Original article

Association Between Ischemic and Bleeding Risk Scores and the Use of New P2Y$_{12}$ Inhibitors in Patients With Acute Coronary Syndrome

Pedro J. Flores-Blanco,[a,*] Francisco Cambronero-Sánchez,[b] Sergio Raposeiras-Roubin,[c] Emad Abu-Assi,[c] Gunnar Leithold,[a] Rafael Cobas-Paz,[c] Ana I. Rodríguez Serrano,[a] Francisco Calvo-Iglesias,[c] Mariano Valdés,[a,d] James L. Januzzi,[e] Andrés Iñiguez-Romo,[c] and Sergio Manzano-Fernández[a,d]

[a] *Departamento de Medicina Interna, Servicio de Cardiología, Hospital Clínico Universitario Virgen de la Arrixaca, Instituto Murciano de Investigación Biosanitaria, El Palmar, Murcia, Spain*
[b] *Departamento de Medicina Interna, Servicio de Cardiología, Hospital General Universitario Los Arcos del Mar Menor, San Javier, Murcia, Spain*
[c] *Departamento de Cardiología, Hospital Universitario Álvaro Cunqueiro de Vigo, Vigo, Pontevedra, Spain*
[d] *Departamento de Medicina Interna, Facultad de Medicina, Universidad de Murcia, Murcia, Spain*
[e] *Division of Cardiology, Massachusetts General Hospital, Boston, United States*

A B S T R A C T

Introduction and objectives: Acute coronary syndrome (ACS) guidelines recommend the use of newer P2Y$_{12}$ inhibitors (prasugrel and ticagrelor) over clopidogrel in patients with moderate-to-high ischemic risk, unless they have an increased bleeding risk. The aim of our study was to assess the GRACE risk score and the CRUSADE bleeding risk score relative to prescription of newer P2Y$_{12}$ inhibitors at discharge in ACS patients.
Methods: Retrospective analysis of a multicenter ACS registry; 3515 consecutive patients were included. The association between risk scores and prescription of newer P2Y$_{12}$ inhibitors was assessed by binary logistic regression analysis.
Results: A total of 1021 patients (29%) were treated with prasugrel or ticagrelor. On multivariate analyses, both GRACE (OR per 10 points, 0.89; 95%CI, 0.86-0.92; $P < .001$) and CRUSADE (OR per 10 points, 0.96; 95%CI, 0.94-0.98; $P < .001$) risk scores were inversely associated with the use of newer P2Y$_{12}$ inhibitors. Moreover, other factors not included in these scores (revascularization approach, in-hospital stent thrombosis, major bleeding, and concomitant indication for anticoagulation therapy) also predicted the use of newer P2Y$_{12}$ inhibitors.
Conclusions: New P2Y$_{12}$ inhibitors were more frequently prescribed among ACS patients with lower CRUSADE bleeding risk. However, an ischemic risk paradox was found, with higher use of these agents in patients with lower ischemic risk based on GRACE risk score estimates. These results underscore the importance of risk stratification to safely deliver optimal therapies.

© 2017 Sociedad Española de Cardiología. Published by Elsevier España, S.L.U. All rights reserved.

Asociación entre las escalas de riesgo isquémico y hemorrágico y el uso de los nuevos inhibidores del P2Y$_{12}$ en pacientes con síndrome coronario agudo

R E S U M E N

Introducción y objetivos: Las guías sobre síndrome coronario agudo (SCA) recomiendan el uso de los nuevos inhibidores del P2Y$_{12}$ (prasugrel y ticagrelor) antes que el clopidogrel para los pacientes con riesgo isquémico moderado-alto, siempre que no tengan un riesgo hemorrágico elevado. El objetivo de nuestro estudio es evaluar la escala de riesgo isquémico GRACE y la de riesgo hemorrágico CRUSADE en relación con la prescripción de los nuevos inhibidores del P2Y$_{12}$ al alta en pacientes con SCA.
Métodos: Análisis retrospectivo de un registro multicéntrico de SCA. Se incluyó a 3.515 pacientes consecutivos. La asociación entre las escalas de riesgo y la prescripción de los nuevos inhibidores del P2Y$_{12}$ se evaluó mediante análisis de regresión logística binaria.
Resultados: Se trató con prasugrel o ticagrelor a 1.021 pacientes (29%). En el análisis multivariable, tanto la escala GRACE (cada 10 puntos, OR = 0,89; IC95%, 0,86-0,92; p < 0,001) como la escala CRUSADE (cada 10 puntos, OR = 0,96; IC95%, 0,94-0,98; p < 0,001) se asociaron inversamente con el uso de los nuevos inhibidores del P2Y$_{12}$. Además, otros factores no incluidos en estas escalas (tipo de revascularización, trombosis del *stent* hospitalaria, hemorragia mayor e indicación concomitante de terapia anti-coagulante) también fueron predictores del uso de los nuevos inhibidores del P2Y$_{12}$.

* Corresponding author: Servicio de Cardiología, Hospital Clínico Universitario Virgen de la Arrixaca, Carretera Madrid Cartagena s/n, 30120, El Palmar, Murcia, Spain.
E-mail address: pedrofb1986@gmail.com (P.J. Flores-Blanco).

Conclusiones: Los nuevos inhibidores del P2Y$_{12}$ se prescribieron con mayor frecuencia a los pacientes con SCA con menor riesgo hemorrágico CRUSADE. Sin embargo, se encontró una paradoja en cuanto al riesgo isquémico, con mayor uso de estos agentes para pacientes con menor riesgo estimado con la escala GRACE. Estos resultados subrayan la importancia de la estratificación de riesgos para prescribir con seguridad las terapias óptimas.

Abbreviations

ACS: acute coronary syndrome

INTRODUCTION

Dual antiplatelet therapy with aspirin and clopidogrel has been considered the mainstay of care in the setting of acute coronary syndrome (ACS).[1] However, despite the benefits of this combination, patients continue to be at risk of further cardiovascular events[2–4] which, to some extent, may be related to some inadequate antiplatelet effects of clopidogrel.[5,6] This has stimulated the search for more effective antiplatelet drugs. Prasugrel and ticagrelor are newer and more potent P2Y$_{12}$ inhibitors, which have been demonstrated to reduce recurrent ischemic events, albeit at the expense of increased bleeding compared with clopidogrel.[7,8] Current guidelines for the management of ACS[9,10] recommend the use of these new P2Y$_{12}$ inhibitors over clopidogrel, mainly in patients with moderate-to-high ischemic risk, unless they have an increased risk of bleeding. Therefore, clinicians must balance risks and benefits to obtain the highest clinical net benefit of the prescribed antiplatelet therapy.

One option to assess both clinical risk as well as the potential for bleeding is the use of risk scores. In patients with ACS, the GRACE score provides the most accurate stratification of risk of death, using scores both on admission and at discharge[11] and its use is recommended by current ACS guidelines.[9,10] Regarding bleeding risk assessment, the CRUSADE score has been found to be the most discriminatory score to assess in-hospital major bleeding risk, mainly in patients undergoing coronary angiography.[12] To date, there is no validated risk model to estimate bleeding risk after discharge in ACS patients. However, because the CRUSADE risk score performed well among patients taking dual antiplatelet therapy, this risk model may be used for bleeding risk stratification in ACS patients after hospital discharge.[13] However, which risk has the higher impact or whether other factors influence clinicians' patterns of antiplatelet selection is unknown. Therefore, the aims of this study were to assess the GRACE risk score and the CRUSADE bleeding risk score relative to prescription of new P2Y$_{12}$ inhibitors (prasugrel and ticagrelor) in patients with ACS.

METHODS

The present study complied with the Declaration of Helsinki and was approved by the local ethics committee. The data analyzed in this study were obtained from a merged retrospective clinical registry including all consecutive patients with an established final diagnosis of ACS who had undergone coronary angiography in 2 tertiary hospitals from January 1, 2011 to December 31, 2015. However, for this analysis, the study population was limited to patients admitted from November 1, 2012 to December 31, 2015. This was the period when the 2 newer P2Y$_{12}$ inhibitors (prasugrel and ticagrelor) were widely available in both participating hospitals, and when the prescription rate of these agents reached a relatively stable level, at around 30%. This analysis excluded early users of ticagrelor or prasugrel, who may differ from those who started these agents later (ie, eagerness to adopt new treatments or abnormal baseline risk). A total of 4653 ACS patients were recruited. Of these, 1138 were excluded (755 were admitted before November 1, 2012, 142 patients died before hospital discharge, and GRACE or CRUSADE risk scores and antiplatelet therapy at discharge were not available in 132 and 109 patients [2.8%], respectively). Therefore, the final study population consisted of 3515 hospitalized patients with ACS.

Data on demographic and clinical characteristics, complementary test results, angiographic parameters, in-hospital events, as well as treatment at discharge were collected in detail by trained cardiologists. For each patient, the GRACE 6-month mortality risk score[14] and the CRUSADE bleeding risk score[15] were calculated retrospectively. Patients were classified into 3 categories as a function of GRACE risk score (low risk < 100 points, intermediate risk 100-127 points, and high risk > 127 points for ST-segment elevation ACS; and low risk < 89 points, intermediate risk 89-118 points, and high risk > 118 points for non–ST-segment elevation ACS) and 5 categories as a function of CRUSADE risk score (very low risk < 21, low risk 21-30 points, moderate risk 31-40 points, high risk 41-50 points, and very high risk > 50 points). Major bleeding was defined according to the Bleeding Academic Research Consortium criteria as bleeding types 3 to 5.[16] Stent thrombosis was defined following the recommendations of the Academic Research Consortium, and only definitive stent thrombosis was considered for analyses.[17] The clinical management decisions about each patient were decided by the treating cardiologist and no protocol was followed to guide selection of dual antiplatelet therapy.

Categorical variables are presented as frequency values and continuous variables as mean ± standard deviation. Categorized analyses were performed according to the prescription of new P2Y$_{12}$ inhibitors at discharge. Differences in baseline characteristics were compared using the Student *t* test for continuous variables and the chi-square test for categorical variables. To assess the independent association of GRACE and CRUSADE risk scores on new P2Y$_{12}$ inhibitor prescription at discharge, we calculated odds ratios (OR) and 95% confidence intervals (95%CI) using multivariate binary logistic regression models with adjustment for other predictors of new P2Y$_{12}$ inhibitor prescription at discharge. To identify variables associated with new P2Y$_{12}$ inhibitor prescription at discharge, univariable binary logistic regression analyses were first performed for the all variables listed in Table 1 of the supplementary material. We next performed a stepwise backward selection binary logistic regression analysis to identify independent predictors of new P2Y$_{12}$ inhibitor prescription at discharge. Covariates with $P < .05$ on univariable analysis and those considered of clinical interest by the investigator (diabetes mellitus) were included in the multivariate models. The entry criterion was set at $P < .05$, and the exit criterion was set at $P = .10$. To investigate the influence of the individual data elements of the CRUSADE and GRACE risk scores on new P2Y$_{12}$ inhibitor prescription, we developed additional multivariate binary

Table 1
Study Population Clinical Characteristics in the Whole Population and as a Function of New $P2Y_{12}$ Inhibitors Prescription at Discharge

Variables	Whole population N = 3515	New $P2Y_{12}$ inhibitors n = 1021	No new $P2Y_{12}$ inhibitors n = 2494	P value
Age, y	66 ± 13	59 ± 11	68 ± 13	< .001
Sex, male	2600 (74)	834 (82)	1766 (71)	< .001
Medical history				
Hypertension	2198 (63)	549 (54)	1649 (66)	< .001
Diabetes mellitus	1102 (31)	330 (32)	772 (31)	.428
Hyperlipidemia	2361 (67)	715 (70)	1646 (66)	.021
Current smoking	1222 (35)	508 (50)	714 (29)	< .001
Low weight (< 60 kg)	243 (7)	49 (5)	194 (8)	.002
Previous ACS	550 (16)	145 (14)	405 (16)	.129
Previous atrial fibrillation	257 (7)	2 (0.2)	255 (10)	< .001
Mechanical valve prosthesis	19 (0.5)	0 (0)	19 (0.8)	.005
Peripheral artery disease	269 (8)	46 (5)	223 (9)	< .001
Previous stroke	215 (6)	33 (3)	182 (7)	< .001
Previous major bleeding	89 (3)	11 (1)	78 (3)	< .001
Clinical status at admission				
Systolic blood pressure, mmHg	138 ± 26	136 ± 26	138 ± 26	.014
Heart rate, bpm	76 ± 19	75 ± 17	76 ± 20	.127
Killip class				
I	2977 (85)	906 (89)	2071 (83)	
II	354 (10)	78 (8)	276 (11)	< .001
III	120 (3)	16 (2)	104 (4)	
IV	64 (2)	21 (2)	43 (2)	
Cardiac arrest at admission	71 (2)	27 (3)	44 (2)	.092
Complementary test results				
Hematocrit, %	42 ± 5	43 ± 4	41 ± 5	< .001
eGFR, mL/min/1.73m^2	80 ± 23	87 ± 19	76 ± 23	< .001
Elevated cardiac markers	3025 (86)	943 (92)	2082 (84)	< .001
ST-segment deviation	2178 (62)	711 (70)	1467 (59)	< .001
LVEF ≤ 50%	1163 (34)	321 (32)	842 (35)	.107
In-hospital procedures and treatments				
LM and/or 3-vessel disease	817 (23)	180 (17)	637 (26)	< .001
Percutaneous coronary intervention	2582 (74)	945 (93)	1637 (66)	< .001
Coronary artery bypass grafting	193 (6)	6 (0.6)	187 (8)	< .001
Thrombolysis	58 (2)	27 (3)	31 (1)	.003
Conservative management	751 (21)	71 (7)	680 (27)	< .001
In-hospital events				
Stent thrombosis	13 (0.4)	9 (0.9)	4 (0.2)	< .001
Atrial fibrillation	240 (7)	29 (3)	211 (9)	< .001
Left ventricular thrombus	46 (1)	1 (0.1)	45 (2)	< .001
Stroke	19 (0.5)	4 (0.4)	15 (0.6)	.719
Major bleeding	71 (2)	8 (0.8)	63 (3)	.001
Final diagnosis				
STEACS	1391 (40)	552 (54)	839 (34)	
NSTEACS	1885 (54)	443 (42)	1442 (58)	< .001
Undetermined ACS	240 (7)	26 (3)	213 (9)	
Risk scores				
GRACE 6-month mortality risk score	114 ± 33	104 ± 29	118 ± 34	< .001
CRUSADE bleeding risk score	25 ± 15	20 ± 13	27 ± 16	< .001
Other				
Indication for OAT at discharge[*]	582 (17)	37 (4)	545 (22)	< .001
Stroke (previous and in-hospital)	231 (7)	37 (4)	194 (8)	< .001
Major bleeding (previous and in-hospital)	155 (4)	19 (2)	136 (6)	< .001

ACS, acute coronary syndrome; eGFR, estimated glomerular filtration rate; LM, left main artery; LVEF, left ventricular ejection function; NSTEACS, non–ST-segment elevation acute coronary syndrome; OAT, oral anticoagulation therapy; STEACS, ST-segment elevation acute coronary syndrome.
Data are expressed as mean ± standard deviation or No. (%).
[*] Indications for OAT at discharge including atrial fibrillation (previous or in-hospital), mechanical valve prosthesis, left ventricular thrombus and other conditions.
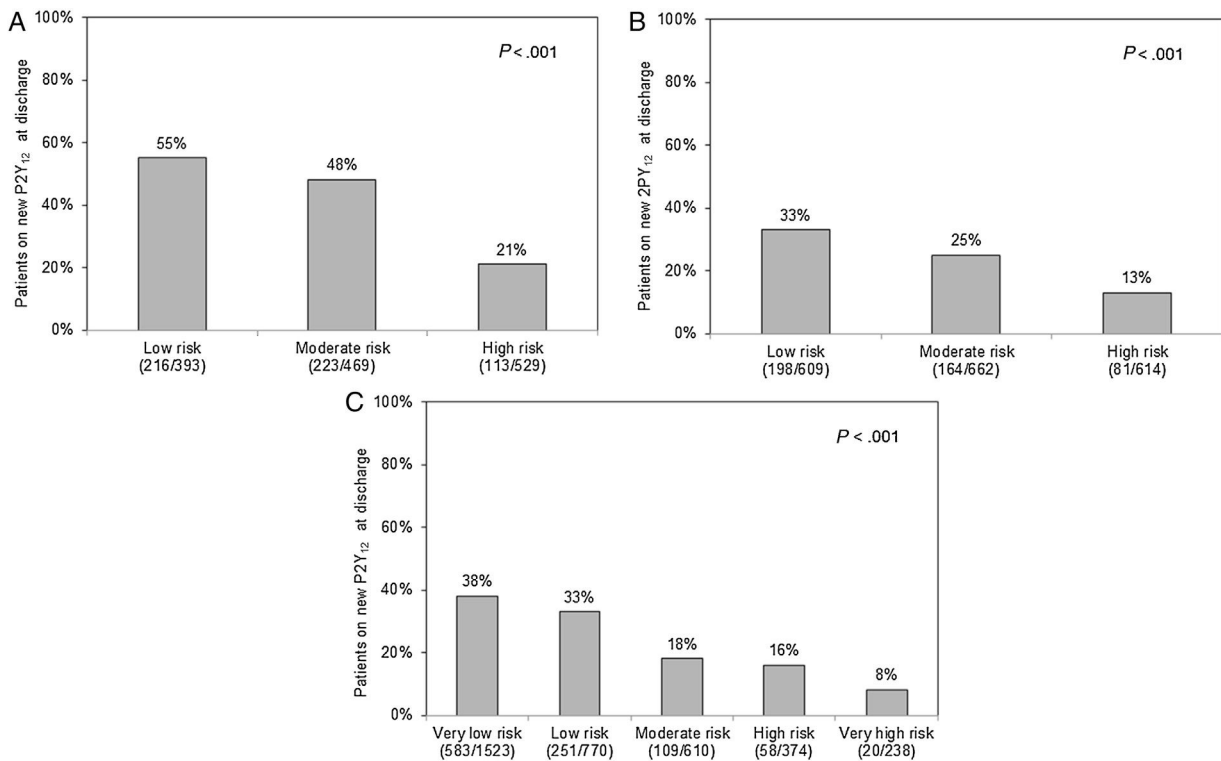
Figure 1. Rate of new $P2Y_{12}$ inhibitor prescription at discharge according to GRACE 6-month mortality risk categories in patients presenting with STEACS (A) or NSTEACS (B) and CRUSADE bleeding risk categories (C). STEACS, ST-segment elevation acute coronary syndrome; NSTEACS, non–ST-segment elevation acute coronary syndrome.

logistic regression models. All P values $< .05$ were accepted as statistically significant. Statistical analysis was performed using SPSS version 18.0 (SPSS, Inc, Chicago, Illinois, United States) and STATA version 13.0 (Stata Corp LP; Texas, United States).Table 1

RESULTS

The study population consisted of 3515 hospitalized patients with ACS. A total of 1021 patients (29%) were treated with new $P2Y_{12}$ inhibitors at discharge. Prasugrel was used in 346 (9.8%) and ticagrelor in 675 (19.2%).

Table 1 shows the study population characteristics according to new $P2Y_{12}$ prescription at discharge. Patients on new $P2Y_{12}$ inhibitors had lower GRACE (104 ± 29 vs 118 ± 34; $P < .001$) and CRUSADE (20 ± 13 vs 27 ± 16; $P < .001$) scores. A stepwise decrease in the proportion of patients on new $P2Y_{12}$ inhibitors was seen with increasing bleeding and ischemic risk categories (Figure 1). This underuse of new $P2Y_{12}$ inhibitors with increasing ischemic risk was seen in all bleeding risk categories (Figure 2). Thus, the higher the ischemic or bleeding risk, the lower the rate of new $P2Y_{12}$ inhibitor prescription.

In multivariate binary logistic regression analyses, we found both GRACE (OR per 10 points, 0.89; 95%CI, 0.86-0.92; $P < .001$) and CRUSADE (OR per 10 points, 0.96; 95%CI, 0.94-0.98; $P < .001$) risk
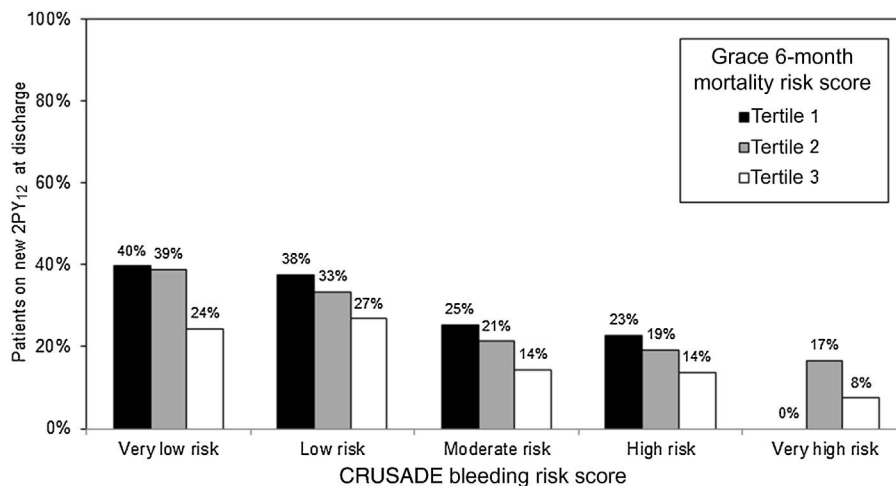

Figure 2. Rate of new $P2Y_{12}$ inhibitor prescription at discharge according to CRUSADE bleeding risk score categories and GRACE 6-month mortality risk score tertiles.
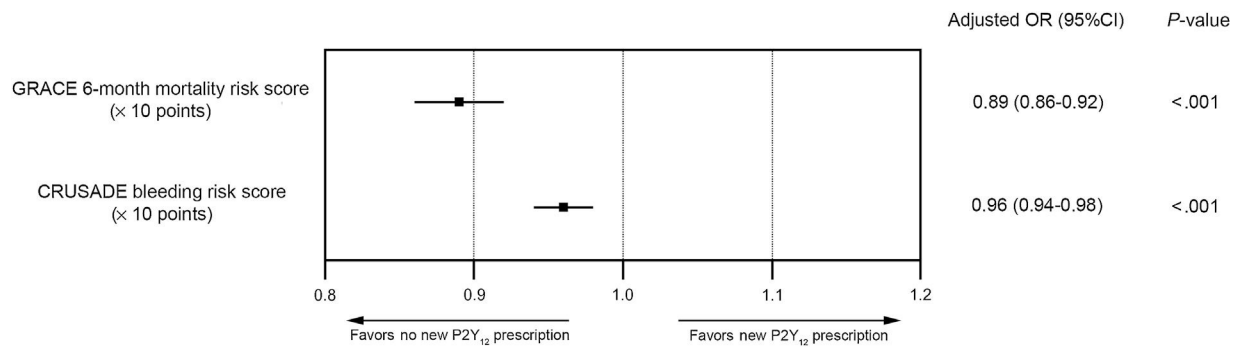
Figure 3. Multivariate odds ratios for the association between GRACE and CRUSADE risk scores and new P2Y$_{12}$ inhibitor prescription at discharge. 95%CI, 95% confidence interval; OR, odds ratio. For variables included in multivariate models, see Table 2A of the supplementary material and Table 2B of the supplementary material.

scores to be associated with new P2Y$_{12}$ inhibitor prescription at discharge (Figure 3). This inverse association with GRACE and CRUSADE risk scores persisted when prasugrel and ticagrelor prescription was analyzed separately (prasugrel = OR per 10 points in the GRACE risk score, 0.86; 95%CI, 0.82-0.90; $P < .001$ and OR per 10 points in the CRUSADE risk score, 0.95; 95%CI, 0.92-0.99; $P = .009$; ticagrelor = OR per 10 points in the GRACE risk score, 0.91; 95%CI, 0.88-0.94; $P < .001$ and OR per 10 points in the CRUSADE risk score, 0.96; 95%CI, 0.94-0.99; $P = .003$). Detailed data on these multivariate analyses are described in Table 2A of the supplementary material and Table 2B of the supplementary material. As shown in Table 2, when the individual data elements of both risk scores were included in a single multivariate model, age (OR per 10 years, 0.60; 95%CI, 0.56-0.65; $P < .001$), diabetes mellitus (OR, 1.69; 95%CI, 1.39-2.05; $P < .001$), peripheral artery disease (OR, 0.64; 95%CI, 0.44-0.93; $P < .020$), hematocrit level (OR per 3%, 1.04; 95%CI, 1.02-1.06; $P < .001$), elevated cardiac markers (OR; 1.60;

95%CI, 1.19-2.15; $P = .002$) and ST-segment deviation (OR, 1.25; 95%CI, 1.03-1.51; $P = .023$) remained as predictors of new P2Y$_{12}$ inhibitor prescription at discharge. Other independent predictors, not included in the GRACE or CRUSADE risk scores, were hyperlipidemia, percutaneous coronary intervention, coronary artery bypass grafting, in-hospital stent thrombosis, major bleeding (previous or in-hospital), and indication for oral anticoagulation therapy at discharge (Table 2).

DISCUSSION

In this study, we evaluated prescription of newer, more potent P2Y$_{12}$ inhibitors at discharge relative to clinical risk and risk for bleeding in patients with ACS. We found that a perceived high bleeding risk led to lower prescription of these agents, despite generally higher risk in such patients. This finding is in accordance with current guidelines that do not support the use of prasugrel or ticagrelor in patients at high risk of bleeding.[9,10] In contrast, current guidelines also recommend the use of prasugrel and ticagrelor in patients at moderate-to-high risk of ischemic events,[9,10] due to the reduction in ischemic events with both new P2Y$_{12}$ inhibitors.[7,8] Furthermore, some authors have proposed specific protocols for the selection of antiplatelet therapy in patients with ACS in which the GRACE risk score is the first discriminative criteria (clopidogrel if GRACE < 109 and prasugrel or ticagrelor if GRACE ≥ 109 and no contraindications or high bleeding risk).[18] However, in our study, we found that higher ischemic risk based on GRACE risk score was not related to prescription of these agents. Indeed, the higher the estimated ischemic risk, the lower the rate of new P2Y$_{12}$ inhibitor prescription at discharge. Specifically, higher age was the only ischemic risk factor included in the GRACE risk score independently associated with lower prescription of novel P2Y$_{12}$ inhibitors. This is not surprising, given that advanced age is a recognized bleeding risk factor.[19] Our findings concur with those of previous studies reporting underuse of prasugrel or ticagrelor in older patients.[20] Although not included in the CRUSADE risk score, many other bleeding risk scores developed for ACS patients include age to estimate bleeding risk.[21–23] Notably, we found that patients with diabetes were more likely to receive the newer P2Y$_{12}$ agents, even though diabetes tends to be associated with a higher incidence of bleeding events.[24] This prescribing behavior may be explained by the accumulating evidence for a net clinical benefit with new P2Y$_{12}$ inhibitors in diabetic patients following ACS.[25] This enhanced benefit in patients with diabetes may be due to an impaired response to clopidogrel in such patients[26] together with their heightened risk for ischemic events.[27] Moreover, we found

Table 2

Multivariate Logistic Regression Analysis Including Individual Data Elements of GRACE and CRUSADE Risk Scores for Predicting new P2Y$_{12}$ Inhibitors Prescription at Discharge

	Multivariate	
	OR (95%CI)	P
Age (per 10 y)	0.60 (0.56-0.65)	< .001
Diabetes mellitus	1.69 (1.39-2.05)	< .001
Hyperlipidemia	1.43 (1.19-1.72)	< .001
Peripheral artery disease	0.64 (0.44-0.93)	.020
Hematocrit (per 3%)	1.04 (1.02-1.06)	< .001
Elevated cardiac markers	1.60 (1.19-2.15)	.002
ST-segment deviation	1.25 (1.03-1.51)	.023
Percutaneous coronary intervention	4.65 (3.53-6.12)	< .001
Coronary artery bypass grafting	0.23 (0.09-0.59)	.002
In-hospital stent thrombosis	4.13 (1.01-16.8)	.048
Major bleeding (previous and in-hospital)	0.56 (0.33-0.96)	.034
Indication for OAT at discharge	0.18 (0.13-0.26)	< .001

95%CI, 95% confidence interval; ACS acute coronary syndrome; LM, left main artery; LVEF, left ventricular ejection function; OAT, oral anticoagulation therapy; OR, odds ratio.

The multivariate model included individual data elements of GRACE and CRUSADE risk scores, hypertension, hyperlipidemia, current smoking, low weight < 60 kg, previous ACS, LVEF ≤ 50%, LM and/or 3-vessel disease, percutaneous coronary intervention, coronary artery bypass grafting, conservative management, in-hospital stent thrombosis, final ACS diagnosis, indications for OAT at discharge (atrial fibrillation [previous or in-hospital], mechanical valve prosthesis, left ventricular thrombus and other), stroke (previous and in-hospital) and major bleeding (previous and in-hospital).

other predictors of novel P2Y$_{12}$ prescription not included in the aforementioned scores. All of them were predictable, such as previous PCI as well as stent thrombosis (in both cases, more potent P2Y$_{12}$ inhibitor use is now widely accepted) or the concomitant indication of oral anticoagulation therapy at discharge (in this scenario, current guidelines do not recommend the use of new P2Y$_{12}$ inhibitors[9,10]). In the case of dyslipidemia, we did not find an obvious explanation, beyond its role as a cardiovascular risk factor, and it could be a hazardous association.

We propose several reasons to explain the lower prescription of new P2Y$_{12}$ inhibitors among patients with higher GRACE risk scores: *a)* the fear of bleeding complications due to the difficult separation between ischemic and bleeding risk in ACS patients because of the high correlation between the 2 scores.[28] In this line, our group has previously found that GRACE risk score is not inferior to the CRUSADE risk score in predicting in-hospital major bleeding[29]; *b)* the phenomenon known as the risk treatment paradox, which postulates that clinicians are more likely to treat ACS based on guidelines in low risk patients[30]; *c)* the perceived high risk of bleeding in older patients and the strong influence of age in the GRACE risk score; and *d)* the existence of other factors not included in the GRACE risk score that influence clinicians' patterns of antiplatelet selection.

The main implication of our study is that it reinforces the importance of appropriate risk assessment, which is an important issue for therapeutic decision-making. There is strong evidence demonstrating that an aggressive treatment approach has the potential to change the prognosis of patients with ACS, although this effect is frequently risk dependent.[31,32] Currently, it is accepted that high risk ischemic patients with ACS deserve more aggressive management, including more potent antithrombotic treatment and a rapid invasive strategy, while lower risk patients may do well with less potent antithrombotic treatment and a more selective invasive strategy.[9,10] The accumulated evidence supports that more potent antithrombotic drugs and invasive procedures can reduce the number of ischemic events in ACS patients, but these treatments usually increase the risk of bleeding.[33] Therefore, both ischemic and bleeding risk scores have become necessary in ACS risk assessment for the calculation of trade-offs between ischemic risk reduction and spontaneous and treatment-related bleeding hazards. The risk paradox we have identified (with lower risk patients being treated more aggressively than higher risk patients) may be partly driven by perceived bleeding risk. How the risks may be balanced may be facilitated by tools with even better discrimination for bleeding and/or ischemic complications. Future studies investigating the impact on patient outcomes by integrating both risks are needed to resolve this important issue.

Limitations

Our study has the inherent limitations of being a retrospective study that included ACS patients undergoing coronary angiography during the index hospitalization in 2 Spanish tertiary hospitals. Therefore, the applicability of the present results should be viewed with caution in centers with other types of patients and medical facilities, and should be considered as hypothesis-generating. The inclusion of patients with ACS undergoing coronary angiography may cause selection bias and favor a high proportion of patients with ST-segment elevation ACS, who are more frequently managed invasively. Moreover, we had no data on socioeconomic status, education, employment situation, or nationality, which may influence newer antiplatelet prescription. Last, although we analyzed the impact of in-hospital events on treatment at discharge, we have no information on the relationship between these events and previous antithrombotic therapy or its modifications.

CONCLUSIONS

In conclusion, our study results suggest that several factors influence clinicians when prescribing new P2Y$_{12}$ at discharge in ACS patients, with an appropriate underuse of these agents in patients at high bleeding risk. This led to an ischemic risk paradox, however, illustrating the complexity of operationalizing clinical practice guidelines in real-world settings. Understanding new antiplatelet prescribing behavior in such settings is crucial to inform interpretation of new studies exploring the benefits of new antiplatelet drugs in ACS, and to identify opportunities for future efforts to improve prescription quality.

CONFLICTS OF INTEREST

E. Abu-Assi is Associate Editor of *Revista Española de Cardiología.*

WHAT IS KNOWN ABOUT THE TOPIC?

– New P2Y$_{12}$ inhibitors (prasugrel and ticagrelor) are recommended by current ACS guidelines in patients with moderate-to-high ischemic risk, unless they have an increased bleeding risk. These guidelines also recommend the GRACE and CRUSADE risk scores for ischemic and bleeding risk assessment, respectively. However, which risk has the stronger impact or whether other factors influence clinicians' patterns of antiplatelet selection is unknown.

WHAT DOES THIS STUDY ADD?

– In this study, we found an appropriate use of new P2Y$_{12}$ inhibitors among patients at high bleeding risk. However, an ischemic risk paradox was found, with higher use of these agents in patients with lower ischemic risk based on GRACE risk score. Moreover, we found that other factors, beyond these scores, influenced clinicians' prescription patterns. This illustrates the complexity of operationalizing clinical practice guidelines in real-world settings and reinforces the importance of appropriate risk assessment for therapeutic decision-making.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version available at https://doi.org/10.1016/j.rec.2017.10.009.

REFERENCES

1. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators, Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation. *N Engl J Med.* 2001;345:494–502.
2. Chen ZM, Jiang LX, Chen YP, et al. COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet.* 2005;366:1607–1621.
3. Abu-Assi E, López-López A, González-Salvado V, et al. The Risk of Cardiovascular Events After an Acute Coronary Event Remains High, Especially During the First Year, Despite Revascularization. *Rev Esp Cardiol.* 2016;69:11–18.

4. Marrugat J, Elosua R, Grau M, Sayols-Baixeras S, Dégano IR. Prevalence and Prognosis of High-risk Myocardial Infarction Patient Candidates to Extended Antiplatelet Therapy. *Rev Esp Cardiol.* 2016;69:480–487.

5. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *J Am Coll Cardiol.* 2007;49:1505–1516.

6. Ferreiro JL, Angiolillo DJ. Clopidogrel response variability: current status and future directions. *Thromb Haemost.* 2009;102:7–14.

7. Wiviott SD, Braunwald E, McCabe CH, et al. TRITON-TIMI 38 Investigators. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med.* 2007;357:2001–2005.

8. Wallentin L, Becker RC, Budaj A, et al. PLATO Investigators. Freij A, Thorsén M. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med.* 2009;361:1045–1057.

9. Marco R, Carlo P, Jean-Philippe C, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J.* 2016;37:267–315.

10. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J.* 2012;33:2569–2619.

11. Aragam KG, Tamhane UU, Kline-Rogers E, et al. Does simplicity compromise accuracy in ACS risk prediction?. A retrospective analysis of the TIMI and GRACE risk scores. *PLoS One.* 2009;4:e7947.

12. Abu-Assi E, Raposeiras-Roubin S, Lear P, et al. Comparing the predictive validity of three contemporary bleeding risk scores in acute coronary syndrome. *Eur Heart J Acute Cardiovasc Care.* 2012;1:222–231.

13. Abu-Assi E, Raposeiras-Roubín S, García-Acuña JM, González-Juanatey JR. Bleeding risk stratification in an era of aggressive management of acute coronary syndromes. *World J Cardiol.* 2014;6:1140–1148.

14. Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ.* 2006;333: 1091–1094.

15. Subherwal S, Bach RG, Chen AY, 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: 1873–1882.

16. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011;123:2736–2747.

17. Cutlip DE, Windecker S, Mehran R, et al. Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344–2351.

18. Roldán-Rabadán I, Tello-Montoliu A, Marín F. Optimicemos el uso de los nuevos antiagregantes orales, Propuesta de protocolos comunes en el síndrome coronario agudo. *Rev Esp Cardiol Supl.* 2014;14(A):38–44.

19. Moscucci M, Fox KA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J.* 2003;24:1815–1823.

20. Zeymer U, Widimsky P, Danchin N, et al. PIRAEUS group. P2Y12 receptor inhibitors in patients with non-ST-elevation acute coronary syndrome in the real world: use, patient selection, and outcomes from contemporary European registries. *Eur Heart J Cardiovasc Pharmacother.* 2016;2:229–243.

21. Nikolsky E, Mehran R, Dangas G, 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;28:1936–1945.

22. Mehran R, Pocock SJ, Nikolsky E, et al. A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol.* 2010;55:2556–2566.

23. Mathews R, Peterson ED, Chen AY, et al. In-hospital major bleeding during ST-elevation and non-ST-elevation myocardial infarction care: derivation and validation of a model from the ACTION Registry®-GWTG™. *Am J Cardiol.* 2011;107:1136–1143.

24. Manoukian SV. Predictors and impact of bleeding complications in percutaneous coronary intervention, acute coronary syndromes, and ST-segment elevation myocardial infarction. *Am J Cardiol.* 2009;104:9C–15C.

25. Rossington JA, Brown OI, Hoye A. Systematic review and meta-analysis of optimal P2Y12 blockade in dual antiplatelet therapy for patients with diabetes with acute coronary syndrome. *Open Heart.* 2016;3:e000296.

26. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Platelet function profiles in patients with type 2 diabetes and coronary artery disease on combined aspirin and clopidogrel treatment. *Diabetes.* 2005;54:2430–2435.

27. Mangiacapra F, Patti G, Peace A, et al. Comparison of platelet reactivity and periprocedural outcomes in patients with versus without diabetes mellitus and treated with clopidogrel and percutaneous coronary intervention. *Am J Cardiol.* 2010;106:619–623.

28. Ariza-Solé A, Sánchez-Salado JC, Lorente V, et al. Is it possible to separate ischemic and bleeding risk in patients with non-ST segment elevation acute coronary syndromes? *Int J Cardiol.* 2014;171:448–450.

29. Manzano-Fernández S, Sánchez-Martínez M, Flores-Blanco PJ, et al. Comparison of the Global Registry of Acute Coronary Events Risk Score Versus the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse outcomes With Early Implementation of the ACC/AHA Guidelines Risk Score to Predict In-Hospital Mortality and Major Bleeding in Acute Coronary Syndromes. *Am J Cardiol.* 2016;117:1047–1054.

30. Fox KA, Anderson Jr FA, Dabbous OH, et al. GRACE investigators. Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics?. The Global Registry of Acute Coronary Events (GRACE). *Heart.* 2007;93:177–182.

31. De Boer SP, Barnes EH, Westerhout CM, et al. results from the Primary Coronary Angioplasty Trialist versus thrombolysis (PCAT)-2 collaboration. High-risk patients with ST-elevation myocardial infarction derive greatest absolute benefit from primary percutaneous coronary intervention. *Am Heart J.* 2011;161:500–507.

32. Fox KA, Clayton TC, Damman P, et al. FIR Collaboration. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. *J Am Coll Cardiol.* 2010;55:2435–2445.

33. Steg PG, Huber K, Andreotti F, et al. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. *Eur Heart J.* 2011;32:1854–1864.