHTUNG-R) and combined/total (ACHTUNG-T) all-cause mortality prediction in patients with a myocardial infarction.

ACHTUNG-IH	B	p	Exp (B) (95% CI)
Age	0.032	0.007	1.032 (1.009–1.056)
Creatinine clearance	–0.004	0.449	0.996 (0.986–1.006)
C-reactive protein	0.033	0.056	1.033 (0.999–1.068)
Haemoglobin	0.027	0.392	1.027 (0.966–1.093)
Haemodynamics (admission)			
Systolic blood pressure	–0.017	< 0.001	0.983 (0.974–0.992)
Heart rate	0.014	0.020	1.014 (1.002–1.026)
Troponin I	0.000	0.725	1.000 (0.998–1.002)
Urea	0.043	0.003	1.044 (1.015–1.074)
NT-proBNP	0.000	0.188	1.000 (1.000–1.000)
Glycaemia	0.076	< 0.001	1.079 (1.038–1.121)
ACHTUNG-R			
Age	0.063	< 0.001	1.065 (1.042–1.090)
Creatinine clearance	–0.004	0.372	0.996 (0.987–1.005)
C-reactive protein	0.079	< 0.001	1.083 (1.041–1.126)
Haemoglobin	–0.073	0.177	0.930 (0.837–1.033)
Maximum troponin I	0.005	< 0.001	1.005 (1.002–1.007)
Urea	0.048	0.013	1.049 (1.010–1.090)
NT-proBNP	0.000	0.004	1.000 (1.000–1.000)
Glycaemia	0.016	0.450	1.016 (0.976–1.058)
Revascularization procedures ^a	–0.957	< 0.001	0.384 (0.248–0.596)
ACHTUNG-T			
Age	0.058	< 0.001	1.059 (1.040–1.079)
Creatinine clearance	–0.005	0.189	0.995 (0.988–1.002)
C-reactive protein	0.079	< 0.001	1.082 (1.043–1.124)
Haemoglobin	–0.029	0.517	0.971 (0.889–1.061)
Haemodynamics			
Systolic blood pressure	–0.009	0.007	0.991 (0.985–0.998)
Heart rate	0.015	0.001	1.015 (1.006–1.025)
Troponin I	0.001	0.450	1.001 (0.999–1.003)
Urea	0.071	< 0.001	1.073 (1.037–1.111)
NT-proBNP	0.000	0.002	1.000 (1.000–1.000)
Glycaemia	0.037	0.030	1.037 (1.004–1.072)

^aCategorical variables.

All analytical and clinical variables collected at admission, except for maximum Troponin I (ACHTUNG-R).

Brier score analysis using this model demonstrated a mean value of 0.068, which suggests a high predictive capacity within individual patients. ACHTUNG's discriminatory power was assessed by calculating the AUC for intrahospital mortality prediction, which was compared to that of GRACE-IH:

- AUC ACHTUNG-IH 0.824 ± 0.022 , 95% CI 0.781–0.868; vs. AUC GRACE-IH 0.826 ± 0.023 , 95% CI 0.781–0.870 (Figure 1).

Category-based NRI provided a more rigorous statistical approach to assess the improvement in reclassification by using ACHTUNG-IH instead of GRACE-IH. ACHTUNG-IH reclassified 21.2% of cases into risk strata that were more accurate representations of observed

mortality risks (NRI 21.2%, 95% CI 14.4–27.9%, p (2-sided) < 0.000001).

Forty-seven patients who did not die during hospitalization were reclassified upward, and 313 were reclassified downward. The net estimate for those not reaching the primary endpoint was the difference between these two estimates divided by the total number of people who did not die $[(313 - 47)/999 = \rightarrow 0.266 \text{ } 26.6\%]$, which was statistically significant. A total of six patients who reached the primary endpoint were reclassified downward (vs. one upward reclassification case). The net estimate for the percentage reclassified upward was the difference between these two estimates divided by the total number of people who died during hospitalization $[(1 - 6)/92 = -0.054 \rightarrow -5.4\%]$, which was not statistically significant. The NRI was then estimated by taking the sum of the net estimates for those who developed an

Table 4. Intrahospital, post-discharge and combined/total mortality rates according to the ACHTUNG-Rule and GRACE score risk-group stratification.

Intrahospital mortality rates				
Derivation cohort				
	Low risk	Intermediate risk	High risk	P
GRACE-IH	1.0%	1.1%	13.2%	< 0.001
ACHTUNG-IH	1.0%	2.0%	15.8%	< 0.001
Validation cohort				
	Low risk	Intermediate risk	High risk	P
GRACE-IH	0%	0%	11.6%	< 0.001
ACHTUNG-IH	0%	1.1%	12.3%	< 0.001
Post-discharge mortality rates				
Derivation cohort (follow-up: 19.8 ± 6.4 months)				
	Low risk	Intermediate risk	High risk	P
GRACE-6PD	1.4%	5.4%	26.6%	< 0.001
ACHTUNG-R	2.0%	5.7%	34.4%	< 0.001
Validation cohort (follow-up: 7.2 ± 4.0 months)				
	Low risk	Intermediate risk	High risk	P
GRACE-6PD	0%	1.8%	14.5%	< 0.001
ACHTUNG-R	0.7%	4.2%	17.3%	< 0.001
Combined/total mortality rates				
Derivation cohort (follow-up: 19.8 ± 6.4 months)				
	Low risk	Intermediate risk	High risk	P
GRACE-6	3.2%	8.1%	39.8%	< 0.001
ACHTUNG-T	3.5%	6.2%	44.5%	< 0.001
Validation cohort (follow-up: 7.2 ± 4.0 months)				
	Low risk	Intermediate risk	High risk	P
GRACE-6	2.0%	4.5%	24.1%	< 0.001
ACHTUNG-T	0.7%	8.0%	24.7%	< 0.001

GRACE-IH: GRACE score for intrahospital mortality; ACHTUNG-IH: ACHTUNG score for intrahospital mortality; GRACE-6: GRACE score for 6-month mortality; ACHTUNG-2: ACHTUNG score for 2-year mortality.

event (intrahospital mortality) and those who did not develop an event, which was 21.2% (−5.4% + 26.6%, p (2-sided) = 0.000001). Cross tabulation between GRACE-IH and ACHTUNG-IH in the derivation sample (according to the level of risk estimated by both: low, intermediate or high), and respective NRI, is described in Table 5.

Validation cohort. Using the predefined cutoff points, the ACHTUNG-IH score classified 41.8% of patients in the low-risk category and 23.3% and 34.9% in the intermediate- and high-risk categories, respectively. Compared to the GRACE score, a considerably higher proportion of patients was classified as low-risk by the ACHTUNG algorithm and a lower proportion was included in the

high-risk group (Table 2). Incidence of the primary end-point (intrahospital mortality) according to ACHTUNG-IH and GRACE-IH risk stratification is reported in Table 4.

A Brier score value of 0.040 confirmed a very high predictive capacity within individual patients. ACHTUNG's discriminatory power was assessed by calculating the AUC for intrahospital mortality prediction, which was compared to that of GRACE-IH:

- AUC ACHTUNG-IH 0.886 ± 0.035 , 95% CI 0.819–0.954; vs. AUC GRACE-IH 0.906 ± 0.026 , 95% CI 0.856–0.957 (Figure 1).

Figure 1. Intrahospital mortality: comparison between the ACHTUNG score for intrahospital mortality prediction and the equivalent GRACE version.

A significant net improvement in risk classification was shown by an NRI value of 17.1% (95% CI 6.2–28.1%, p (2-sided) = 0.0021). Nineteen patients who did not die during hospitalization were classified upward, whereas 102 were reclassified downward. The net estimate for those not reaching the primary endpoint was $[(102 - 19)/379 = 0.219 \rightarrow 21.9\%]$, which was statistically significant. One patient who reached the primary endpoint was reclassified downward (vs. no upward reclassification cases). The net estimate for the percentage reclassified upward was $[(0 - 1)/21 = -0.048 \rightarrow -4.8\%]$, which was not statistically significant. The NRI was estimated by taking the sum of the net estimates for those who developed an event and those who did not develop an event, which was 17.1% ($-4.8\% + 21.9\%$, p (2-sided) = 0.0021). Cross tabulation between GRACE-IH and ACHTUNG-IH, and respective NRI, is described in Table 6.

Validation of ACHTUNG-IH according to the type of myocardial infarction. The discriminatory power of ACHTUNG-IH according to type of MI and potential improvement in risk reclassification (compared to GRACE-IH) was assessed by calculating the AUC and the NRI index, respectively, in both the derivation and validation samples.

Derivation sample

- STEMI: AUC ACHTUNG-IH 0.833 ± 0.031 , 95% CI 0.773–0.894; vs. AUC GRACE-IH 0.803 ± 0.035 , 95% CI 0.735–0.872. A significant net improvement in risk classification was demonstrated by a NRI value of 26.8% in favour of ACHTUNG-IH (95% CI 17.2–36.5%, p (2-sided) < 0.00001).
- NSTEMI: AUC ACHTUNG-IH 0.825 ± 0.031 , 95% CI 0.765–0.886; vs. AUC GRACE-IH 0.845 ± 0.028 ,

95% CI 0.790–0.901. A significant net improvement in risk classification was shown by an NRI value of 16.4% (95% CI 6.7–26.1%, p (2-sided) = 0.0009).

Validation sample

- STEMI: AUC ACHTUNG-IH 0.902 ± 0.046 , 95% CI 0.812–0.992; vs. AUC GRACE-IH 0.877 ± 0.037 , 95% CI 0.805–0.950. A 24.7% NRI value in favour of ACHTUNG-IH (95% CI 8.9–40.4%, p (2-sided) = 0.0021) was achieved.
- NSTEMI: AUC ACHTUNG-IH 0.858 ± 0.056 , 95% CI 0.748–0.951; vs. AUC GRACE-IH 0.914 ± 0.048 , 95% CI 0.820–0.971. A significant net improvement in risk classification was shown by an NRI value of 16.1% (95% CI 8.7–23.5%, p (2-sided) = 0.00002).

Validation of the ACHTUNG-IH in particular subgroups. The discriminatory power of ACHTUNG-IH was assessed in particular subgroups, namely patients older than 75 years old, male or female patients, individuals with diabetes mellitus or renal dysfunction and those submitted to revascularization procedures. ACHTUNG's AUC for intrahospital mortality prediction was compared to that of GRACE-IH (Table 7).

ACHTUNG score for post-discharge mortality prediction – ACHTUNG-R

Overall validation of ACHTUNG-R

Derivation cohort. According to predefined cutoff points, the ACHTUNG-R score classified 30.2% of patients in the

Table 5. Derivation cohort: Net reclassification improvement obtained by the ACHTUNG models (ACHTUNG-IH, ACHTUNG-R and ACHTUNG-T) compared to the GRACE algorithms (GRACE-IH, GRACE-6PD and GRACE-6).

Intrahospital all-cause mortality			GRACE-IH			
			Low risk	Moderate risk	High risk	
Events (<i>n</i> = 92)	ACHTUNG-IH	Low risk	3	1	1	NRI = 21.2% <i>p</i> < 0.00001
		Moderate risk	0	1	4	
		High risk	0	1	81	
Non-events (<i>n</i> = 999)		Low risk	191	137	52	
		Moderate risk	11	81	124	
		High risk	2	34	367	
Post-discharge all-cause mortality			GRACE-6PD			
			Low risk	Moderate risk	High risk	
Events (<i>n</i> = 165)	ACHTUNG-R	Low risk	2	4	1	NRI = 27.8% <i>p</i> < 0.00001
		Moderate risk	1	5	6	
		High risk	0	5	141	
Non-events (<i>n</i> = 843)		Low risk	194	144	30	
		Moderate risk	7	85	110	
		High risk	2	15	392	
Combined/total all-cause mortality			GRACE-6			
			Low risk	Moderate risk	High risk	
Events (<i>n</i> = 249)	ACHTUNG-T	Low risk	9	3	0	NRI = 17.1% <i>p</i> < 0.00001
		Moderate risk	0	5	8	
		High risk	0	11	213	
Non-events (<i>n</i> = 842)		Low risk	210	97	14	
		Moderate risk	9	129	67	
		High risk	0	25	291	

p values are 2-sided.

GRACE-IH: GRACE score for intrahospital mortality; ACHTUNG-IH: ACHTUNG score for intrahospital mortality; GRACE-6PD: GRACE score for post-discharge 6-month mortality; ACHTUNG-R: ACHTUNG score for post-discharge mortality; GRACE-6: GRACE score for post-admission 6-month mortality; ACHTUNG-T: ACHTUNG score for combined/total mortality; NRI: net reclassification improvement index.

low-risk group, 17.1% in the intermediate-risk category and 52.7% in the high-risk group. Compared to the GRACE score for post-discharge 6-month mortality (GRACE-6PD), more patients were eligible for the low-risk category and a much lower proportion of patients was included in the high-risk group (Table 2). Occurrence of the primary endpoint (intrahospital mortality) according to ACHTUNG-R and GRACE-6PD risk categories is reported in Table 4.

Brier score analysis using this model demonstrated a mean value of 0.103, which suggests a good predictive capacity within individual patients. ACHTUNG's discriminatory power was assessed by calculating the AUC for post-discharge mortality prediction, which was compared to that of GRACE-6PD:

- AUC ACHTUNG-R 0.853 ± 0.016 , 95% CI 0.821–0.884; vs. AUC GRACE-6PD 0.795 ± 0.019 , 95% CI 0.759–0.832 (Figure 2).

The net improvement estimate for those not reaching the primary endpoint was 30.8%, whereas the net estimate for the percentage reclassified upward was –3.0%. Overall risk classification improved significantly, with an NRI value of 27.8% (95% CI 21.7–34.5%, *p* (2-sided) < 0.000001). Cross tabulation between the GRACE-6PD and ACHTUNG-R models in the derivation sample, and respective NRI, is described in Table 5. A clinically less intuitive method to assess reclassification is the calculation of the integrated discrimination improvement, which does not rely on prespecified risk categories but represents a continuous measure: in this case, the IDI and relative IDI were 0.093 (*p* < 0.001) and 39.4%, respectively, translating significant improvement in risk classification.

Validation cohort. The ACHTUNG-R score classified 37.9% of patients in the low-risk group, 19.7% in the intermediate-risk category and 42.2% in the high-risk

Table 6. Validation cohort: Net reclassification improvement obtained by the ACHTUNG models (ACHTUNG-IH, ACHTUNG-R and ACHTUNG-T) compared to the GRACE algorithms (GRACE-IH, GRACE-6PD and GRACE-6).

Intrahospital all-cause mortality			GRACE-IH			
			Low risk	Moderate risk	High risk	
Events (<i>n</i> = 21)	ACHTUNG-IH	Low risk	0	0	0	NRI = 17.1% <i>p</i> = 0.0021
		Moderate risk	0	0	1	
		High risk	0	0	16	
Non-events (<i>n</i> = 379)		Low risk	92	50	14	
		Moderate risk	5	43	38	
		High risk	2	12	100	
Post-discharge all-cause mortality			GRACE-6PD			
			Low risk	Moderate risk	High risk	
Events (<i>n</i> = 32)	ACHTUNG-R	Low risk	0	0	1	NRI = 22.0% <i>p</i> = 0.0002
		Moderate risk	0	2	1	
		High risk	0	0	28	
Non-events (<i>n</i> = 347)		Low risk	72	66	8	
		Moderate risk	3	28	39	
		High risk	0	12	119	
Combined/total all-cause mortality			GRACE-6			
			Low risk	Moderate risk	High risk	
Events (<i>n</i> = 53)	ACHTUNG-T	Low risk	0	0	1	NRI = 18.6% <i>p</i> = 0.0012
		Moderate risk	2	5	1	
		High risk	0	2	42	
Non-events (<i>n</i> = 347)		Low risk	89	45	3	
		Moderate risk	7	41	22	
		High risk	0	14	106	

p values are 2-sided.

GRACE-IH: GRACE score for intrahospital mortality; ACHTUNG-IH: ACHTUNG score for intrahospital mortality; GRACE-6PD: GRACE score for post-discharge 6-month mortality; ACHTUNG-R: ACHTUNG score for post-discharge mortality; GRACE-6: GRACE score for post-admission 6-month mortality; ACHTUNG-T: ACHTUNG score for combined/total mortality; NRI: net reclassification improvement index.

group. Compared to GRACE, more patients were eligible for the low-risk category and a lower proportion was included in the high-risk group (Table 2). Occurrence of the primary endpoint (intrahospital mortality) according to ACHTUNG-R and GRACE-6PD risk strata is reported in Table 4.

A Brier score value of 0.084 suggested high overall performance within individual patients. ACHTUNG's discriminatory power was assessed and compared to that of GRACE-6PD:

- AUC ACHTUNG-R 0.827 ± 0.036 , 95% CI 0.757–0.897; vs. AUC GRACE-6PD 0.811 ± 0.034 , 95% CI 0.745–0.878 (Figure 2).

The net improvement estimate for those not reaching the primary endpoint was 28.9%, whereas the net estimate for the percentage reclassified upward was –6.9%. Overall risk

classification improved significantly, with an NRI value of 22.0% (95% CI 10.4–33.6%, p (2-sided) = 0.0002). Cross tabulation between GRACE-6PD and ACHTUNG-R is illustrated in Table 5. The IDI index was 0.085 ($p < 0.001$) (relative IDI of 27.3%), suggesting significant improvement in risk classification.

Validation of ACHTUNG-R according to the type of myocardial infarction. The discriminatory power of ACHTUNG-R according to type of MI and the net improvement in risk reclassification (compared to GRACE-6PD) were assessed through ROC curves and the NRI index, respectively, in both the derivation and validation samples.

Derivation sample

- STEMI: AUC ACHTUNG-R 0.854 ± 0.031 , 95% CI 0.794–0.914; vs. AUC GRACE-6PD 0.786 ± 0.035 ,

Table 7. Assessment of the ACHTUNG score for intrahospital mortality prediction in particular subgroups.

	Sample	n	AUC ACHTUNG-IH	AUC GRACE-IH
≥ 75 years old	Derivation	422	0.753 ± 0.033, 95% CI 0.689–0.818	0.783 ± 0.035, 95% CI 0.714–0.851
	Validation	151	0.811 ± 0.054, 95% CI 0.705–0.917	0.858 ± 0.050, 95% CI 0.759–0.956
Males	Derivation	706	0.847 ± 0.026, 95% CI 0.796–0.898	0.840 ± 0.027, 95% CI 0.786–0.894
	Validation	274	0.885 ± 0.063, 95% CI 0.750–0.985	0.953 ± 0.024, 95% CI 0.904–0.991
Females	Derivation	385	0.787 ± 0.037, 95% CI 0.715–0.859	0.802 ± 0.039, 95% CI 0.726–0.878
	Validation	126	0.847 ± 0.046, 95% CI 0.756–0.938	0.816 ± 0.056, 95% CI 0.706–0.925
With diabetes mellitus	Derivation	390	0.819 ± 0.030, 95% CI 0.761–0.877	0.802 ± 0.033, 95% CI 0.737–0.868
	Validation	114	0.890 ± 0.045, 95% CI 0.802–0.978	0.919 ± 0.044, 95% CI 0.826–0.989
Invasive revascularization	Derivation	651	0.828 ± 0.046, 95% CI 0.737–0.919	0.775 ± 0.049, 95% CI 0.678–0.871
	Validation	276	0.891 ± 0.050, 95% CI 0.792–0.989	0.914 ± 0.031, 95% CI 0.854–0.974
Creatinine clearance < 60 ml/min	Derivation	423	0.768 ± 0.029, 95% CI 0.710–0.825	0.808 ± 0.030, 95% CI 0.750–0.866
	Validation	115	0.804 ± 0.072, 95% CI 0.664–0.945	0.833 ± 0.065, 95% CI 0.705–0.960

AUC: area under the curve; ACHTUNG-IH: ACHTUNG score for intrahospital mortality; GRACE-IH: GRACE score for intrahospital mortality.

Figure 2. Post-discharge mortality prediction: comparison between the ACHTUNG score for post-discharge mortality prediction and the equivalent GRACE version.

95% CI 0.717–0.855. NRI of 31.8% (95% CI 17.9–45.7%, p (2-sided) < 0.00001).

- NSTEMI: AUC ACHTUNG-R 0.843 ± 0.019 , 95% CI 0.805–0.881; vs. AUC GRACE-6PD 0.791 ± 0.022 , 95% CI 0.748–0.835. NRI of 29.4% (95% CI 22.0–36.9%, p (2-sided) < 0.00001).

Validation sample

- STEMI: AUC ACHTUNG-R 0.853 ± 0.067 , 95% CI 0.720–0.985; vs. AUC GRACE-6PD 0.896 ± 0.038 , 95% CI 0.821–0.971. However, a 6.6% net

improvement in risk reclassification was attained by ACHTUNG-R, although not reaching statistical significance (95% CI –23.3–36.6%, p (2-sided) = 0.66).

- NSTEMI: AUC ACHTUNG-R 0.823 ± 0.043 , 95% CI 0.739–0.806; vs. AUC GRACE-6PD 0.770 ± 0.046 , 95% CI 0.680–0.860. NRI value of 29.3% (95% CI 17.1–41.4%, p (2-sided) = 0.000002).

Validation of the ACHTUNG-R in particular subgroups. The discriminatory power of ACHTUNG-R was assessed in particular subgroups, namely patients older than 75 years

old, male or female patients, individuals with diabetes mellitus or renal dysfunction and those submitted to revascularization. ACHTUNG's AUC for intrahospital mortality prediction was compared to that of GRACE-6PD (Table 8).

ACHTUNG score for combined/total all-cause mortality prediction (intrahospital plus post-discharge mortality) – ACHTUNG-T

Overall validation of ACHTUNG-T

Derivation cohort. The ACHTUNG-T model classified 29.7% of patients in the low-risk group, 20.3% in the intermediate-risk category and 50.0% in the high-risk group. Compared to GRACE-6, more patients were eligible for the low-risk category and a lower proportion of patients was included in the high risk group (Table 2). Occurrence of the primary endpoint (intrahospital mortality) according to ACHTUNG-T and GRACE-6 risk categorization is reported in Table 4.

Brier score analysis in the derivation sample demonstrated a mean value of 0.12 (median 0.024), suggesting reasonable accuracy within individual patients. ACHTUNG's discriminatory power was assessed by calculating the AUC for combined/total mortality prediction, which was compared to that of GRACE-6:

- AUC ACHTUNG-T 0.852 ± 0.014 , 95% CI 0.824–0.880; vs. AUC GRACE-6 0.816 ± 0.016 , 95% CI 0.786–0.847 (Figure 3).

The net improvement estimate for those not reaching the primary endpoint was 17.1%, whereas reclassification of patients reaching the primary outcome was neutral (0%). Overall risk classification improved significantly, with an NRI value of 17.1% (95% CI 13.2–23.4%, p (2-sided) < 0.000001).

Cross tabulation between GRACE-6 and ACHTUNG-T in the derivation sample is illustrated in Table 5.

Validation cohort. The ACHTUNG-T score classified 36.9% of patients in the low-risk group, 20.9% in the intermediate-risk category and 42.2% in the high-risk group. More patients were eligible for the low-risk category and a lower proportion was included in the high-risk group (Table 2). Occurrence of the primary endpoint (intrahospital mortality) according to ACHTUNG-T and GRACE-6 risk category is reported in Table 4.

A Brier score analysis confirmed the reasonable prognostic utility of this risk-stratification model within each individual patient (mean value 0.11, median 0.014). ACHTUNG's discriminatory power was assessed by calculating the AUC for combined/total mortality prediction:

- AUC ACHTUNG-T 0.831 ± 0.028 , 95% CI 0.776–0.887; vs. AUC GRACE-6 0.815 ± 0.033 , 95% CI 0.751–0.880 (Figure 3).

The net improvement estimate for those not reaching the primary endpoint was 14.5%, whereas the net estimate for the percentage reclassified upward was 4.1%. Overall risk classification improved significantly, with an NRI value of 18.6% (95% CI 7.3–30.0%, p (2-sided) = 0.0012). Cross tabulation between the GRACE-6 and ACHTUNG-T models in the validation sample is illustrated in Table 6.

Validation of ACHTUNG-T according to the type of myocardial infarction. The discriminatory power of ACHTUNG-T according to type of MI and the net improvement in risk reclassification were assessed through ROC curves and the NRI index, respectively, in both the derivation and validation samples.

Table 8. Assessment of the ACHTUNG score for post-discharge mortality prediction in particular subgroups.

	Sample	n	AUC ACHTUNG-R	AUC GRACE-6PD
≥ 75 years old	Derivation	422	0.781 ± 0.027 , 95% CI 0.728–0.834	0.683 ± 0.031 , 95% CI 0.623–0.742
	Validation	151	0.768 ± 0.053 , 95% CI 0.664–0.871	0.768 ± 0.053 , 95% CI 0.664–0.871
Males	Derivation	706	0.853 ± 0.021 , 95% CI 0.812–0.893	0.803 ± 0.025 , 95% CI 0.755–0.851
	Validation	274	0.840 ± 0.041 , 95% CI 0.760–0.919	0.824 ± 0.038 , 95% CI 0.749–0.899
Females	Derivation	385	0.857 ± 0.026 , 95% CI 0.806–0.908	0.773 ± 0.030 , 95% CI 0.715–0.831
	Validation	126	0.811 ± 0.071 , 95% CI 0.672–0.951	0.786 ± 0.066 , 95% CI 0.656–0.917
With diabetes mellitus	Derivation	390	0.811 ± 0.028 , 95% CI 0.757–0.866	0.715 ± 0.034 , 95% CI 0.649–0.781
	Validation	114	0.698 ± 0.073 , 95% CI 0.556–0.840	0.680 ± 0.061 , 95% CI 0.561–0.799
Invasive revascularization	Derivation	651	0.854 ± 0.023 , 95% CI 0.808–0.900	0.791 ± 0.029 , 95% CI 0.735–0.847
	Validation	276	0.859 ± 0.051 , 95% CI 0.758–0.959	0.835 ± 0.043 , 95% CI 0.751–0.919
Creatinine clearance < 60 ml/min	Derivation	423	0.826 ± 0.024 , 95% CI 0.778–0.873	0.756 ± 0.028 , 95% CI 0.700–0.811
	Validation	115	0.729 ± 0.068 , 95% CI 0.595–0.862	0.699 ± 0.076 , 95% CI 0.550–0.848

AUC: area under the curve; ACHTUNG-R: ACHTUNG score for post-discharge mortality; GRACE-6PD: GRACE score for post-discharge 6-month mortality.

Figure 3. Combined/total (intrahospital plus post-discharge) mortality prediction: comparison between the ACHTUNG score for total mortality prediction and the equivalent GRACE version.

Derivation sample

- STEMI: AUC ACHTUNG-R 0.854 ± 0.031 , 95% CI 0.794–0.914; vs. AUC GRACE-6PD 0.786 ± 0.035 , 95% CI 0.717–0.855. NRI value of 31.8% (95% CI 17.9–45.7%, p (2-sided) < 0.00001).
- NSTEMI: AUC ACHTUNG-R 0.843 ± 0.019 , 95% CI 0.805–0.881; vs. AUC GRACE-6PD 0.791 ± 0.022 , 95% CI 0.748–0.835. NRI value of 29.4% (95% CI 22.0–36.9%, p (2-sided) < 0.00001).

Validation sample

- STEMI: AUC ACHTUNG-T 0.838 ± 0.044 , 95% CI 0.752–0.925; vs. AUC GRACE-6 0.848 ± 0.036 , 95% CI 0.777–0.920. However, a 11.8% net improvement in risk reclassification was attained by ACHTUNG-T, although not reaching statistical significance (95% CI –3.8–27.5%, p (2-sided) = 0.13).
- NSTEMI: AUC ACHTUNG-T 0.825 ± 0.037 , 95% CI 0.753–0.897; vs. AUC GRACE-6 0.789 ± 0.048 , 95% CI 0.695–0.884. A significant net improvement in risk classification was shown by an NRI value of 25.3% (95% CI 9.2–41.3%, p 2-sided = 0.0020).

Validation of the ACHTUNG-R in particular subgroups. The discriminatory power of ACHTUNG-T was assessed in particular subgroups, namely patients older than 75 years old, male or female patients, individuals with diabetes mellitus or renal dysfunction and those submitted to

revascularization. ACHTUNG's AUC for intrahospital mortality prediction was compared to that of GRACE-6 (Table 9).

Discussion

In this study, we included patients with an MI and focused on mortality as the GRACE score was developed and validated mainly for this indication. In our unselected and contemporary derivation and validation cohorts of patients with MI, all versions of the ACHTUNG-Rule have shown excellent discriminative power and good calibration for predicting in-hospital, post-discharge and combined in-hospital plus post-discharge mortality. The ACHTUNG version for intrahospital mortality prediction was not inferior to its equivalent GRACE model, and ACHTUNG versions for post-discharge and combined/total mortality demonstrated apparent superiority. In fact, through ROC curve analyses and measures of reclassification (NRI and IDI), we have shown that the ACHTUNG-Rule has an overall prognostic discriminative performance at least as good as that of the most widely validated risk model for patients with ACS, the GRACE algorithm.

Most of the existing risk scores for prognostication of patients with ACS were developed from clinical trials, which tend to enrol highly selected patients.²⁰ The GRACE score was developed from a multinational registry of less selected patients, reflecting real world clinical practice. Its very high discriminatory power, reasonable versatility and

Table 9. Assessment of the ACHTUNG score for combined/total mortality prediction in particular subgroups.

	Sample	n	AUC ACHTUNG-T	AUC GRACE-6
≥ 75 years old	Derivation	422	0.776 ± 0.024, 95% CI 0.728–0.823	0.724 ± 0.026, 95% CI 0.673–0.776
	Validation	151	0.740 ± 0.049, 95% CI 0.645–0.835	0.751 ± 0.049, 95% CI 0.655–0.846
Males	Derivation	706	0.863 ± 0.018, 95% CI 0.828–0.898	0.828 ± 0.020, 95% CI 0.788–0.867
	Validation	274	0.822 ± 0.038, 95% CI 0.748–0.896	0.797 ± 0.048, 95% CI 0.704–0.891
Females	Derivation	385	0.828 ± 0.024, 95% CI 0.782–0.874	0.788 ± 0.026, 95% CI 0.737–0.839
	Validation	126	0.824 ± 0.046, 95% CI 0.734–0.915	0.823 ± 0.049, 95% CI 0.727–0.919
With diabetes mellitus	Derivation	390	0.814 ± 0.024, 95% CI 0.767–0.862	0.756 ± 0.027, 95% CI 0.704–0.809
	Validation	114	0.724 ± 0.058, 95% CI 0.611–0.837	0.707 ± 0.063, 95% CI 0.582–0.831
Invasive revascularization	Derivation	651	0.826 ± 0.025, 95% CI 0.777–0.874	0.774 ± 0.028, 95% CI 0.720–0.828
	Validation	276	0.858 ± 0.037, 95% CI 0.785–0.930	0.834 ± 0.040, 95% CI 0.756–0.912
Creatinine clearance	Derivation	423	0.804 ± 0.022, 95% CI 0.761–0.848	0.782 ± 0.024, 95% CI 0.736–0.828
< 60 ml/min	Validation	115	0.732 ± 0.058, 95% CI 0.619–0.845	0.713 ± 0.063, 95% CI 0.590–0.836

AUC: area under the curve; ACHTUNG-T: ACHTUNG score for combined/total mortality; GRACE-6: GRACE score for post-admission 6-month mortality.

reported superiority compared to other renowned prognostic algorithms⁸ make GRACE the most widely used risk score in patients with an MI.

The ROC curve analysis is designed ideally to measure the accuracy of a single predictor or combination of predictors or to compare two single predictors (or combination of predictors) in a head-to-head fashion. However, as it may lack sensitivity, other methods have been proposed for assessing and comparing the accuracy of different risk classifications.¹⁸ Most important for clinical risk prediction is whether a new model can more accurately stratify individuals into higher or lower risk categories of clinical importance. In fact, in the setting of prospective risk prediction, the proportion of patients reclassified correctly, rather than the *c*-statistic, may be more relevant. Therefore, in the present study, we compared the predictive ability of the different models using the NRI index (and the IDI index for the post-discharge mortality endpoint). The NRI index is designed to quantify improvement in performance and hence its magnitude is more important than statistical significance.¹⁸ All versions of the ACHTUNG score accurately reclassified a significant number of patients in different, more appropriate, risk categories.

The addition of analytical variables that have been shown before to have solid prognostic value in patients with an MI explains the high performance of ACHTUNG-Rule, compared to an almost purely clinical approach by the GRACE score, which includes one analytical variable only (creatinine).

- Palmer and colleagues reported that ten year rates of mortality and heart failure were five to ten times higher when lower GFR is present together with increased NT-proBNP levels or depressed left ventricular ejection fraction.²¹ Different authors shared

the same opinion about the prognostic role of renal function (evaluated by the GFR) in patients with an MI.^{22,23}

- Ang and colleagues reported that BNP's accuracy as a strong prognosticator had been clearly demonstrated even in the absence of left ventricular dysfunction and independently of certain elements of the GRACE score such as age, ST deviation and cTn concentration, adding that most of their analyses suggested BNP could predict cardiovascular events over and above the GRACE score.²⁴ The prognostic value of NT-proBNP was reported by other authors as well.^{25–27}
- Serum blood urea nitrogen (BUN) is a sensitive marker for haemodynamic and renal perfusion abnormalities. Its role as a prognostic marker in patients with heart failure is unequivocal, yet only in the last few years has its high prognostic value in patients with an MI been reproducibly tested. Aronson et al. reported that elevated BUN and BUN/creatinine ratio on admission were independent predictors of long-term mortality in patients with STEMI,²⁸ a finding corroborated by other authors.^{29,30} This parameter may emerge in the near future as a biomarker of neurohormonal activation not only in patients with heart failure but also in ACS.³¹
- Cardiac troponin I role as a prognostic tool has not received as much consensus as it has for diagnostic purposes. The prognostic impact of an elevation of troponin I (vs. absence of elevation) in patients with non-ST elevation ACS is well known, as it allows the identification of those patients with ongoing necrosis and whose prognosis is worse. The GRACE score takes this into account. The inclusion of troponin I in the ACHTUNG-IH version (as a continuous

variable) is an indirect way of quantifying the amount of time from the beginning of the myocardial ischaemic insult until first presentation, thus the extension of necrosis at the time of admission. Also, more extensive myocardial necrosis (grossly translated by the maximum achieved I troponin) increases subsequent post-discharge risk of heart failure and mortality, a reason why we chose to include maximum I troponin in the ACHTUNG-R model.

- An investigation by Shah and colleagues demonstrated that there is a strong association between low haemoglobin concentration and increased mortality in patients with angina and MI,³² an association that is seen both at intrahospital level and during follow-up and which was corroborated by other published studies.^{33–35}
- Admission hyperglycaemia has been shown to independently predict both in-hospital and long-term mortality in diabetic and non-diabetic patients admitted for an MI.^{36,37} Elevated plasma glucose levels reflect not only acute stress, but also disturbed glucose metabolism that worsens intrahospital and long-term prognosis.

Applicability and advantages of the ACHTUNG-Rule (compared to the GRACE score)

The ideal score for risk stratification should have a good balance between intuitiveness, complexity, applicability, usefulness and prognostic discriminatory performance. Variables included in the ACHTUNG model are objective and readily obtained by routine clinical and laboratory investigations, even in smaller community hospitals. This new prognostic rule provides a novel, widely applicable and apparently improved method for assessing the intrahospital, post-discharge and combined/total all-cause mortality risk across the spectrum of patients admitted to hospital with an MI. The usefulness of an accurate risk score is unquestionable, as good prognostication of patients is extremely cost-effective.

Several points could limit the current applicability of the GRACE models. Firstly, it was designed to enrol an unselected and generalizable population of patients, although some participating centres were required to obtain informed consent from patients before enrolment. Therefore, some patients who died early or who experienced major clinical complications immediately on arrival in hospital could be under-represented. This potential bias was not experienced in the development of the ACHTUNG-Rule. Second, the GRACE risk scores were developed in the late 1990s and early 2000s and most validations were performed in patient populations recruited between 1999 and 2002^{11,14,38} when several breakthroughs for management of ACS had not been widely used. Third, some authors have suggested a

slightly lower performance of the GRACE score in higher risk subgroups such as those with diabetes mellitus or chronic renal failure,³⁹ although this has been questioned in more recent studies¹⁶ and has not been confirmed in our study. Nevertheless, the discriminative performance of ACHTUNG-R and ACHTUNG-T in patients with renal dysfunction at admission was significantly higher than that of GRACE. Fourth, GRACE's discriminative capacity for 6-month mortality in patients who undergo in-hospital PCI appears to be lower, as suggested by some authors,¹⁶ which probably results from the fact that only 26.6% of patients from its development cohort were submitted to percutaneous revascularization. The ACHTUNG-Rule performed exceptionally well in patients who were revascularized.

Limitations of this study

The moderate size of our single-centre derivation and validation samples, especially the latter, should be considered the main limitation of this research. In fact, our derivation and validation cohorts are very small compared with the registries (comprising several thousands of patients) that were used to create and validate the multiple versions of the GRACE score.⁷

Furthermore, although we validated the ACHTUNG-Rule in an independent patient sample and demonstrated overall robustness of all its versions, internal validation cannot control for unrecognized biases in different institutions. These models should be subjected to external validation in larger cohorts of patients, preferably involving multicentre and prospective registries, before potential implementation. As external validation requires a second large population for whom all necessary data and long-term outcomes are available, we encourage other institutions to test our scores in their populations. Before such external validation, our results should be applied with caution to other centres with different population and medical service profiles.

Although the prognostic value of the GRACE score for 6-month mortality (either post-admission or post-discharge) has been demonstrated to outrun the 6-month period of follow-up that was used in the original research,^{8,10,40} we remember that application of a model outside its original intended use leaves more room for biomarkers to improve on the score or for being outscored by a new prognostic rule.

Another important limitation of this investigation concerns the different lengths of follow-up in the derivation (19.7 ± 6.4 months) and validation (7.2 ± 4.0 months) samples, which is explained by the later in-hospital admission of patients assigned to the validation cohort. The ACHTUNG versions for combined/total and post-discharge mortality prediction were thus derived and validated for slightly different endpoints. Nevertheless, comparisons between GRACE-6PD vs. ACHTUNG-R and GRACE-6

vs. ACHTUNG-T were performed for exactly the same lengths of follow-up. Furthermore, the length of the follow-up in our validation sample was closer to the original length of the GRACE's original research, which highlights the performance of the ACHTUNG-Rule.

Additional limitations concerning statistical analysis must be stated:

- A backward stepwise elimination multivariate logistic regression analysis was used for the development of the GRACE score, implying that all variables included in this model were independent predictors of mortality in the overall registry. We purposely chose technique Enter of multivariate logistic regression analysis, which explains why some 95% CI include 1.0.
- Although the NRI may be a clinically relevant parameter, it is predicated on knowledge of existing categories of risk. The original GRACE score research states such categories for the intrahospital and post-discharge models,¹⁶ but not to the post-admission 6-month mortality prediction score. Therefore, cutoff values used in this study for the GRACE-6 score were not based on published scientific data.

A calculator is needed for the quantification of the ACHTUNG-Rule, as with the GRACE score. This may be overcome with the development of a web calculator.

Conclusion

We performed a derivation and preliminary validation of a new and potentially improved model for all-cause mortality risk prediction in patients with an MI – the ACHTUNG-Rule. It comprises three versions for intrahospital, post-discharge and combined/total mortality prediction, respectively, revealing good calibration, accuracy and overall discriminatory power. Compared to the GRACE algorithm, the most widely validated risk score for patients with an MI, it showed similar prognostic value in terms of intrahospital mortality risk and apparently superior discriminatory power regarding the prediction of post-discharge or total (intrahospital plus post-discharge) mortality risk. Furthermore, ACHTUNG-Rule's versatility was confirmed by its considerable prognostic discriminatory value irrespective of the type of MI, advanced age, the presence of diabetes mellitus or renal dysfunction and the performance of a revascularization procedure.

Considering the preliminary nature of this study, the ACHTUNG-Rule should be validated in wider, independent, multicentre registries before its potential clinical implementation. Further analyses of the ACHTUNG-Rule in different populations will evaluate whether it can lead to different, more appropriate, treatment decisions, the ultimate goal of any prognostic score.

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