

The Bleeding Risk Score as a Mortality Predictor in Patients with Acute Coronary Syndrome

José Carlos Nicolau¹, Humberto Graner Moreira¹, Luciano Moreira Baracioli¹, Carlos Vicente Serrano Jr.¹, Felipe Galego Lima¹, Marcelo Franken¹, Roberto Rocha Giraldez¹, Fernando Ganem¹, Roberto Kalil Filho¹, José Antônio Franchini Ramires¹, Roxana Mehran²

Instituto do Coração (InCor) – Universidade de São Paulo¹, SP – Brazil; Mount Sinai School of Medicine², New York, NY - USA

Abstract

Background: It is well known that the occurrence of bleeding increases in-hospital mortality in patients with acute coronary syndromes (ACS), and there is a good correlation between bleeding risk scores and bleeding incidence. However, the role of bleeding risk score as mortality predictor is poorly studied.

Objective: The main purpose of this paper was to analyze the role of bleeding risk score as in-hospital mortality predictor in a cohort of patients with ACS treated in a single cardiology tertiary center.

Methods: Out of 1,655 patients with ACS (547 with ST-elevation ACS and 1,118 with non-ST-elevation ACS), we calculated the ACUITY/HORIZONS bleeding score prospectively in 249 patients and retrospectively in the remaining 1,416. Mortality information and hemorrhagic complications were also obtained.

Results: Among the mean age of 64.3 ± 12.6 years, the mean bleeding score was 18 ± 7.7 . The correlation between bleeding and mortality was highly significant ($p < 0.001$, OR = 5.296), as well as the correlation between bleeding score and in-hospital bleeding ($p < 0.001$, OR = 1.058), and between bleeding score and in-hospital mortality (adjusted OR = 1.121, $p < 0.001$, area under the ROC curve 0.753, $p < 0.001$). The adjusted OR and area under the ROC curve for the population with ST-elevation ACS were, respectively, 1.046 ($p = 0.046$) and 0.686 ± 0.040 ($p < 0.001$); for non-ST-elevation ACS the figures were, respectively, 1.150 ($p < 0.001$) and 0.769 ± 0.036 ($p < 0.001$).

Conclusions: Bleeding risk score is a very useful and highly reliable predictor of in-hospital mortality in a wide range of patients with acute coronary syndromes, especially in those with unstable angina or non-ST-elevation acute myocardial infarction. (Arq Bras Cardiol. 2013; 101(6):511-518)

Keywords: Acute Coronary Syndrome/complications; Hemorrhage/mortality; Probability.

Introduction

The administration of an adequate and intensive antithrombotic treatment while minimizing bleeding complications presents a major challenge to the effective management of Acute Coronary Syndromes (ACS). In the last decade, antithrombotic regimen options have increased substantially, resulting in numerous unique combinations of the available drugs. Previously, bleeding complications were considered to be a manageable "side effect" of antithrombotic therapy. However, the development of increasingly potent drugs along with concomitant utilization of antithrombotic therapies, has raised concern for bleeding risk, as there is also

mounting evidence to suggest an independent association between bleeding complications and other detrimental outcomes in patients with ACS, including higher rates of reinfarction, stroke and death¹⁻⁵.

The development of effective tools for predicting patient bleeding risk may help in therapeutic decision making to maximize the benefits and minimize the risk of bleeding associated with antithrombotics. Although there are well established models for ischemic complications risk stratification as TIMI, GRACE, and PURSUIT, among others, tools for predicting the bleeding risk are less common. Several studies identified bleeding risk factors for complications but most did not use them to develop a stratification tool for predict bleeding⁶⁻⁸. The demonstration that a more intensive antithrombotic regimen increases bleeding, which in turn increases ischemic events, has led investigators to conclude that antithrombotic treatment in patients with ACS should be personalized⁹. The recently published American College of Cardiology/American Heart Association 2011 focused update of the guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction (NSTEMI) reiterates the

Mailing Address: José Carlos Nicolau •

Aureliano Coutinho 355, apt. 1401. Postal Code 01224-020. São Paulo - Brazil
e-mail: corjnicolau@incor.usp.br

tel.: +55-11-26615058/+55-11-26615196

fax: +55-11-30883809

Manuscript received August 15, 2013; revised manuscript August 22, 2013; accepted August 22, 2013.

DOI: 10.5935/abc.20130223

importance of balancing antithrombotic strategies with the bleeding risk¹⁰. Actually, despite more aggressive treatment, bleeding rates did not increase over time, suggesting that clinicians are better tailoring antithrombotic therapy to each patient, which support the idea that better and more reliable bleeding scores would be welcome¹¹. On the other hand, it is well demonstrated the correlation between bleeding and in-hospital mortality, and between bleeding scores and incidence of bleeding; however, the predictive value of bleeding risk score for in-hospital mortality is poorly studied.

We contend that valuable advancements are obtained by continually developing simpler and improved calculation methods. Recently, Mehran et al⁸ published a simple and easy to assess tool for bleeding risk stratification. They combined the ACUITY and HORIZONS-AMI data, both contemporary and complimentary ACS trials, and proposed a score comprised of 6 baseline factors (gender, age, creatinine, leukocyte, anemia, type of ACS) and 1 modifiable parameter based on antithrombotic regime (heparin + GP IIb/IIIa inhibitor or bivalirudin)⁸. The main purpose of the present study was to evaluate the role of this score as in-hospital mortality predictor in a cohort of patients with ACS treated in a single cardiology tertiary center, comparing its value in STEMI and non-ST-elevation ACS.

Methods

We included 1,655 patients with ACS (547 with ST-elevation ACS and 1,118 with non-ST-elevation ACS). The bleeding score was calculated prospectively in 249 patients and retrospectively in the remaining 1,416. The mean age of the population was 64.3 ± 12.6 years and 67% were male. It is important to note that because bivalirudin is not available in Brazil, the component of the score regarding antithrombotic therapy was always zero. Despite that just 48.1% of the total population was administered with IIb/IIIa inhibitors, there were no significant differences between the groups with or without IIb/IIIa inhibitors with respect to the role of the bleeding score as a mortality or bleeding predictor.

Statistical Analyses

Categorical variables are described as numbers and percentages and continuous variables as median (25th, 75th percentiles) or mean \pm SD.

For the developed univariate analyses regarding the correlation between bleeding score and mortality or in-hospital bleeding, the Mann-Whitney U test was applied. The Chi-square test was applied for the comparison between categorical variables.

Multivariate stepwise logistic regression models with 0.05 for entry and 0.10 for removal were applied in order to adjust the results for confounding factors. Mortality was the dependent variable, and the baseline and in-hospital variables listed in Table 1 were included as independent variables (except age and gender,

which were already included in the bleeding score). Different models were constructed to better analyze the influence of the bleeding score on mortality. The first envisioned scenario was at the patient's hospital arrival where the models in this situation included baseline variables for the global population and the corresponding TIMI risk scores^{12,13} in the subgroups with or without ST-elevation ACS. In order to analyze the influence of in-hospital invasive therapies on the obtained results, a second set of analyses were developed in the same subgroups, with the inclusion of primary angioplasty, non-primary angioplasty, and surgical revascularization in the models.

Finally, the discriminatory power of the bleeding score and the TIMI risk scores as in-hospital mortality predictors was analyzed by Receiver Operator Characteristic (ROC) curves, with the DeLong method¹⁴, being applied for the statistical comparisons between the curves.

All the above analyses were developed separately for the whole population and also for the ST-elevation ACS and non-ST-elevation ACS.

Table 1 - Characteristics of the population

Baseline Characteristics	
Age [median (25 th , 75 th) years]	64 (55,74)
Bleeding score [median (25 th , 75 th)]	18 (13,23)
TIMI-NSTEACS score [median (25 th , 75 th)]	4 (2,5)
TIMI-STEMI score [median (25 th , 75 th)]	4 (3,5)
Male gender	67%
Previous angina pectoris	31.4%
Previous coronary angioplasty	23.4%
Previous surgical myocardial revascularization	19.9%
Previous heart failure	10%
Previous stroke	5.2%
Previous myocardial infarction	33.6%
Known diabetes	32.4%
Known dyslipidemia	55.9%
Known hypertension	79.2%
Relatives with coronary artery disease	22.5%
Smokers	22.7%
Anterior wall myocardial infarction	28%
In-hospital invasive therapies	
Primary angioplasty	16.8%
Non-primary angioplasty	39.3%
Surgical myocardial revascularization	17.4%

NSTEACS: non-ST-elevation acute coronary syndromes; STEMI: ST-elevation acute myocardial infarction.

P-values < 0.05 (2-sided) were considered significant. MedCalc version 11.4.2.0 statistical software (MedCalc Software, Marakerke, Belgium) was used for the ROC curve comparisons and SPSS version 19.0 (SPSS Inc., Chicago, IL) was used for the other analyses.

Results

The characteristics of the population are depicted in Table 1. The median bleeding score was 18; from the analyzed population, 14.8% were classified as low risk, 20.3% as medium risk, 24.3% as high risk, and 40.8% as very high risk. One third of the patient population had diabetes, another third previous myocardial infarction, 43.3% were submitted previously to surgical or catheter revascularization, and 73% were revascularized during the present hospitalization. Our patient population was comprised of a typical contemporary population commonly seen in a tertiary cardiology center.

Correlation between bleeding score and in-hospital mortality

Univariate analyses showed highly significant correlations between bleeding score and mortality. As shown in Figure 1, p-values <0.001 were obtained for the correlation between both variables in the global population as well as in the subgroups with or without ST-segment-elevation ACS. Other variables that correlated significantly with in-hospital mortality included previous heart failure ($p = 0.005$, OR = 2.033) or stroke ($p = 0.041$, OR = 1.951), current smoking ($p = 0.006$, OR = 0.465), relatives with coronary artery disease ($p = 0.001$, OR = 0.397), and anterior wall location ($p = 0.047$, $p = 1.481$). As expected, the correlation between bleeding and mortality was also statistically significant ($p < 0.001$, OR = 5.296) as was the correlation between bleeding score and in-hospital bleeding ($p < 0.001$, OR = 1.058). Finally, for patients with ST-elevation ACS and with non-ST-elevation ACS, the correlations between the respective TIMI risk scores with mortality were also significant ($p < 0.001$, OR = 1.586 and $p < 0.001$, OR = 1.454, respectively).

The main results of the adjusted models are shown in Tables 2, 3 and 4. The bleeding score correlated significantly and independently with mortality in all models, however, the TIMI risk score showed a stronger correlation with mortality than the bleeding score for patients with ST-elevation myocardial infarction. Conversely, the bleeding score showed a better correlation relative to the TIMI risk score for patients with non-ST-elevation ACS. Importantly, the inclusion of in-hospital bleeding in the final models did not change the results for the bleeding score where $p < 0.001$ (OR = 1.123) for the whole population, and p-values of 0.050 (OR = 1.045) and < 0.001 (OR = 1.146), respectively, were obtained for patients with or without ST-elevation ACS. These findings are further evaluated in the following ROC curve analyses (Figure 2).

Discriminatory value of bleeding score and TIMI risk scores for in-hospital mortality prediction

Figure 2 shows the ROC curve for bleeding score for the whole population. As can be seen, this score is a good predictor of in-hospital mortality, showing an area under the

curve (AUC) of 0.753. Table 5 shows the comparison of the AUC for bleeding score and TIMI risk score in the subgroups with and without ST-elevation ACS. As suggested by the multivariate analyses, in comparison with the respective TIMI scores the bleeding score is a better predictor of in-hospital mortality for patients without ST-elevation ACS and, vice versa, is a worse mortality predictor in the population with ST-elevation ACS.

Discussion

Different bleeding scores have been proposed in order to better evaluate patients with ACS, allowing the attending physician to better utilize the available antithrombotic therapies. In common, these bleeding scores show excellent correlation with bleeding^{1,6,8}. However, there are important differences between them regarding their complexity and difficulty of utilization. The score proposed by Mehran et al⁸, and tested in the present paper, is one of the most user-friendly in the literature, and in this population derived from a tertiary center, also showed excellent correlation with bleeding.

In our databank the definition for bleeding is broad, and takes any bleeding requiring specific action from the staff including that for surgery for pseudo aneurysm, transfusion, or that requiring a third party opinion – generally a angiologist/vascular surgeon, neurologist or hematologist into account. Interestingly, the observed incidence of in-hospital bleeding in the present population was the same as described by Mehran et al⁸ for 30 days (4.3%,) and close to the percentage described in the GRACE Registry (3.9%) for in-hospital major bleeding¹.

On the other hand, it is well demonstrated that the presence of bleeding during hospitalization in patients with ACS increases significantly the incidence of ischemic events, including mortality, in this population^{4,5,15}. Consequently, we found a significant correlation between the presence of bleeding and mortality, with an odds-ratio > 5.

Regarding the TIMI risk scores in both, ACS with or without ST-segment elevation, they show clear correlations with mortality/ischemic events, which could also be demonstrated in the present population^{12,13}. The discriminatory power of the non-ST-elevation ACS TIMI risk score to predict ischemic events (all-cause mortality, myocardial infarction, urgent revascularization) was 0.65¹³, being 0.62 in the present publication, that took into account only all-cause mortality. The ST-elevation myocardial infarction TIMI risk score was studied in a broad population of patients included in the North-American registry of myocardial infarction (submitted to fibrinolysis, primary angioplasty or without reperfusion)¹⁶; overall, its discriminatory power for all-cause mortality was 0.74, being 0.798 in the present study. This value is near the 0.83 proposed by Diamond¹⁷ as the maximal value for a perfectly calibrated prediction rule, while at the same time the authors explain that higher values are possible but come at the cost of poorer calibration.

An analysis of bleeding score as a mortality risk factor, and its relationship with TIMI risk scores and in-hospital bleeding, have not been published previously. Our major findings were 1)

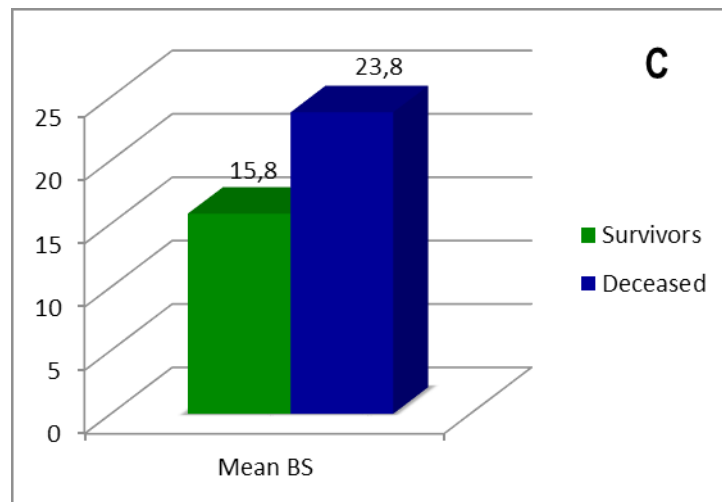
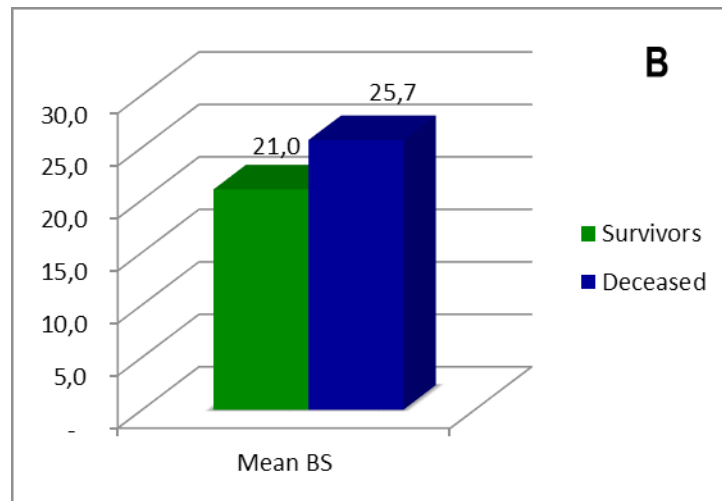
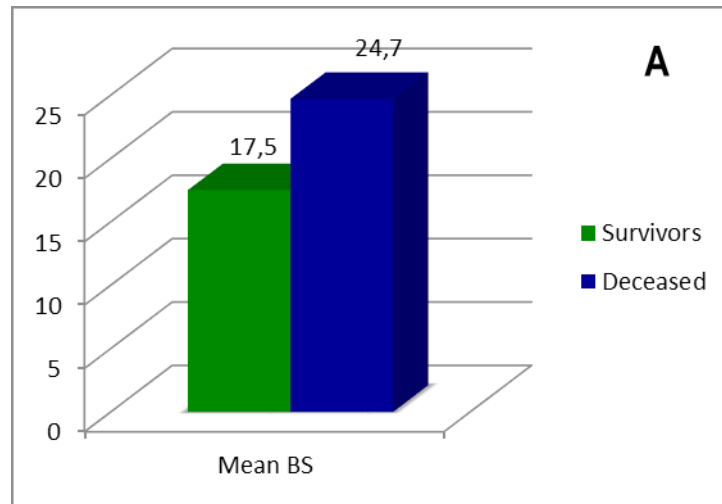


Figure 1 - A) Bleeding score and in-hospital mortality for the whole population; **B)** subgroup with ST-elevation myocardial infarction; and **C)** subgroup with non-ST-elevation ACS. BS - bleeding score; ACS - acute coronary syndromes.

Table 2 - Variables that correlated significantly and independently with in-hospital mortality in the whole population

A. Only baseline variables included in the model

Variables	Adjusted odds-ratio	p-value
Bleeding score	1.121	< 0.001
Previous surgical myocardial revascularization	0.577	0.041
Relatives with coronary artery disease	0.516	0.032

B. Baseline variables and in-hospital invasive therapies included in the model

Variables	Adjusted odds-ratio	p-value
Bleeding score	1.126	< 0.001
In-hospital surgical myocardial revascularization	2.040	0.003
Relatives with coronary artery disease	0.500	0.025

Table 3 - Variables that correlated significantly and independently with in-hospital mortality in patients with ST-elevation acute myocardial infarction

Baseline variables (including STEMI TIMI risk score) included in the model*

Variables	Adjusted odds-ratio	p-value
Bleeding score	1.046	0.046
Previous myocardial infarction	2.329	0.022
Smoking	0.361	0.032
Known diabetes	2.066	0.032
Known dyslipidemia	0.477	0.038
STEMI TIMI risk score	1.535	< 0.001

*The inclusion of invasive in-hospital therapies in the model did not change the showed results; STEMI: ST-elevation acute myocardial infarction.

Table 4 - Variables that correlated significantly and independently with in-hospital mortality in the subgroup with non-ST-elevation acute coronary syndromes

A. Baseline variables (including NSTEMI TIMI risk score) included in the model

Variables	Adjusted odds-ratio	p-value
Bleeding score	1.142	< 0.001
Previous surgical myocardial revascularization	0.478	0.031
NSTEMI TIMI risk score	1.402	0.004

B. Baseline variables (including NSTEMI TIMI risk score) and in-hospital invasive therapies included in the model

Variables	Adjusted odds-ratio	p-value
Bleeding score	1.150	< 0.001
In-hospital surgical myocardial revascularization	2.109	0.015
NSTEMI TIMI risk score	1.297	0.020

NSTEMI: non-ST-elevation acute coronary syndromes.

The bleeding risk score proposed by Mehran et al⁸ is an excellent predictor of in-hospital mortality in patients with acute coronary syndromes and 2) Regarding in-hospital mortality when compared with the TIMI risk scores, the bleeding risk score

was more reliable than the corresponding TIMI risk score for patients with non-ST-elevation ACS, and performed worse as an indicator in patients with ST-elevation myocardial infarction. However, we found that both variables correlated significantly

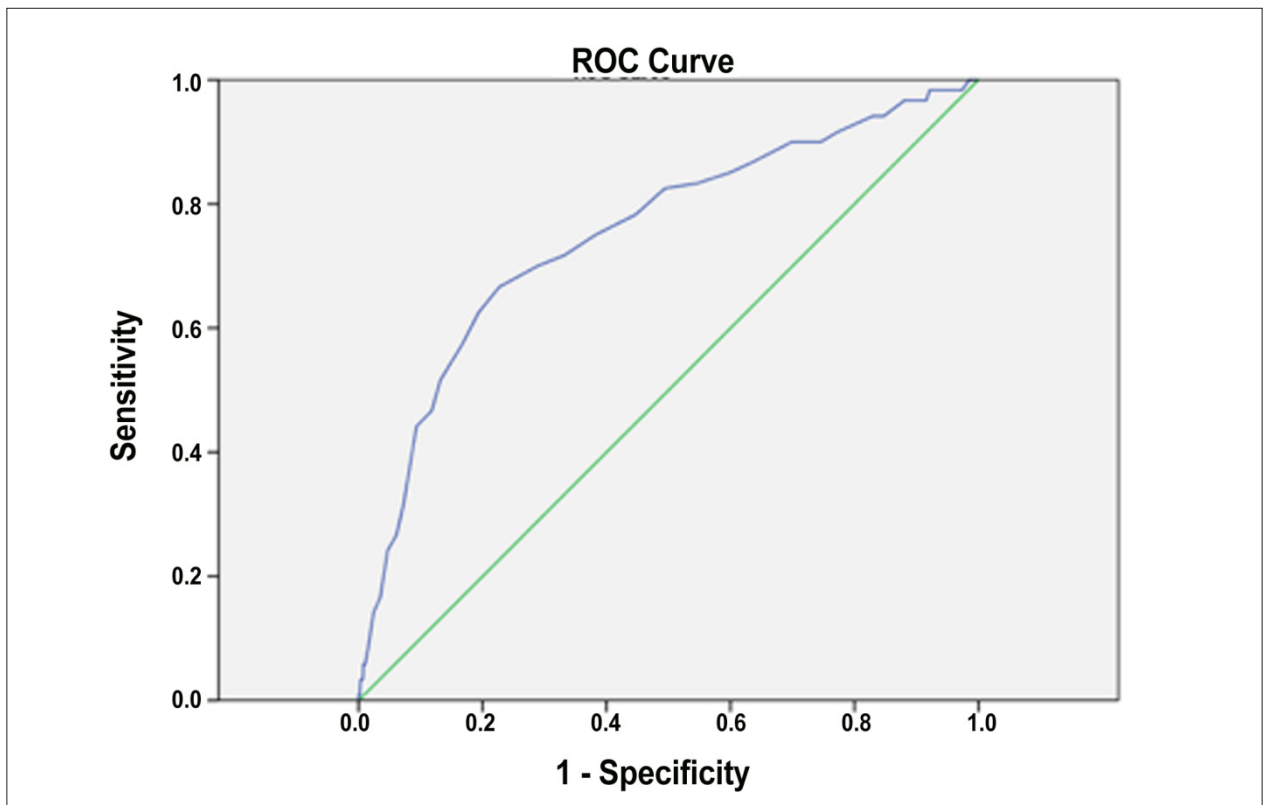


Figure 2 - ROC curve for the whole population (area under the curve = 0.753 ± 0.025 , $p < 0.001$).

Table 5 - Results of the ROC curves for the whole population and subgroups with or without ST segment elevation acute coronary syndromes

	AUC (\pm SE)	p-value
Global population		
Bleeding score	0.753 ± 0.025	< 0.001
STEMI		
Bleeding score	0.686 ± 0.040	< 0.001
TIMI risk score	0.798 ± 0.032	< 0.001
NSTEACS		
Bleeding score	0.769 ± 0.036	< 0.001
TIMI risk score	0.616 ± 0.037	0.002

* $p = 0.029$ for the comparison between bleeding score and TIMI risk score; ** $p = 0.003$ for the comparison between bleeding score and TIMI risk score; AUC: area under the curve; STEMI: ST-elevation acute myocardial infarction; NSTEMACS: non-ST-elevation acute coronary syndromes.

and independently with mortality in the broad spectrum of patients with ACS that we analyzed for this study. Interestingly, despite the excellent correlation between the bleeding risk score and the observed bleeding, both variables correlated significantly and independently with in-hospital mortality. These findings suggest that other variables included in the bleeding score could influence in-hospital mortality independently of bleeding itself, as could be the case for age.

Limitations of the Study

As with any databank-derived study, it is possible that confounders not included in the adjusted models could have influenced the results with respect to the correlation of the bleeding score and mortality. Certainly the ROC curve analyses, which showed excellent discriminatory power of the bleeding score to predict mortality, is useful in order to give a more reliable and complete answer

to the proposed hypothesis. Secondly, bivalirudin is not available in Brazil and this could have affected the results. However, the non-utilization of bivalirudin is a common scenario even in countries where the drug is available. In the USA alone, more than one million angioplasties are performed each year (<http://www.nhlbi.nih.gov/health/health-topics/topics/angioplasty>), whereas the worldwide sales of bivalirudin (2010) is estimated at about \$400 million per year (<http://prescriptions.blogs.nytimes.com/2010/10/05/angiomax-may-get-patent-extension>) at a cost varying between \$824/patient¹⁸ up to \$1675/patient¹⁹, which comes out to a number between 238,000 and 485,000 patients per year worldwide.

Conclusion

The bleeding score proposed by Mehran et al is an excellent predictor of in-hospital mortality in the broad spectrum of patients with acute coronary syndromes, especially those with unstable angina or non-ST-elevation acute myocardial infarction.

References

1. Moscucci M, Fox KA, Cannon CP, Klein W, Lopez-Sendon J, Montalescot G, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J*. 2003;24(20):1815-23.
2. Rao SV, O'Grady K, Pieper KS, Granger CB, Newby LK, Van de Werf F, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. *Am J Cardiol*. 2005;96(9):1200-6.
3. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation*. 2006;114(8):774-82.
4. Pocock SJ, Mehran R, Clayton TC, Nikolsky E, Parise H, Fahy M, et al. Prognostic modeling of individual patient risk and mortality impact of ischemic and hemorrhagic complications: assessment from the Acute Catheterization and Urgent Intervention Triage Strategy trial. *Circulation*. 2010;121(1):43-51.
5. Mehran R, Pocock S, Nikolsky E, Dangas GD, Clayton T, Claessen BE, et al. Impact of bleeding on mortality after percutaneous coronary intervention results from a patient-level pooled analysis of the REPLACE-2 (randomized evaluation of PCI linking angiomax to reduced clinical events), ACUITY (acute catheterization and urgent intervention triage strategy), and HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trials. *JACC Cardiovasc Interv*. 2011;4(6):654-664.
6. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. *Circulation*. 2009;119(14):1873-82.
7. Nikolsky E, Mehran R, Dangas G, Fahy M, Na Y, Pocock SJ, et al. Development and validation of a prognostic risk score for major bleeding in patients undergoing percutaneous coronary intervention via the femoral approach. *Eur Heart J*. 2007;28(16):1936-45.

Author contributions

Conception and design of the research: Nicolau JC. Acquisition of data: Nicolau JC, Moreira HG. Analysis and interpretation of the data: Nicolau JC. Statistical analysis: Nicolau JC. Writing of the manuscript: Nicolau JC, Mehran R. Critical revision of the manuscript for intellectual content: Nicolau JC, Moreira HG, Baracoli LM, Serrano Jr CV, Lima F, Franken M, Giraldez RR, Ganem F, Kalil Filho R, Ramires JAF, Mehran R.

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

This study is not associated with any post-graduation program.

8. Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, et al. A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2010;55(23):2556-66.
9. Van de Werf F. Balancing benefit and bleeding risk of antithrombotic agents in the individual patient with an acute coronary syndrome. *Circulation*. 2010;121(1):5-7. Erratum in: *Circulation*. 2010;121(25):e462.
10. Wright RS, Anderson JL, Adams CD, Bridges CR, Casey DE, Ettinger SM, et al. 2011 ACCF/AHA focused update of the Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction (updating the 2007 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the American College of Emergency Physicians, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2011;57(19):1920-59. Erratum in: *J Am Coll Cardiol*. 2011;57(19):1960.
11. Elbarouni B, Elmanfud O, Yan RT, Fox KA, Kornder JM, Rose B, et al. Temporal trend of in-hospital major bleeding among patients with non ST-elevation acute coronary syndromes. *Am Heart J*. 2010;160(3):420-7.
12. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation*. 2000;102(17):2031-7.
13. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA*. 2000;284(7):835-42.
14. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44(3):837-845.

15. Baber U, Kovacic J, Kini AS, Sharma SK, Dangas G, Mehran R. How serious a problem is bleeding in patients with acute coronary syndromes? *Curr Cardiol Rep.* 2011;13(4):312-9.
16. Morrow DA, Antman EM, Parsons L, de Lemos JA, Cannon CP, Giugliano RP, et al. Application of the TIMI risk score for ST-elevation MI in the National Registry of Myocardial Infarction 3. *JAMA.* 2001;286(11):1356-9.
17. Diamond GA. What price perfection? Calibration and discrimination of clinical prediction models. *J Clin Epidemiol.* 1992;45(1):85-9.
18. Pinto DS, Stone GW, Shi C, Dunn ES, Reynolds MR, York M, et al; ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) Investigators. Economic evaluation of bivalirudin with or without glycoprotein IIb/IIIa inhibition versus heparin with routine glycoprotein IIb/IIIa inhibition for early invasive management of acute coronary syndromes. *J Am Coll Cardiol.* 2008;52(22):1758-68.
19. Wiggins BS, Spinler S, Wittkowsky AK, Stringer KA. Bivalirudin: a direct thrombin inhibitor for percutaneous transluminal coronary angioplasty. *Pharmacotherapy.* 2002;22(8):1007-18.