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# Mid-term Risk Stratification of Patients with a Myocardial Infarction and Atrial Fibrillation: Beyond GRACE and CHADS

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## Abstract

**Background** :We hypothesize that the discriminative performance of GRACE, ACHTUNG-Rule, $CHADS_2$ or $CHA_2DS_2$-VASc may be lower in patients with a Myocardial Infarction (MI) and concurrent atrial fibrillation (AF), as none of these scores seem able to fully capture both atherothrombotic/thromboembolic risks. This study aims to evaluate the mid-term prognostic performance of these algorithms in patients with these two conditions and to analyze the utility of a score combining GRACE and $CHA_2DS_2$-VASc.

**Methods:** Observational retrospective single-centre cohort study including 1852 patients admitted with a MI. We tested the prognostic performance of the aforementioned risk stratification schemes in patients with vs. without AF at admission or during hospitalization. Primary endpoints: a) total all-cause mortality, comprising intrahospital and post-discharge all-cause mortality; b) intrahospital all-cause mortality and c) all-cause mortality during follow-up. Furthermore, all three versions of the ACHTUNG-Rule were directly compared to their equivalent GRACE score versions, and a new score, entitled GRACE-$CHA_2DS_2$-VASc, was developed and compared with GRACE..

**Results:** The mid-term prognostic performance of all scores was considerably lower in patients with AF, corroborating our hypothesis. The ACHTUNG-Rule seemed superior to GRACE in the prediction of post-discharge (AUC 0.790±0.032 vs. 0.685±0.038, p=0.079; integrated discrimination improvement index [IDI] of 0.166 and relative IDI of 83.7%) and total mortality (0.762±0.031 vs. 0.712±0.033, p=0.144; IDI of 0.042, relative IDI of 11.7%), but its performance decreased in those with AF as well. GRACE-$CHA_2DS_2$-VASc was only marginally superior to GRACE in discriminative performance, but detected truly low- ($CHA_2DS_2$-VASc <2; total mortality 0%) and high-risk patients (GRACE high-risk stratum, and $CHA_2DS_2$-VASc >4; total mortality 44.3%) with considerable efficacy.

**Conclusions:** In patients with MI and concurrent AF, the GRACE, $CHADS_2$ and $CHA_2DS_2$-VASc scores seemed less accurate in the prediction of all-cause mortality. A hypothetic GRACE-$CHA_2DS_2$-VASc score or the recently developed ACHTUNG-Rule may eventually provide a more rigorous approach to risk stratification in this high-risk setting.

## Introduction

Risk stratification of patients with a Myocardial Infarction (MI) has been the target of multiple studies. 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 demonstrated reliable risk stratification performance. The GRACE score is the most validated and widely used risk model in acute coronary syndromes, with established superior discriminative performance in the prediction of all-cause mortality when compared to TIMI and PURSUIT.[8,9]Recently, the ACHTUNG-Rule, derived from a cohort of patients with myocardial infarction (MI), has been preliminarily validated in an independent sample.[10]

Atrial fibrillation prognosis (AF) is also a particularly pertinent subject, and scores such as $CHADS_2$[11] or $CHA_2DS_2$-VASc[12] have been developed to estimate overall stroke risk and identify patients benefiting from antithrombotic therapies. Originally developed to predict thromboembolic risk in individuals with AF, the $CHADS_2$ algorithm can also predict all-cause mortality and stroke risk in patients with a MI irrespective of the presence of AF.[13]

However, to this date no study has evaluated the prognostic performance of currently available risk scores in patients admitted for MI and with AF at admission or during hospitalization. Each of

## Key Words:

Myocardial Infarction, Atrial Fibrillation, Prognosis, Risk Scores.

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None.

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these conditions influences prognosis in distinct ways and, therefore, AF may hinder the efficacy of risk stratification schemes such as GRACE, ACHTUNG-Rule, $CHADS_2$ or $CHA_2DS_2$-VASc. Atherothrombotic and thromboembolic risks associate with all-cause mortality risk and might not be accurately and quantitatively predicted by only one of the currently used risk scores.

Therefore, we hypothesize that the discriminative performance of GRACE, ACHTUNG-Rule, $CHADS_2$ or $CHA_2DS_2$-VASc may be lower in patients with both a MI and AF than in their AF free counterparts, as none of these scores seem able to fully capture both atherothrombotic and thromboembolic risks. Furthermore, as we also hypothesize the recently developed ACHTUNG-Rule may provide a more accurate quantification of both atherotrombotic and thromboembolic risk (as it incorporates analytical variables known to predict stroke in different clinical contexts), it will be tested in patients with AF and compared directly with the GRACE score. Finally, we aim at analyzing whether a score combining both GRACE and either $CHADS_2$ or $CHA_2DS_2$-VASc can enhance the prediction of all-cause mortality in the presence of both conditions.

## Methods

### Study Design

Observational retrospective single-centre cohort study including all patients admitted to our hospital's Acute Coronary Care Unit (ACCU) diagnosed with Myocardial Infarction between December 1, 2006 and September 30, 2011. Using collected baseline data at the time of MI diagnosis and outcome data from this cohort, we tested the prognostic performance of four different risk stratification schemes - the GRACE model, the $CHADS_2$ and $CHA_2DS_2$-VASc scores and the ACHTUNG-Rule - in patients with AF at admission or occurring during hospitalization and compared it with their efficacy in those without AF. All prediction models were evaluated for their overall discriminative performance, accuracy and calibration in the prediction of short- to mid-term all-cause mortality. Furthermore, all three versions of the ACHTUNG-Rule[10] were directly compared to their equivalent GRACE score versions, and a new score, entitled GRACE-$CHA_2DS_2$-VASc, was developed and compared with GRACE.

### Patients and Eligibility Criteria

A total of 1852 patients (age 68.3±13.5, from 29 to 99) were consecutively admitted to our ACCU diagnosed with MI according to its Universal Definition.[14] This sample included both the derivation and validation cohorts of the ACHTUNG-Rule,[10] plus 401 additional and consecutively admitted patients. AF was detected in 294 patients (15.9%) either at admission or during hospitalization. Table 1 describes the study sample.

### Data Collection

Through extensive review done by 4 co-investigators blind to the purpose of the study, the following data were collected: demographic features, cardiovascular risk factors and previous medical history (including history of AF), physical examination and analytical study at admission (including complete blood count, biochemical and clotting tests), angiographic data and results of electrocardiograms performed during hospitalization. Glomerular filtration rate (GFR - by MDRD formula), the GRACE scores for intrahospital, 6-month post-admission and 6-month post-discharge mortality, the $CHADS_2$ and $CHA_2DS_2$-VASc scores and the ACHTUNG versions for intrahospital, post-discharge and total all-cause mortality were calculated for all patients. The presence of AF was defined as the electrocardiographic documentation of at least one episode of this arrhythmia (through 12-lead electrocardiogram, 24-hour Holter or electrocardiographic monitoring in the ACCU; in all cases, the presence of AF must have been validated by at least one Cardiologist), irrespective of its timing, duration (paroxysmal, persistent or permanent) or overall patient characteristics (valvular or nonvalvular AF) and symptomatology. To collect this information, a comprehensive review of available electrocardiographic recordings and daily medical history notes was made.

### Study End Points

The primary endpoints of this study were: a) total all-cause mortality, comprising intrahospital and post-discharge all-cause mortality; b) intrahospital all-cause mortality and c) all-cause mortality during follow-up. The specific cause of mortality in patients discharged following hospitalization for a MI is sometimes very hard to ascertain, and thus all-cause mortality is likely to be the most robust and objective endpoint. The secondary outcome was the occurrence of a primary International Classification of Diseases diagnosis of stroke, confirmed through cerebral computed tomography (CT).

This information was collected from hospital charts and clinical records from outpatient clinic and hospital ward and emergency department admission(s), including the reports of performed cerebral CT, and through proxy interviews when appropriate.

### Patient Follow-up

Patients were followed for 17.4±8.7 months following their discharge. Follow-up data was obtained through review of 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 institution.

**Table 1: Characteristics of study sample.**

| | OVERALL SAMPLE (n=1852) | WITH AF (n=294) | WITHOUT AF (n=1558) | p |
|---|---|---|---|---|
| Age | 68.3±13.5 | 76.1±9.6 | 66.8±13.7 | < 0.001 |
| Male gender | 65.7% | 57.1% | 67.4% | < 0.001 |
| STEMI | 45.5% | 33.9% | 47.7% | 0.007 |
| Diabetes Mellitus | 33.7% | 38.1% | 32.8% | 0.078 |
| History of stroke | 8.9% | 16.7% | 7.4% | < 0.001 |
| GFR (mL/min/1.73m2) | 69.6±30.4 | 58.1±25.7 | 71.9±30.6 | < 0.001 |
| NT-proBNP (pg/mL) | 6984.4±15556 | 9756.6±16595 | 6429.5±15315 | < 0.001 |
| Maximum Killip class | 1.51±0.9 | 1.82±1.0 | 1.45±0.87 | < 0.001 |
| Performance of revascularization | 66.9% | 49.8% | 70.1% | < 0.001 |
| Mean $CHADS_2$ | 1.91±1.27 | 2.60±1.19 | 1.78±1.25 | < 0.001 |
| Mean $CHA_2DS_2$-VASc | 3.57±1.73 | 4.49±1.58 | 3.42±1.71 | < 0.001 |
| Mean GRACE-IH | 152.3±44.1 | 176.8±41 | 147.4±42.9 | < 0.001 |
| Mean GRACE-6PD | 125.3±44.7 | 146.4±31.6 | 121.1±45.6 | < 0.001 |
| Intrahospital mortality | 7.6% | 11.6% | 6.9% | 0.004 |
| Mortality during follow-up | 14.0% | 28.5% | 11.2% | < 0.001 |
| Stroke during follow-up | 4.0% | 7.2% | 3.4% | 0.005 |

Legends: STEMI – Myocardial infarction with ST segment elevation; CAD – Coronary artery disease; GFR – Glomerular filtration rate; GRACE-IH – GRACE score for intrahospital mortality; GRACE-6PD – GRACE score for post-discharge mortality.

**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. The Kolmogorov-Smirnov test was used to test the normal distribution of continuous variables. The Chi-square test, Student's t-test and non-parametric equivalent tests were used when appropriate. Regression estimation techniques were applied to replace missing values whenever the number of missing values was negligible, otherwise cases with missing values would be omitted. P values < 0.05 (two-sided) were considered statistically significant.

Univariate analysis was performed to evaluate a potential association between AF at admission or any time during hospitalization and the study endpoints.

The three versions of the ACHTUNG-Rule were calculated according to their respective coefficients obtained from its original derivation cohort and described elsewhere.[10]

Discrimination is usually measured in terms of the area under each receiver operating characteristic curve (AUC) and refers to the ability of a prediction model to assign a higher probability to patients reaching the study endpoint than to those not reaching it.Through the calculation of the AUC, an assessment of the discriminatory power of the GRACE score versions for intrahospital (GRACE-IH), 6-month post-admission (GRACE-6PA) and 6-month post-discharge (GRACE-6PD) all-cause mortality, the $CHADS_2$ and $CHA_2DS_2$-VASc scores and the ACHTUNG versions for intrahospital (ACHTUNG-IH), post-discharge (ACHTUNG-R) and total (ACHTUNG-T) all-cause mortality was performed.

**Table 2: Prognostic performance of GRACE, ACHTUNG, $CHADS_2$ and $CHA_2DS_2$-VASc in patients without atrial fibrillation.**

| | | GRACE-IH | ACHTUNG-IH | $CHADS_2$ | $CHA_2DS_2$-VASc |
|---|---|---|---|---|---|
| Intrahospital mortality | AUC | 0.837±0.029 | 0.854±0.031 | 0.709±0.032 | 0.718±0.031 |
| | HL test p value | 0.796 | 0.788 | 0.770 | 0.428 |
| | Brier score | 0.052 | 0.052 | 0.061 | 0.043 |
| | | GRACE-6PD | ACHTUNG-R | $CHADS_2$ | $CHA_2DS_2$-VASc |
| Mortality during follow-up | AUC | 0.785±0.023 | 0.837±0.018 | 0.760±0.022 | 0.745±0.021 |
| | HL test p value | < 0.001 | < 0.001 | 0.057 | 0.016 |
| | Brier score | 0.100 | 0.089 | 0.098 | 0.083 |
| | | GRACE-6PA | ACHTUNG-T | $CHADS_2$ | CHA2DS2-VASc |
| Total mortality | AUC | 0.790±0.019 | 0.833±0.017 | 0.752±0.019 | 0.748±0.017 |
| | HL test p value | 0.018 | < 0.001 | 0.158 | 0.057 |
| | Brier score | 0.117 | 0.112 | 0.134 | 0.111 |
| | | | | $CHADS_2$ | $CHA_2DS_2$-VASc |
| Stroke | AUC | | | 0.625±0.052 | 0.651±0.044 |
| | HL test p value | | | 0.585 | 0.302 |
| | Brier score | | | 0.032 | 0.026 |

Legends: GRACE-IH – GRACE version for intrahospital mortality; GRACE-6PD – GRACE version for post-discharge mortality; GRACE-6PA – GRACE version for total mortality; ACHTUNG-IH – ACHTUNG version for intrahospital mortality; ACHTUNG-R – ACHTUNG version for post-discharge mortality; ACHTUNG-T – ACHTUNG version for total mortality; AUC – Area under the curve; HL – Hosmer and Lemeshow.

**Table 3: Prognostic performance of GRACE, ACHTUNG, $CHADS_2$ and $CHA_2DS_2$-VASc in patients with atrial fibrillation.**

| | | GRACE-IH | ACHTUNG-IH | $CHADS_2$ | $CHA_2DS_2$-VASc |
|---|---|---|---|---|---|
| Intrahospital mortality | AUC | 0.788±0.042 | 0.741±0.044 | 0.625±0.060 | 0.717±0.053 |
| | HL test p value | 0.845 | 0.291 | 0.898 | 0.856 |
| | Brier score | 0.087 | 0.092 | 0.099 | 0.075 |
| | | GRACE-6PD | ACHTUNG-R | $CHADS_2$ | $CHA_2DS_2$-VASc |
| Mortality during follow-up | AUC | 0.685±0.038 | 0.790±0.032 | 0.654±0.050 | 0.680±0.045 |
| | HL test p value | 0.057 | 0.076 | 0.681 | 0.324 |
| | Brier score | 0.215 | 0.157 | 0.196 | 0.151 |
| | | GRACE-6PA | ACHTUNG-T | $CHADS_2$ | $CHA_2DS_2$-VASc |
| Total mortality | AUC | 0.712±0.033 | 0.762±0.031 | 0.657±0.043 | 0.702±0.039 |
| | HL test p value | 0.192 | 0.002 | 0.752 | 0.295 |
| | Brier score | 0.205 | 0.190 | 0.216 | 0.181 |
| | | GRACE-6PD | ACHTUNG-R | $CHADS_2$ | $CHA_2DS_2$-VASc |
| Stroke | AUC | 0.534±0.065 | 0.627±0.053 | 0.646±0.068 | 0.655±0.060 |
| | HL test p value | 0.099 | 0.278 | 0.097 | 0.234 |
| | Brier score | 0.069 | 0.070 | 0.067 | 0.068 |

Legends: GRACE-IH – GRACE version for intrahospital mortality; GRACE-6PD – GRACE version for post-discharge mortality; GRACE-6PA – GRACE version for total mortality; ACHTUNG-IH – ACHTUNG version for intrahospital mortality; ACHTUNG-R – ACHTUNG version for post-discharge mortality; ACHTUNG-T – ACHTUNG version for total mortality; AUC – Area under the curve; HL – Hosmer and Lemeshow.

- Intrahospital mortality: assessment of the AUC of GRACE-IH, $CHADS_2$, $CHA_2DS_2$-VASc and ACHTUNG-IH.
- Mortality during follow-up: assessment of the AUC of GRACE-6PD, $CHADS_2$, $CHA_2DS_2$-VASc and ACHTUNG-R.
- Total mortality (intrahospital mortality plus mortality during follow-up): evaluation of the AUC of GRACE-6PA, $CHADS_2$, $CHA_2DS_2$-VASc and ACHTUNG-T.
- Stroke: $CHADS_2$ and $CHA_2DS_2$-VASc.

Accuracy and calibration of each score were also assessed through the Brier score and the Hosmer-Lemeshow test, respectively. 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.[15] 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, while a Brier score of 0.25 or higher suggests lack of utility in endpoint prediction].

A comparison through ROC curve analysis and the integrated discrimination improvement index (IDI) was performed between each of the GRACE score versions and their equivalent ACHTUNG-Rule versions. The IDI, which may be seen as a continuous form of the net reclassification improvement index, 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.[16] AUC comparisons were

**Table 4:** Overall tendency of increasing total mortality event rates with increasing GRACE-6PA or ACHTUNG-T risk scores, tested using chi-square for trend (gamma).

| With atrial fibrillation | | | | | | | |
|---|---|---|---|---|---|---|---|
| **GRACE-6PA** | | | | **ACHTUNG-T** | | | |
| **Low risk** | **Intermediate risk** | **High risk** | Gamma for trend 0.783±0.044, p < 0.001 | **Low risk** | **Intermediate risk** | **High risk** | Gamma for trend 0.829±0.036, p < 0.001 |
| 2.2% | 3.9% | 24.6% | | 2.1% | 6.8% | 28% | |
| **Without atrial fibrillation** | | | | | | | |
| **GRACE-6PA** | | | | **ACHTUNG-T** | | | |
| **Low risk** | **Intermediate risk** | **High risk** | Gamma for trend 0.421±0.151, p = 0.041 | **Low risk** | **Intermediate risk** | **High risk** | Gamma for trend 0.843±0.086, p < 0.001 |
| 11.1% | 18.6% | 32.8% | | 2.0% | 14.3% | 36.5% | |

Legends: GRACE-6PA – GRACE version for total mortality; ACHTUNG-T – ACHTUNG version for total mortality.

performed using MedCalc for Windows version 9.2.0.1. The overall tendency of increasing total mortality event rates with increasing GRACE-6PA or ACHTUNG-T risk scores was tested using chi-square for trend (gamma). ACHTUNG's risk strata were defined as described in ACHTUNG-Rule's original paper.[10]

Finally, binary logistic regression was performed to analyse whether the $CHADS_2$ or $CHA_2DS_2$-VASc scores would improve GRACE's ability to predict total or post-discharge all-cause mortality. A new score, entitled GRACE-$CHA_2DS_2$-VASc, was evaluated for its discriminative performance, accuracy and calibration in both the overall cohort and patients with AF. Intrahospital and total mortality rates according to both GRACE and $CHA_2DS_2$-VASc risk strata were also reported aiming to identify truly low- or high-risk subgroups of patients. GRACE's risk strata were defined according to published criteria.[17] Kaplan-Meier curves were constructed to evaluate survival during follow-up according to combined GRACE and $CHA_2DS_2$-VASc risk strata: a $CHA_2DS_2$-VASc score ≤ 1 was defined as low risk and a score ≥ 2 as high risk.

### Ethical Approval

This study complies with the Declaration of Helsinki and has been approved by our institution's review board.

## Results

### Prognostic role of Atrial Fibrillation

In univariate analysis, the occurrence of AF at admission or during hospitalization associated with higher risk for intrahospital mortality (11.6% vs. 6.7%, p=0.004, OR 1.81, 95% CI 1.20-2.73), mortality during follow-up (28.5% vs. 12.2%, p<0.001, OR 2.88, 95% CI 2.1-4.0), total mortality (37.1% vs. 18.3%, p<0.001, OR 2.63, 95% CI 2.0-3.46) and non-fatal stroke (7.2% vs. 3.4%, p=0.005, OR 2.24, 95% CI 1.25-3.98). In multivariate analysis, the presence/absence of AF did not improve the ability of GRACE-IH in predicting intrahospital mortality, but AF predicted mortality during follow-up independently of the GRACE-6PD score. A multivariate predictive model for post-discharge mortality included variables GRACE-6PD (p<0.001, OR 1.0123, 95% CI 1.018-1.028) and AF (p=0.001, OR 1.84, 95% CI 1.30-2.59).

### GRACE, ACHTUNG, $CHADS_2$ and $CHA_2DS_2$-VASc in patients without AF

See table 2.

### GRACE, ACHTUNG, $CHADS_2$ and $CHA_2DS_2$-VASc in patients with AF

See table 3.

### ACHTUNG-Rule: prediction of mortality risk in patients with AF

Compared to their equivalent GRACE score versions, the ACHTUNG-Rule versions have shown non significantly lower discriminative performance when predicting intrahospital mortality risk (0.741±0.044 vs. 0.788±0.042, p=0.289), a trend for higher discriminative power in the prediction of post-discharge mortality (0.790±0.032 vs. 0.685±0.038, p=0.079) and non significantly higher ability to predict total mortality (0.762±0.031 vs. 0.712±0.033, p=0.144).

The IDI index provided a more rigorous and powerful statistical approach to assess the potential improvement in risk reclassification with the ACHTUNG-Rule. For post-discharge mortality, the IDI and relative IDI were 0.166 and 83.7%, respectively, translating a very sizeable improvement in risk reclassification with the use of ACHTUNG-R instead of GRACE-6PD. The IDI index for total mortality prediction was 0.042 (relative IDI of 11.7%), suggesting an improvement in risk stratification with ACHTUNG-T in detriment of GRACE-6PA.

Table 4 reports the overall tendency of increasing mortality event rates with increasing GRACE-6PD or ACHTUNG-R risk scores, tested using chi-square for trend (gamma).

### GRACE-$CHA_2DS_2$-VASc: Combining both atherothrombotic and thromboembolic risk prediction in patients with AF

Multivariate analysis by binary logistic regression (method forward conditional) did not include the $CHADS_2$ or $CHA_2DS_2$-VASc scores along with GRACE in a prediction model for intrahospital mortality in patients with AF. However, the post-discharge prediction model included GRACE-6PD (p<0.001, OR 1.022, 95% CI 1.015-1.030) and $CHA_2DS_2$-VASc (p<0.001, OR 1.631, 95% CI 1.46-1.822), while the multivariate model for total all-cause mortality prediction included GRACE-6PA (p<0.001, OR 1.017, 95% CI 1.012-1.023)

**Table 5:** Performance of GRACE-$CHA_2DS_2$-VASc in patients without atrial fibrillation.

| | AUC | HL test p value | BS |
|---|---|---|---|
| **Intrahospital all-cause mortality** ($CHA_2DS_2$-VASc plus GRACE-IH) * | 0.864±0.041 | 0.839 | 0.036 |
| **All-cause mortality during follow-up** ($CHA_2DS_2$-VASc plus GRACE-6PD) | 0.796±0.020 | 0.002 | 0.079 |
| **Total all-cause mortality** ($CHA_2DS_2$-VASc plus GRACE-6PA) | 0.799±0.017 | 0.129 | 0.102 |

Legends: GRACE-IH – GRACE version for intrahospital mortality; GRACE-6PD – GRACE version for post-discharge mortality; GRACE-6PA – GRACE version for total mortality; AUC – Area under the curve; HL – Hosmer and Lemeshow; BS – Brier score.
* Method Enter of binary logistic regression was used in the development of the prediction model for intrahospital all-cause mortality (as CHA2DS2-VASc was not included in the model with the forward conditional method).

**Table 6: Comparison between GRACE and GRACE- CHA2DS2-VASc scores in patients with atrial fibrillation.**

| **Intrahospital mortality** | | | |
|---|---|---|---|
| | AUC | HL test p value | BS |
| GRACE-IH | 0.788±0.042 | 0.845 | 0.087 |
| GRACE-CHA2DS2-VASc | 0.864±0.054 | 0.715 | 0.061 |
| p | 0.225 | | |
| **Post-discharge mortality** | | | |
| | AUC | HL test p value | BS |
| GRACE-6PD | 0.685±0.038 | 0.057 | 0.215 |
| GRACE-CHA2DS2-VASc | 0.699±0.050 | 0.441 | 0.15 |
| p | 0.499 | | |
| **Total mortality** | | | |
| | AUC | HL test p value | BS |
| GRACE-6PA | 0.712±0.033 | 0.192 | 0.205 |
| GRACE-CHA2DS2-VASc | 0.727±0.041 | 0.545 | 0.17 |
| p | 0.404 | | |

Legends: GRACE-IH – GRACE score version for intrahospital mortality; GRACE-6PD – GRACE score version for post-discharge mortality; GRACE-6PA – GRACE score version for total mortality; AUC – Area under the curve; HL – Hosmer and Lemeshow; BS – Brier score.

and $CHA_2DS_2$-VASc (p<0.001, OR 1.411, 95% CI 1.261-1.578).

GRACE-$CHA_2DS_2$-VASc performance in patients without AF is reported in table 5, while the ability of GRACE-$CHA_2DS_2$-VASc to predict all-cause mortality in patients with AF is described in table 6. Intrahospital and total mortality rates according to GRACE and $CHA_2DS_2$VASc risk strata are reported in table 7 and Kaplan-Meier curves in figure 1 illustrate survival during follow-up (including intrahospital events). It must be noted that no deaths were observed in patients with AF and a $CHA_2DS_2$-VASc score < 2. Additionally, high-risk patients according to GRACE and with a $CHA_2DS_2$-VASc score > 4 had a very high total all-cause mortality rate (39.6%).

## Discussion

As expected, AF was a strong predictor of post-discharge all-cause mortality, improving GRACE's ability to predict this endpoint. Currently available risk stratification schemes, such as GRACE, ACHTUNG, $CHADS_2$ and $CHA_2DS_2$-VASc, predict mortality to a reasonable extent in patients admitted for acute MI and with AF at admission or any time during hospitalization. However, their mid-term prognostic performance was considerably lower than in patients without AF, suggesting a decrease in their capacity to predict mortality when both conditions are concurrent. In fact, GRACE's ability to predict mortality during follow-up in the AF group was considerably modest, as demonstrated by its proportionally low discriminative performance (AUC 0.685±0.038), borderline calibration (HL test p=0.057) and low accuracy (Brier score of 0.215), suggesting suboptimal applicability/utility.

Interestingly, the $CHADS_2$ and $CHA_2DS_2$-VASc models predicted intrahospital, post-discharge and total all-cause mortality with reasonable efficacy in the overall population, but, similarly to GRACE, their performance decreased considerably in patients with AF, especially that of $CHADS_2$ algorithm. Prediction of the secondary outcome (stroke) was slightly less accurate in patients with this atrial arrhythmia, although the decrease in prediction capacity was not as significant as that seen for the primary endpoints.

In patients with AF, the recently developed ACHTUNG-Rule[10] was apparently superior to GRACE in terms of total and post-discharge all-cause mortality prediction, especially the latter. Although the areas under the curves were not significantly different, comparison of both algorithms through measures of risk reclassification such as the IDI suggested the ACHTUNG-Rule may provide a very sizeable improvement in total and post-discharge risk stratification. Nevertheless, the ACHTUNG models demonstrated a similar decrease in prognostic power in patients with AF. Moreover, GRACE maintained its excellent discriminative performance for intrahospital mortality prediction, which the ACHTUNG-Rule was not able to improve.

The new GRACE-$CHA_2DS_2$-VASc score, comprising both GRACE and $CHA_2DS_2$-VASc, improved mid-term risk stratification. Compared to GRACE, it showed slightly higher discriminative performance and accuracy and better calibration in the prediction of post-discharge and total all-cause mortality, although differences were not statistically significant, probably as a result of the small cohort of patients with AF and low number of events in this sub-group. However, it is noteworthy that the combination of GRACE and $CHA_2DS_2$-VASc provided a reliable identification of those truly low-risk (the sub-group of patients with a $CHA_2DS_2$-VASc score ≤ 1, irrespective of the GRACE score) and high-risk patients ($CHA_2DS_2$-VASc score ≥ 4 and high-risk GRACE score stratum).

Large epidemiological studies have shown that AF associates with increased mortality and morbidity,[18] especially in the presence of congestive heart failure.[19] In the context of an acute MI, AF may impair coronary circulation and left ventricular function and contribute to elevated filling pressures, ongoing myocardial ischaemia, ventricular arrhythmogenesis and volume overload. Some researchers have shown that AF associates with an increased risk of death independently of heart failure and any clinical characteristics.[20] In general, a consensus has been reached regarding the importance of AF as both an independent predictor of intrahospital all-cause mortality and a surrogate marker for heart failure. The bulk of evidence also suggests AF has mid-term adverse prognostic implications in patients hospitalized for a MI ,[21-23] although studies evaluating its long-term prognostic meaning are scarce. Despite these considerations, and as highlighted by Schmitt J et al in their systematic review of the prognostic implications of AF in acute MI,[24] there are no therapeutic guidelines addressing issues such as the role of antiarrhythmic drugs, pharmacological rate control and prevention of thromboembolism in these high-risk patients. Furthermore, as AF may also be a marker for unmeasured co-morbidities or general frailty that will not be amenable to treatment, the presence of this arrhythmia does not necessarily lead to clinically worthwhile improvements in mortality prediction. Nevertheless, the importance of accurate prognostication of these patients is unequivocal and newer prognostic models should be able to capture the strong deleterious effect of the presence of AF in a MI setting.

Prognostication in this context may be influenced by many known or unknown confounders and may express a multitude of pathophysiological mechanisms. Atherosclerosis, atherothrombosis, systemic and venous thromboembolism (with an emphasis on stroke), left ventricular dysfunction, heart failure, activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, the extent of coronary artery disease, completeness/appropriateness

of coronary revascularization and overall co-morbidity are notably associated to short-, mid- and long-term prognosis in patients with a MI and may interact even more intensively in those MI patients with concurrent AF. Hence, the mechanism for this excess mortality is not a simple one. Few studies have addressed the potential mechanisms of death in the presence of AF in an MI setting: Berton G et al. proposed patients with an acute MI and AF or atrial flutter (AFL) would portend a poorer prognosis in the long-term chiefly because of an excess of sudden death,[25] while Pederson OD et al. suggested that the excess mortality observed in patients with AF/AFL following an acute MI was due to a significant increase in both sudden and non-sudden death.[26]

To this date, no studies have been made to evaluate the prognostic performance of the GRACE score in the particular context of an acute MI with concomitant AF. We hypothesized that the GRACE algorithms would not accurately quantify both atherosclerotic / atherothrombotic and thromboembolic risk and our results support this notion, as GRACE was clearly less accurate in the prediction of mid-term all-cause mortality in patients with AF. The inclusion of $CHA_2DS_2$-VASc along with GRACE in a multivariate prediction model improved mid-term prognostication to an extent, although differences in AUC were not particularly impressive. Nevertheless, the new model may offer a more accurate approach to risk stratification through a more reliable identification of truly low- and high-risk patients, and may thus warrant future prospective validation.

The apparently more comprehensive approach of the ACHTUNG-Rule versions for post-discharge and total mortality, comprising clinical, analytical and therapeutic variables may offer a superior quantification of the multitude of processes involved in the prognostication of the two conditions. In fact, the ACHTUNG models include indirect measures of co-morbidity (through age, renal function and haemoglobin), systemic inflammation (through C-reactive protein), high ventricular filling pressures (NT-proBNP), acute impairment of hemodynamics (blood pressure and heart rate at admission), renal dysfunction and the extent of myocardial damage (through troponin I at admission and the highest achieved value and the performance of revascularization). Furthermore, the fact that ACHTUNG-R predicted stroke with reasonable discriminative power (contrary to GRACE) may help explain its apparently superior mid-term prognostic performance in patients with AF. Some of the variables incorporated in the ACHTUNG models (and absent in GRACE) have been shown before to predict stroke in different clinical contexts or associate with larger/more severe cerebral infarcts (C-reactive protein[27,28] haemoglobin,[29] NT-proBNP,[30] glycaemia[31]). Moreover, a recent sub-analysis of the RE-LY trial has shown elevations of troponin I and NT-proBNP to be common in patients with AF and to independently relate to increased risks of stroke and mortality.[32] Inspite of these considerations, the apparent superiority of the ACHTUNG-Rule does not mitigate the fact that this prediction score has also performed less well in patients with AF.

The $CHADS_2$ and $CHA_2DS_2$-VASc scores performed reasonably well in both patients with and without AF, however with a significant decrease in discriminative power in the AF group, especially with $CHADS_2$. Moreover, the $CHA_2DS_2$-VASc model demonstrated higher discrimination capacity and calibration than $CHADS_2$ in stroke prediction. When considering the risk for cerebrovascular event, $CHA_2DS_2$-VASc may provide a more refined risk stratification in the MI setting.

## Limitations of the Study

The relatively small number of patients with AF (294) represents the main limitation of this study. Our findings should be validated in larger cohorts of patients admitted for MI and presenting AF at admission or during hospitalization, preferably involving multicentre and/or prospective registries.

The difference between de novo AF occurring during hospitalization or previously known permanent AF has not been addressed. Although this study was not performed to evaluate the prognostic impact of AF, it should be noted that some studies have shown that the development of AF during hospitalization associates with higher mortality rate, while those who are in AF at the time of admission have a mortality rate that is not significantly different from that of patients in sinus rhythm.[33,34] The latter is presumably a reflection of the difference between persistent/chronic AF

**Table 7:** Intrahospital and total mortality rates according to GRACE and CHA2DS2-VASc risk strata.

| | GRACE* | CHA2DS2-VASc | Intrahospital mortality 6.7% (104/1558) | | Total mortality 18.3% (285/1558) | |
|---|---|---|---|---|---|---|
| Without Atrial Fibrillation | Low risk | 0-1 | 0% | 0/85 | 1.4% | 2/143 |
| | | ≥ 2 | 2.1% | 5/241 | 4.3% | 13/302 |
| | Intermediate risk | 0-1 | 0% | 0/67 | 0% | 0/61 |
| | | ≥ 2 | 1.9% | 7/363 | 8.6% | 38/444 |
| | High risk | 0-1 | 0% | 0/30 | 0% | 0/9 |
| | | ≥ 2 | 11.9% | 92/772 | 34.9% | 232/664 |
| With Atrial Fibrillation | GRACE* | CHA2DS2-VASc | Intrahospital mortality 11.6% (34/294) | | Total mortality 37.1% (109/294) | |
| | Low risk | 0-1 | 0% | 0/3 | 0% | 0/4 |
| | | ≥ 2 | 0% | 0/16 | 16.7% | 3/18 |
| | Intermediate risk | 0-1 | 0% | 0/1 | 0% | 0/3 |
| | | ≥ 2 | 0% | 0/41 | 21.8% | 12/55 |
| | High risk | 0-1 | 0% | 0/2 | 0% | 0/2 |
| | | ≥ 2 | 15.8% | 34/215 | 44.3% | 94/212 |

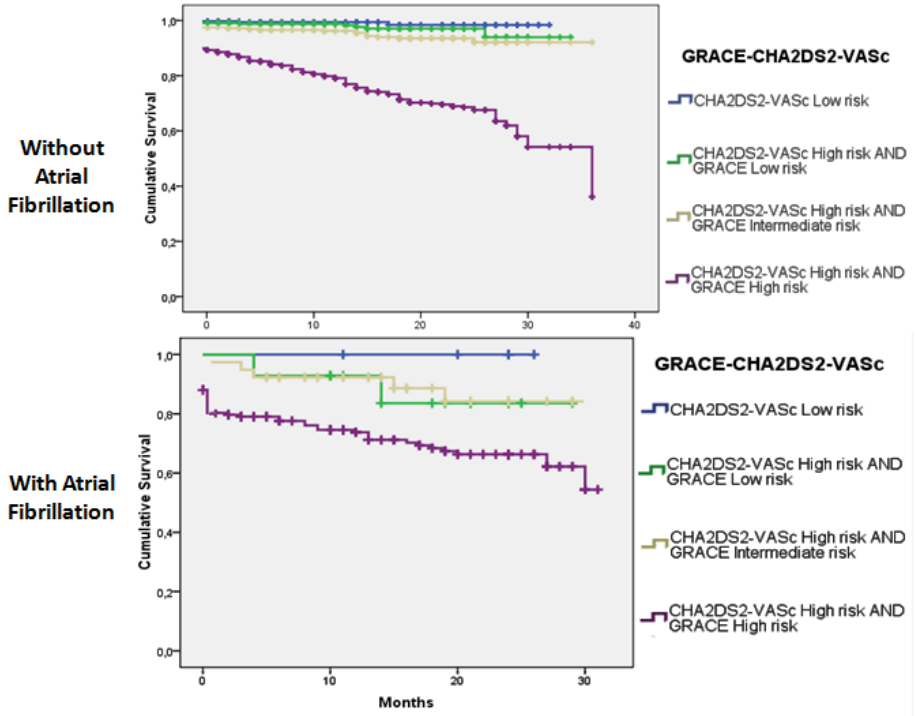


**Figure 1:** **Kaplan-Meier curves illustrating cumulative survival according to GRACE and CHA2DS2-VASc risk strata.**

documented at admission and de novo AF as a manifestation of acute haemodynamic compromise in the acute MI setting. Despite the fact that some studies have not confirmed these data, [21,35] the prognostic performance of GRACE, ACHTUNG, $CHADS_2$ and $CHA_2DS_2$-VASc might have been different in these two clinical contexts (chronic AF vs. de novo AF). Future studies should address this subject.

As many patients were not submitted to autopsy, the cause of death has not been systematically evaluated. It would have been worthwhile assessing whether GRACE's apparent limitation in the prognostication of these patients is due to an excess of fatal thromboembolic events. Such data could help explain our results.

Our study sample included the 1051 patients assigned to ACHTUNG-Rule's derivation cohort, the 400 assigned to the validation sample and 401 new patients. Therefore, comparisons between the GRACE score and the ACHTUNG-Rule may have been biased towards the latter. A more reliable comparison between these two risk stratification schemes might be obtained in a larger, independent, patient sample. The potential validation of the ACHTUNG-Rule in multicentre registries may eventually confirm the attributed versatility that its original research has suggested.

Patients with AF and a $CHA_2DS_2$-VASc score ≤ 1 had a very low mortality risk irrespective of their GRACE score. However, very few AF patients had a $CHA_2DS_2$-VASc score ≤ 1. Although similar results were found in the sub-group without AF (comprising 213 [13.7%] individuals with a $CHA_2DS_2$-VASc score ≤ 1) this analysis is far from being conclusive and should be validated in bigger cohorts considering its potential clinical value.

Even if our findings are validated in future studies, the optimal way to stratify the risk of these patients and its potential clinical impact remains to be determined. A new score should have a good balance between complexity, applicability and prognostic discriminatory performance. Most importantly, it should lead to improved risk reclassification and impact on therapeutic decisions. Further studies will be necessary to evaluate whether the GRACE-$CHA_2DS_2$-VASc score or the ACHTUNG-Rule may help lower mid-term mortality of patients with both an MI and AF through a more reliable identification of individuals eligible for aggressive therapies and those who should be treated rather more conservatively.

## Conclusions:

The GRACE score seems less accurate in the prediction of all-cause mortality in patients admitted for an acute MI who are in AF at the time of hospital admission or who develop AF during hospitalization. The $CHADS_2$ and $CHA_2DS_2$-VASc scores appear less effective in this context as well. Although a hypothetic GRACE-$CHA_2DS_2$-VASc score, comprising both GRACE and $CHA_2DS_2$-VASc, or the recently developed ACHTUNG-Rule may eventually provide a more rigorous approach to risk stratification in this context, they have also shown a decrease in prognostic performance in patients with AF. These findings should be validated in larger cohorts, preferably involving multicenter registries, before any potential recommendations regarding prognostication of these patients may be considered.

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