Prognostic Value of GRACE Scores versus TIMI Score in Acute Coronary Syndromes

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Abstract
Background: Although the TIMI score is the one most frequently used in acute coronary syndromes (ACS) without ST-segment elevation, the GRACE score has potential prognostic superiority, as it was created based on an observational registry, part of the variables is treated in a semi-quantitative form and renal function is taken into account in its calculation.

Objective: To test the hypothesis that the GRACE risk score has superior in-hospital prognostic value, when compared to the TIMI score in patients admitted with ACS.

Methods: Individuals with unstable angina or myocardial infarction without ST-segment elevation, consecutively admitted at the coronary unit between August 2007 and January 2009, were included in the study.

Results: A total of 154 patients aged 71 ± 13 years, of which 56% were females, with a GRACE median of 117 and a TIMI median of 3 were studied. During the hospitalization period, the incidence of events was 8.4% (12 deaths and 1 non-fatal infarction). The Hosmer-Lemeshow test applied to the GRACE score presented an $\chi^2$ of 5.3 ($P = 0.72$), whereas the TIMI score presented an $\chi^2$ of 1.85 ($P = 0.60$). Therefore, both scores presented good calibration. As for the analysis of discrimination, the GRACE score presented a C-statistics of 0.91 (95%CI = 0.86 - 0.97), significantly superior to the C-statistics of 0.69 of the TIMI score (95%CI = 0.55 - 0.84) - $P = 0.02$ for the difference between the scores.

Conclusion: Regarding the prediction of hospital events in patients with ACS, the GRACE score has superior prognostic capacity when compared to the TIMI score. (Arq Bras Cardiol 2010;94(5):576-582)

Key words: Acute coronary syndrome; risk assessment; clinical evolution; GRACE; TIMI.

Introduction
Patients with acute coronary syndromes (ACS) without ST-segment elevation present a broad spectrum of severity, which varies according to the clinical and laboratory characteristics. Therefore, the clinical decision-making requires an effective risk stratification. It has been demonstrated that the use of multivariate models as scores represent the most accurate means of risk prediction, superior to that obtained subjectively through clinical impression.

The TIMI risk score was the first validated model, which originated from the study of cohorts of interventionist clinical trials. This score was rapidly disseminated in clinical practice, on account of being easy to apply. The GRACE score has been validated more recently and presents a more complex use, as it considers a higher number of variables, some of them treated semi-quantitatively. On the other hand, some characteristics support its predictive capacity: the GRACE score was created based on an observational registry, age is computed at several levels, renal function and signs of left ventricular dysfunction are part of this score. Therefore, it becomes important to compare the predictive value of these two scores in order to determine whether the higher complexity of the GRACE score is compensated by a clinically relevant prognostic superiority.

Therefore, the objective of the present study was to test the hypothesis that the GRACE score has a superior prognostic capacity when compared to the TIMI score, regarding recurrent events during the in-hospital phase of patients with ACS.

This hypothesis was tested in a sample of patients consecutively admitted with unstable angina or acute myocardial infarction without ST-segment elevation and the performance of both scores was compared regarding the outcomes of death, nonfatal infarction and refractory angina during hospitalization.

Methods
Population Selection
Individuals consecutively admitted at the coronary unit of our institution hospital between August 2007 and January
2009, with a diagnosis of unstable angina or infarction without ST-segment elevation, were considered candidates to the study. The inclusion criterion was defined as precordial discomfort in the last 48 hours, associated with at least one of the following characteristics: 1) positive myocardial necrosis marker, defined as Troponin T ≥ 0.01 μg/l, which corresponds to values > 99th percentile of the normal reference population; 2) ischemic electrocardiographic alterations, consisting of T-wave inversion (≥ 0.1 mV) or transient ST-segment depression (≥ 0.05 mV); 3) previously documented coronary artery disease, defined by a history of myocardial infarction or previous angiography demonstrating coronary obstruction ≥ 50%. Individuals that met the inclusion criteria and gave their free and informed consent were included in the study. This protocol was approved by the ethics committee in research of the hospital.

Risk scores

To calculate the scores, we used the clinical data presented by the patient at the Emergency department, electrocardiographic records performed in the first 6 hours after the patient arrived at the hospital, Troponin T measurements performed during the first 12 hours of hospitalization and the value of the first plasma creatinine measurement. An increase in the myocardial necrosis marker as a component of the scores was defined as Troponin T levels ≥ 0.01 μg/l, that is, > 99th percentile. The Killip classification was also applied to patients with unstable angina, so that the GRACE score could be calculated.

We used previously defined criteria in the respective studies of validation. In brief, the TIMI risk score consists of seven variables, all dichotomous. The presence of each variable adds a point to the total score, which ranges from zero to seven (0-7). These variables are related to the clinical presentation of the acute coronary syndrome (ST-segment depression, myocardial necrosis marker increase, > 1 episode of angina in 24 hours) or previous characteristics of the patients (age ≥ 65 years, use of aspirin, coronary obstruction ≥ 50%, ≥ 3 risk factors for atherosclerotic disease).

The GRACE score consists of 8 variables: 5 of them are computed semi-quantitatively, i.e., a different weight for each stratum of age, systolic arterial pressure, heart rate, plasma creatinine and Killip classification; three of them are computed dichotomously (ST-segment depression, increase in the myocardial necrosis marker, cardiac arrest at admission). The final score can range from 0 to 372.

In-hospital clinical outcomes

The primary outcome was defined by the combination of death or nonfatal infarction during hospitalization, whereas the secondary outcome was defined by death, nonfatal infarction or refractory angina. Nonfatal infarction was recorded during the hospitalization when the troponin T levels increased in patients whose values were negative during the first 24 hours. For patients with infarction at hospital admission, a new CK-MB peak (> 50% of the previous value and above the normal value) was necessary to define reinfarction. An increase in the levels of necrosis markers induced by percutaneous coronary procedure or revascularization surgery was not recorded as a recurrent event. Refractory angina during hospitalization was defined as recurrent precordial pain, at least twice, in spite of the use of nitrates and controlled double product.

Statistical analysis

The calibration of the scores (goodness-of-fit) was assessed by the Hosmer-Lemeshow test, using c² to define the level of significance. P values > 0.05 define an adequate calibration, considering that the null hypothesis of the test is defined by the divergence between the incidence of event predicted by scores versus the observed incidence. The discriminatory capacity of the scores was evaluated through C-statistics, defined by the area under the ROC curve in relation to the primary and secondary outcomes. The Henley and McNeil method was used to compare the C-statistics of both scores.

Based on the cutoff with the best accuracy, the sensitivity and specificity of each score were calculated for the prediction of in-hospital outcomes. The incidence of events among individuals below or above (high risk) the cutoff was compared by c² test. Moreover, the patients were divided in four different combinations of the TIMI and GRACE scores (both high risk, both low risk, only GRACE high risk or only TIMI high risk) and the incidence of events was compared by the c² test.

As they were ordinal variables, the distributions of the GRACE and TIMI scores were described by medians and interquartile intervals (25th percentile - 75th percentile, IQI) and the same was done with numerical variables with non-normal distribution. Continuous variables with normal distribution were described by means and standard deviations. The SPSS Statistical Software Package (Release 9.0, SPSS Inc., Chicago, Illinois, USA) and MedCalc Statistical Software Package (Release 9.3.2.0, MedCalc Software, Mariakerke, Belgium) were used for the data analysis. P values < 0.05 were considered statistically significant.

Results

Sample characteristics

A total of 154 patients, aged 73 ± 13 years, of which 53% were females, 46% defined at hospital admission as presenting infarction without ST-segment elevation and the others as presenting unstable angina, were studied. The time between symptom onset and the initial treatment presented a median of 4.6 hours (IQI: 2 - 11 hours). The median of the GRACE score was 117 (IQI: 95 - 148), whereas the TIMI score presented a median of 3 (IQI: 2 - 4). The median of the time of hospitalization was 8 days (IQI: 6 - 18 days). One hundred and five patients underwent coronary angiography during the hospital stay and 97 of them underwent the examination as part of an invasive stratification strategy. The 8 remaining patients were submitted to a coronary angiography after a positive scintigraphy for ischemia as part of a selective invasive strategy. The other clinical characteristics are described in Table 1.

Primary outcome: GRACE score versus TIMI score

During the hospitalization, the incidence of the primary outcome was 8.4% (12 deaths and 1 nonfatal infarction). The
The present study confirms the hypothesis that the prognostic value of the GRACE score is superior to that of the TIMI score, regarding hospital events in patients admitted with ACS.

The magnitude of the difference in the discriminative performance between the two scores is significant, represented...
Table 2 - Comparison of the components of the scores between patients with and without hospital events such as death, infarction or refractory angina

<table>
<thead>
<tr>
<th>Variables</th>
<th>Events (N = 19)</th>
<th>No events (N = 135)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>78 ± 11</td>
<td>70 ± 12</td>
<td>0.006</td>
</tr>
<tr>
<td>Positive troponin</td>
<td>16 (84%)</td>
<td>54 (40%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ST-segment depression</td>
<td>9 (47%)</td>
<td>20 (15%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Killip &gt;1</td>
<td>9 (47%)</td>
<td>21 (16%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dl)- median</td>
<td>1.3 (0.9 - 1.9)</td>
<td>1.0 (0.8 - 1.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>146 ± 33</td>
<td>155 ± 33</td>
<td>0.27</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>86 ± 21</td>
<td>75 ± 17</td>
<td>0.04</td>
</tr>
<tr>
<td>Pain episodes ≥ 2</td>
<td>3 (16%)</td>
<td>39 (29%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Previous coronary disease</td>
<td>13 (68%)</td>
<td>90 (67%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Risk factors ≥ 3</td>
<td>4 (21%)</td>
<td>37 (27%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Previous use of aspirin</td>
<td>8 (42%)</td>
<td>52 (39%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3 - Predicting accuracy of the GRACE and TIMI scores regarding cardiovascular events

<table>
<thead>
<tr>
<th></th>
<th>Death and infarction</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>C-statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRACE ≥ 136</td>
<td>100 (79 - 100)</td>
<td>75 (68 - 82)</td>
<td>0.91 (0.86 - 0.97)</td>
<td></td>
</tr>
<tr>
<td>TIMI ≥ 4</td>
<td>54 (27 - 79)</td>
<td>72 (64 - 79)</td>
<td>0.69 (0.55 - 0.84)</td>
<td></td>
</tr>
<tr>
<td>P value (GRACE vs TIMI)</td>
<td>-</td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Death, infarction and refractory angina</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>C-statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRACE ≥ 136</td>
<td>84 (63 - 96)</td>
<td>76 (69 - 83)</td>
<td>0.82 (0.75 - 0.88)</td>
<td></td>
</tr>
<tr>
<td>TIMI ≥ 4</td>
<td>47 (26 - 69)</td>
<td>72 (64 - 79)</td>
<td>0.68 (0.60 - 0.75)</td>
<td></td>
</tr>
<tr>
<td>P value (GRACE vs TIMI)</td>
<td>0.04</td>
<td>0.46</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values between parentheses represent the 95% confidence intervals. The P value of the difference in sensitivity between the two scores regarding death and infarction cannot be calculated, as there were no events in patients with GRACE < 136.

Figure 1 - ROC Curves for GRACE Score versus TIMI Score. Numbers represent the areas under the ROC curves (C-statistics). Panel A compares the two curves regarding the combined events of death or nonfatal infarction, showing the superiority of the GRACE score (P = 0.02). Panel B compares the curves regarding the combined event of death, nonfatal infarction and refractory angina, suggesting the superiority of the GRACE score (P = 0.08).

by a gain of 0.22 at the C-statistics when the GRACE score is used, instead of the TIMI score. This superiority of the GRACE score is due to a better performance in prognostic sensitivity, considering that all patients that presented cardiovascular events during hospitalization were identified by the GRACE score, whereas only 54% of these patients presented a high TIMI score. On the contrary, the prognostic specificity, that is, the capacity to correctly identify those that will not present events, is similar between the two predictive methods. It is noteworthy the fact that most hospital outcomes was represented by cardiovascular death, which gives more relevance to the analysis of combined outcomes.

In clinical practice, the GRACE score is less often used than the TIMI score. This might be due to its higher complexity. Therefore, its use instead of the TIMI score is justified if the gain in discriminatory accuracy is significant. To consider a clinically relevant difference it is necessary that the C-statistics superiority be at least 0.05. In the present study, the difference
was four times this value regarding the primary outcome and three times this value regarding the secondary outcome. Although more complex than the TIMI score, the GRACE score can be rapidly calculated by consulting the tables of variables, or calculators available for use in palmtops or computers. Therefore, the association between complexity and prognostic accuracy is favorable to the use of the GRACE score.

With the objective of clarifying the reasons of the GRACE score superiority in our sample, we compared the components of the scores between the individuals with and without cardiovascular events: the three variables shared by the two scores (age, positive Troponin and ST-segment depression) were associated with events. None of the four variables that pertained exclusively to the TIMI score (> 1 episode of angina in 24 hours, previous use of aspirin, coronary obstruction ≥ 50%, ≥ 3 risk factors for atherosclerotic disease) was associated to events, whereas 3 of the 5 variables that pertained exclusively to the GRACE score (heart rate, plasma creatinine and Killip classification) were associated to events. Therefore, it can be observed that the TIMI score has variables that contribute little to risk prediction and does not contemplate others that are strongly associated to the risk of recurrent events.

It is worth mentioning that in the validation work of the TIMI score, some variables did not participate in the analysis that gave origin to this score (heart rate, plasma creatinine and Killip classification). Had they been part of this analysis, these might have shown to be significant, as well as some exclusive TIMI variables might have lost their statistical significance. Another reason why the GRACE score is superior might be related to the age analysis at several strata, different from the reductionist dichotomization carried out by the TIMI score. It
has been demonstrated that age is a strong determinant of risk and benefit for the invasive strategy in ACS\(^9\). In our sample, the analysis of the ROC curve shows that the age cutoff with the best prognostic performance is 75 years. Additionally, in the group without events, the mean age observed was 70 ± 12 years, suggesting that the cutoff of 65 years is not the best discriminant of risk. Finally, the variables of the TIMI score were identified based on a sample of two randomized clinical trials\(^12\). Thus, the selection bias typical of these study designs might have generated a population that was non-representative of the ACS universe. On the other hand, the GRACE score was obtained from an observational registry, which gives higher consistency to its external validity and might be the reason of its difference in relation to the TIMI score.

Two previous studies evaluated this question in patients with ACS. The Portuguese study by Gonçalves et al.\(^14\) demonstrated the superiority of the GRACE score when compared to the TIMI score with a difference of 0.12 in C-statistics for the combination of death and in-hospital infarction.\(^14\) The second study was the Canadian registry, which also demonstrated a difference of 0.12 between the C-statistics of the two scores.\(^11\) Therefore, the present study is the third one on the subject and the first Brazilian study to confirm these findings. Additionally, our data suggest that the information given by the two scores present some complementary level, when both indicate high risk. In this case, the incidence of events was higher than when only the GRACE score suggested high risk. It is noteworthy the fact that the present data apply to patients with a defined diagnosis of ACS. In other clinical scenarios, the fact that the TIMI score is easier to apply can be an advantage. For instance, Lyon et al.\(^16\) demonstrated a similar accuracy between the two scores in patients with chest pain at the Emergency Department, a situation in which it was easier to obtain information for the TIMI score, when compared to the GRACE score\(^16\).

The limitations of the present study are worth discussing. Although the sample size is enough to conclude that the GRACE score is superior (null hypothesis rejected, with a level of significance of 2%), the confidence intervals of the C-statistics are not very precise regarding the magnitude of this superiority. For this reason, the difference between the scores, higher than the one demonstrated in previous studies, can be overestimated. Finally, the present study does not show outcomes regarding long-term events, as the patients’ prospective follow-up is still going on.

**Conclusion**

Considering its superior prognostic ability, the GRACE score must be chosen over the TIMI score to predict cardiovascular events during the in-hospital phase of individuals with ACS without ST-segment elevation.

**Potential Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

**Sources of Funding**

There were no external funding sources for this study.

**Study Association**

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**References**


