ORIGINAL ARTICLE

Antiplatelet Therapy in Non-ST-Segment Elevation Acute Coronary Syndromes in Elderly Patients. POPular AGE Hypothesis

Antiagregación en el síndrome coronario agudo sin elevación del segmento ST en adultos mayores. Hipótesis POPular AGE

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ABSTRACT

Background: The POPular AGE study demonstrated that in patients over 70 years of age clopidogrel would be the P2Y12 receptor inhibitor (P2Y12i) of choice due to its association with lower bleeding incidence and no difference in ischemic events.
Objective: We analyzed the safety and efficacy of different treatment regimens with P2Y12i, in patients ≥70 years with non-ST-segment elevation acute coronary syndromes (NSTE-ACS) to test the "POPular AGE" hypothesis in the real world.
Methods: This subanalysis of the prospective BUENOS AIRES I registry analyzed data corresponding to 1100 patients from 21 medical centers in Buenos Aires, Argentina, followed-up for 15 months. We considered the subgroup of patients ≥70 years, stratified according to the P2Y12i indicated at discharge.
Results: This subgroup had a high burden of comorbidities, with 85.1% hypertension, 30.3% diabetes mellitus, and 43.2% chronic kidney disease. Patients treated with ticagrelor/prasugrel (n=54) presented with higher prevalence of active smoking, less atrial fibrillation and lower CRUSADE score, with no differences in the GRACE score, compared whit those treated with clopidogrel (n=286). At the 15-month follow-up, no significant differences were observed in the BARC ≥2 bleeding rate, with more events in the clopidogrel group, although without statistical significance, (25.4% vs. 18.2%; p=0.327) and a benefit in the incidence of major adverse cardiovascular events (MACE) in the ticagrelor/prasugrel treatment group (18.6% vs 36.3%, p= 0.023).
Conclusions: In adequately selected patients with NSTE-ACS ≥70 years, treatment with ticagrelor/prasugrel could be a safe and effective strategy.

Key words: Thienopyridine - Acute coronary syndrome - Elderly

RESUMEN

Introducción: El estudio POPular AGE demostró que, en pacientes mayores de 70 años, el clopidogrel sería el inhibidor del receptor P2Y12 (iP2Y12) de elección por su asociación con menor incidencia de sangrado, sin diferencia en eventos isquémicos.
Objetivos: Analizar la seguridad y eficacia de los diferentes esquemas de tratamiento con iP2Y12 en mayores de 70 años con síndrome coronario agudo sin elevación del segmento ST (SCASEST), a fin de contrastar la hipótesis "POPular AGE" en el mundo real.
Material y métodos: Para el presente subanálisis del registro prospectivo BUENOS AIRES I, se analizaron datos correspondientes a 1100 pacientes de 21 centros médicos de Buenos Aires, Argentina, con seguimiento a 15 meses. Consideramos al subgrupo de pacientes mayores de 70 años, estratificados de acuerdo al iP2Y12 indicado al alta sanatorial.
Resultados: Observamos gran carga de comorbilidades, con un 85,1% de hipertensión, 30,3% de diabetes mellitus y 43,2% de enfermedad renal crónica. Los pacientes tratados con ticagrelor/prasugrel (n = 54) presentaron mayor prevalencia de tabaquismo activo, menor fibrilación auricular y menor puntaje de score CRUSADE, sin diferencias en el puntaje de score GRACE, en relación a los tratados con clopidogrel (n = 286). A 15 meses de seguimiento, en la tasa, con más eventos de sangrado BARC ≥ 2 en el grupo clopidogrel (25,4% vs. 18,2%) aunque sin diferencias significativas (p = 0,327), y beneficio en la incidencia de eventos adversos cardíacos mayores (MACE) en el grupo de tratamiento con ticagrelor/prasugrel (18,6% vs 36,3%, p= 0,023).
Conclusiones: En pacientes con SCASEST mayores de 70 años, adecuadamente seleccionados, el tratamiento con ticagrelor/prasugrel podría ser una estrategia segura y efectiva.

Palabras clave: Tienopiridina - Síndrome coronario agudo - Ancianos

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On behalf of the BUENOS AIRES I investigators (See list)

INTRODUCTION

Increase in life expectancy has faced medical care with a growing number of elderly patients with cardiovascular disease, many times manifested as acute coronary syndrome (ACS). The management of this subgroup of patients requires a delicate balance at the time of diagnostic and therapeutic decision making, which include studies to be performed, the consideration of comorbidities and frailty, choice of medications, selection of the optimal revascularization strategy and the accurate ischemic-hemorrhagic risk assessment of each individual patient by the treating team.

Currently, clinical management guidelines recommend antiplatelet therapy with more potent P2Y12 receptor inhibitors (P2Y12i), as ticagrelor or prasugrel, since they present a net clinical benefit compared with clopidogrel in patients coursing a non-ST-segment elevation acute coronary syndrome (NSTE-ACS). (1) The POPular AGE study showed that in patients ≥70 years, clopidogrel would be the P2Y12i of choice due to its association with less hemorrhagic events, with no significant differences in terms of ischemic events. (2)

The aim of the present analysis was to analyze the efficacy and safety of different antiplatelet regimens in patients ≥70 years coursing a NSTE-ACS, using the population corresponding to the BUENOS AIRES I registry, (3) to test the POPular AGE hypothesis in a representative local population.

METHODS

A post hoc sub-analysis of the prospective BUENOS AIRES I registry was carried out to describe the treatment of NSTE-ACS patients from high complexity centers of the Autonomous City of Buenos Aires (CABA) and the Buenos Aires Province (PBA), and to analyze the clinical in-hospital an outpatient evolution. The inclusion criteria of the registry were age ≥18 years and presenting with primary NSTE-ACS, and exclusion criteria was inability to comply with the prespecified follow-up at 6 and 15 months since the index coronary event. The present analysis considered the subgroup of patients ≥70 years, stratified into "clopidogrel" and "ticagrelor/prasugrel" groups according to the P2Y12i treatment indicated at discharge. For more information, it is recommended to read the BUENOS AIRES I registry published in this Journal. (3) The study included 21 centers from CABA and PBA participating in the BUENOS AIRES I registry, which were required to have a coronary care unit, 24-hour interventional cardiology, cardiac surgery and affiliation to the Argentine Society of Cardiology (SAC). Follow-up was conducted at 6 and 15 months since hospital discharge from the index coronary event. Data were obtained from the clinical records of the BUENOS AIRES I registry participating centers, complemented with phone calls to patients.

Event definition

- Non-ST-segment elevation acute myocardial infarction (NSTEMI): defined according to the Fourth Universal Definition of Myocardial Infarction. (1)
- Unstable angina (UA)
- ACS: composed of NSTEMI and UA
- Stroke: ischemic or hemorrhagic
- Transient ischemic attack (TIA)
- Cardiovascular (CV) mortality: death due to acute myocardial infarction (AMI), stroke, ventricular arrhythmia or unexplained sudden death
- All-cause death
- Major adverse cardiovascular events (MACE): consisting of CV mortality, ACS and stroke/TIA
- Bleeding: according to the Bleeding Association Research Consortium (BARC) classification.

Ethical considerations

Prior to the study, all participants were requested to sign a written informed consent, clearly stating the purpose of the study and data confidentiality, as well as the mechanisms used to safeguard the identity of patients. They were explained that their participation was voluntary and that the patient could refuse to participate without any consequences or differences in his/her medical care, as well as the right to withdraw from the study if he/she so wished. During the evaluation process for inclusion in the study, the investigator verbally explained to the patient the information contained in the informed consent, and answered all the participant questions regarding the study. The consent was submitted for approval by the Ethics Committees of each participating center, under the regulations of the Central Ethics Committee. The study was carried out in compliance with the National Personal Protection Act N° 25 326, so patient identity and all his/her data will remain anonymous, only with access to the investigators and members of the Teaching and Research and Ethics in Research Committee, if so required. The study was conducted according to national ethical regulations (Law 3301, the National Law on Clinical Research in Human Beings, the Declaration of Helsinki, and others).

Statistical analysis

IBM SPSS 25.0 software (for Mac iOS) was used for the statistical analysis. Continuous variables were expressed as mean and standard deviation, or median and interquartile range, according to their distribution characteristics. The Kolmogorov-Smirnov or Shapiro-Wilk tests were used for the analysis of normality, as appropriate. Categorical variables were analyzed with the chi-square test or Fisher's test, and numerical variables using Student's t test or the U Mann-Whitney test, according to their distribution. A multivariate analysis was performed to identify predictive covariates of clinical events of interest. Event-free survival was analyzed with the Log-Rank test, expressed according to the Kaplan-Meier estimator. A type I error below 5% (two-tailed $p < 0.05$) was considered statistically significant.

RESULTS

The BUENOS AIRES I registry included a total of 1100 patients with NSTE-ACS. Mean age of the population was 65.4±11.47 years, and 72.2 % of patients were men. Among the total NSTE-ACS analyzed, 62.6% were classified as non-ST-segment elevation acute myocardial infarction (NSTEMI), and 37.4% as unstable angina (UA). On hospital admission, the mean GRACE score of the total cohort was 133.8±52.09 points, and the mean CRUSADE score 24.31±13.99 points.

Patients ≥70 years comprised 36.5% of the population, with 70.9% men, 85.1% with hypertension, 30.3% with diabetes and 43.2% with kidney failure. At discharge, 72.1% had diagnosis of NSTEMI and the average GRACE score was 161 (Table 1).

Among the total number of patients ≥70 years included in the registry, 84.5% received P2Y12i at discharge, 84% clopidogrel and the rest ticagrelor/prasugrel (92% ticagrelor). There was a higher percentage of men among those receiving ticagrelor/prasugrel, as well as of smoking. The prevalence of atrial fibrillation (AF) was lower in the ticagrelor/prasugrel group, as well as the CRUSADE score, but without differences in the GRACE score.

Procedures performed during hospitalization showed that the ticagrelor/prasugrel group had a higher rate of use of radial access and number of treated vessels. This group received in greater proportion the P2Y12i in the hemodynamics lab. (Table 2)

At the 15-month follow-up, no significant differences were observed in the Bleeding Academic Research Consortium (BARC) rate ≥2, with a greater number of events in the clopidogrel group (25.4% vs. 18.2%; p=0.327), and a lower rate of major adverse cardiovascular events (MACE) in the group treated with ticagrelor/prasugrel (18.6% vs. 36.3%, p=0.023) (Table 3, Figures 1 and 2).

DISCUSSION

Elderly patients comprise a rapidly growing subgroup within ACS, in which NSTE-ACS are the most frequent form of presentation. In our real-life registry, the percentage of patients ≥70 years, (36%), is significant and comparable with the 31.6% of the GRACE registry (4), the 39.9% of the CRUSADE registry (5) or the 38.3% of the North American NRMI registry (6). This contrasts with patients included in randomized studies, in which this percentage does not exceed 20%. The differences probably imply that elderly patients included in randomized studies are systematically "healthier" than those in real life, with lower rates of traditional cardiovascular risk factors, less comorbidities and less hemodynamic and renal deterioration. Our work shows rates of kidney failure, diabetes, and atrial fibrillation similar to those of populations in international registries, with a significant rate of comorbidity.

One of the problems of elderly patients with NSTE-ACS lies in their particularly higher risk of recurrent ischemic episodes, but also of hemorrhagic complications with clinical impact. The TRILOGY ACS study, for example, showed a greater risk of ischemic episodes (HR 2.65, 95% CI 2.37-2.97) and major bleeding episodes (HR 3.33, 95% CI 1.89-5.85) in elderly compared with non-elderly patients (7). Choosing the optimal antiplatelet strategy for the elderly patient with NSTE-ACS may therefore pose a dilemma in daily practice. Should dual antiplatelet therapy in an

Table 1. Baseline characteristics.

Variable	Total (n=1100)	≥70 years (n = 402)			
		Total (n = 402)	Clopidogrel (n = 286)	Ticagrelor/Prasugrel (n = 54)	p§
Male gender – n (%)	849 (77.2)	285 (70.9)	**201 (70.3)**	**46 (85.2)**	**0.024**
Hypertension – n (%)	821 (74.6)	342 (85.1)	244 (85.3)	47 (87.0)	0.741
Diabetes mellitus – n (%)	304 (27.6)	122 (30.3)	89 (31.1)	13 (24.1)	0.300
Smoking - n (%)	240 (21.8)	28 (7)	**17 (5.9)**	**8 (14.8)**	**0.022**
Dyslipidemia - n (%)	661 (60.1)	255 (63.4)	178 (62.2)	38 (70.4)	0.255
CKD - n/tot (%)	223 (21.0)	166/384 (43.2)	119/270 (44.1)	21/53 (39.6)	0.550
Cardiovascular history					
AMI - n (%)	347 (31.5)	127 (31.6)	100 (35.0)	14 (25.9)	0.197
PCI - n (%)	361 (32.8)	152 (37.8)	114 (39.9)	23 (42.6)	0.707
CABG- n (%)	121 (11.0)	68 (16.9)	54 (18.9)	10 (18.5)	0.950
Stroke/TIA - n (%)	63 (5.7)	31 (7.7)	25 (8.7)	2 (3.7)	0.209
PVD - n (%)	70 (6.4)	44 (10.9)	36 (12.6)	3 (5.6)	0.137
COPD - n (%)	43 (3.9)	15 (3.7)	11 (3.8)	2 (3.7)	0.960
AF - n (%)	75 (6.8)	55 (13.7)	**46 (16.1)**	**1 (1.9)**	**0.005**
Index cardiovascular event					
NSTEMI - n (%)	689 (62.6)	290 (72.1)	213 (74.5)	46 (85.2)	0.090
UA - n (%)	411 (37.4)	112 (27.9)	73 (25.5)	8 (14.8)	0.090
GRACE - m±SD	133.83±52.08	160.94±49.40	164.66±49.30	162.26±42.35	0.410
CRUSADE - m±SD	24.31±13.98	32.78±12.88	**33.57±12.83**	**27.48±10.74**	**0.001**

§ p value for the difference between clopidogrel vs. ticagrelor/prasugrel

Abbreviations: m: mean; SD: Standard deviation; CKD: Chronic kidney disease (creatinine clearance <60ml/min/m2); AMI: acute myocardial infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft surgery; TIA: Transient ischemic attack; PVD: Peripheral vascular disease; COPD: Chronic obstructive pulmonary disease; AF: atrial fibrillation; NSTEMI: Non-ST-segment elevation acute myocardial infarction; UA: Unstable angina

Variables	Clopidogrel (n=286)	Ticagrelor/Prasugrel (n=54)	p
CCA - n(%)	269 (94.1)	53 (98.1)	0.218
Radial access - n(%)	**177/269 (65.8)**	**45/53 (84.9)**	**0.002**
PCI - m(%)	**194/269 (72.1)**	**48/53 (90.5)**	**0.002**
DES - n(%)	155/194 (79.9)	38/48 (79.2)	1.000
Number of Vessels -n/tot(%)			
1 vessel	**115/245 (46.9)**	**27/47 (57.4)**	**0.011**
2 vessels	**46/245 (18.7)**	**11/47 (23.4)**	**0.011**
≥3 vessels	**9/245 (3.7)**	**4/47 (8.5)**	**0.011**
IIbIIIai - n(%)	1/194 (0.5)	1/48 (2.1)	0.186
Admission-CCA – h, med(IQR)	**20 (7-48)**	**11 (2.5-24)**	**0.002**
Admission-PCI – h, med(IQR)	**21 (8.75-60)**	**12 (3.5-24)**	**0.001**
Admission-P2Y12i – h, med(IQR)	**2 (0-8)**	**4 (1-18)**	**0.010**
P2Y12i-CCA- h, med(IQR)	**11 (0-24)**	0 (0-7)	**0.001**
CABG - n(%)	26/286 (9.1)	3/54 (5.6)	0.394
MT - n(%)	**67/286 (23.4)**	**3/54 (5.6)**	**0.003**

Abbreviations: med: Median; IQR: Interquartile range; h: hours; CCA: Cine coronary angiography; PCI: Percutaneous coronary intervention; DES: Drug-eluting stent; IIbIIIai: Glycoprotein IIbIIIa inhibitor; P2Y12i: P2Y12 receptor inhibitor; CABG: Coronary artery bypass graft surgery; MT: Medical treatment

Table 2. Treatment according to group.

Variables	Clopidogrel (n=286)	Ticagrelor/Prasugrel (n=54)	p
MACE n/tot (%)	**273/201 (36.3)**	**8/43 (18.6)**	**0.023**
Death n/tot (%)	31/189 (16.4)	3/43 (7.0)	0.115
CV n/tot (%)	18/187 (9.6)	2/43 (4.7)	0.297
ACS n/tot (%)	57/176 (32.4)	8/42 (19.0)	0.090
PCI	23/162 (14.2)	3/40 (7.5)	0.257
CABG	10/157 (6.4)	2/41 (4.9)	0.722
AMI n/tot (%)	35/171 (20.5)	6/42 (14.3)	0.363
Stroke/TIA n/tot (%)	3/157 (1.9)	1/40 (2.5)	0.814
CHF n/tot (%)	50/178 (28.1)	7/43 (16.3)	0.112
BARC bleeding n/tot (%)	49/193 (25.4)	8/44 (18.2)	0.313

Abbreviations: MACE: Major adverse cardiovascular event; CV: Cardiovascular; ACS: Acute coronary syndrome; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass graft surgery; AMI: Acute myocardial infarction; TIA: Transient ischemic attack; CHF: Congestive heart failure; BARC: Bleeding Academic Research Consortium.

Table 3. Events at 15 months according to treatment group

older patient include clopidogrel, a less potent P2Y12i, with minimization of hemorrhagic risk, or should a more potent P2Y12i such as ticagrelor or prasugrel be used, to avoid recurrent ischemic events? In the primary outcome of the POPular AGE study, any bleeding requiring medical intervention was significantly lower in the clopidogrel group [88/500 patients (18%)], than in the ticagrelor group [118/502 patients (24%)], with HR 0.71, 95% CI 0.54–0.94; p=0.02. The reduced hemorrhagic risk with clopidogrel was not only due to a fewer number of minor hemorrhagic episodes, but also to a lower risk of major bleeding. The POPular AGE registry was designed with the primary objective of demonstrating a reduction in bleeding events with clopidogrel, and not to find differences in ischemic events, which were not different a priori. In the PLATO trial, patients ≥75 years (2878) had fewer ischemic events with ticagrelor than with clopidogrel, with no enhanced risk of bleeding (8). No increase was observed in overall major bleeding defined by the study with ticagrelor vs. clopidogrel in patients ≥75 years (HR 1.02; 95% CI: 0.82-1.27) or patients <75 years (HR 1.04, 95% CI: 0.94-1.15). However, in a subanalysis of the PLATO trial, only with NSTE-ACS patients, ticagrelor improved outcomes in younger patients but not in those ≥65 years (p for interaction <0.01). In the TRITON study, prasugrel reduced the risk of cardiovascular mortality, infarction, or stroke in the

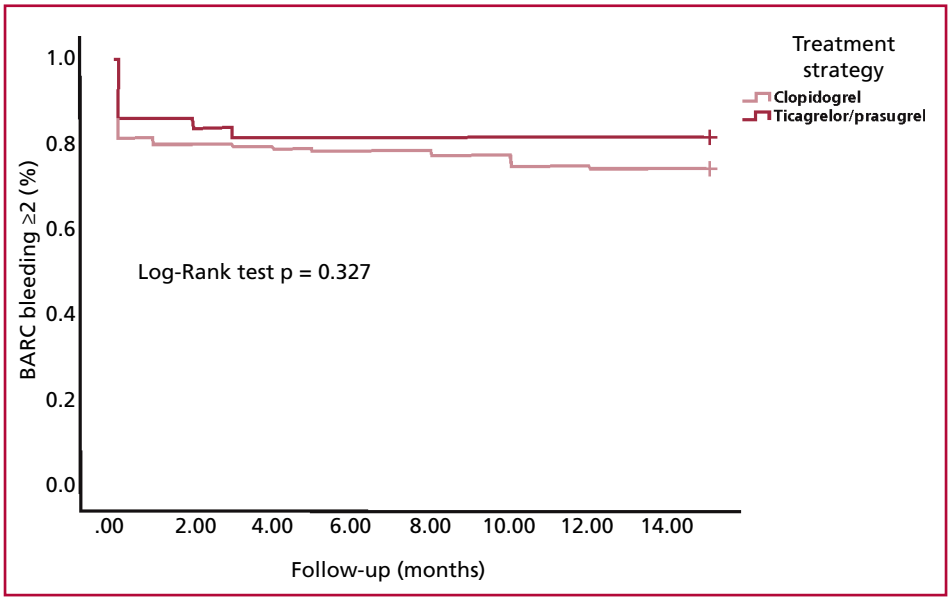

Fig. 1. Freedom from BARC bleeding events ≥2 curve at 15 month-follow-up, according to the P2Y12 inhibitor used

BARC: Bleeding Academic Research Consortium

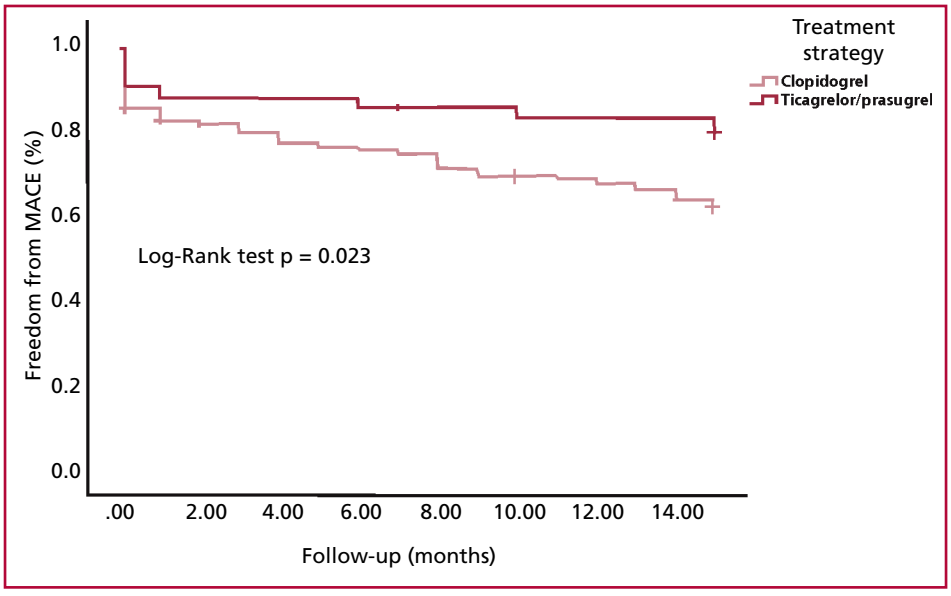

Fig. 2. Freedom from MACE curve at 15 month-follow-up, according to the P2Y12 inhibitor used

MACE: Major adverse cardiac event

general population; however, bleeding not related to coronary surgery was higher. A post hoc analysis identified patients ≥75 years as the group that is affected by increased bleeding and, hence, full dose prasugrel is not recommended in the context of NSTE-ACS. (9).

The POPular AGE study had some peculiarities that are worth highlighting, compared with our registry. First, early discontinuation or change in the P2Y12i occurred in both treatment groups, but was greater with ticagrelor (47% vs. 22%) and higher than in the double-blind PLATO trial. In our study, the group that received ticagrelor/prasugrel had 95% adherence at 12 months.

Secondly, in the POPular AGE study, radial access was used in 75% of patients, compared with almost 85% in our registry. Multiple studies have shown a reduction in hemorrhagic events when this access is used instead of the femoral one. The RIVAL study demonstrated that the elderly benefit much more from radial access due to a greater reduction in access site complications (10).

Thirdly, in in the POPular AGE study, most patients received pretreatment with ticagrelor, compared with a minority in our registry. Pretreatment with potent antiplatelet agents appears to increase hemorrhagic events with a marginal ischemic benefit in the subgroup of patients at high ischemic risk.

We understand that beyond the limitations of our registry, the results may indicate that when well selected, older patients may benefit from treatment with potent P2Y12i. It is possible that selecting patients without high hemorrhagic risk, with good ther-

apeutic adherence and avoiding pretreatment, are adequate tools to indicate potent antiplatelet agents. In turn, the recent TWILIGHT or TICO studies showed that ticagrelor could be used safely in monotherapy after a period of 3 months of association with aspirin, and that this fact would reduce hemorrhagic events while maintaining anti-ischemic protection (11,12). De-escalation to clopidogrel after 1 or 3 months of treatment could be another alternative according to the results of the TOPIC and TROPICAL-ACS studies (13,14). Both monotherapy and de-escalation appear to be attractive strategies for elderly patients, providing anti-ischemic protection benefit in the initial period of increased thrombotic risk and reducing hemorrhagic risk during follow-up.

Limitations

It is important to highlight the observational nature of this registry, which does not present the methodological design required to obtain decisive conclusions in relation to the proposed pharmacological strategies; however, we find it useful to have a real-life perspective with patients who are "selected" for one treatment or another.

CONCLUSIONS

This sub-analysis of the BUENOS AIRES I registry showed that in properly selected patients with NSTE-ACS ≥70 years, treatment with ticagrelor/prasugrel could be a safe and effective strategy, with no significant differences with clopidogrel in the rate of bleeding at 15 months.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

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ANNEX:

ANNEX 1

List of participating centers and researchers in alphabetical order:

CEMIC: Mirza Rivero.
Clínica Olivos: Sebastián Nani y Gonzalo Pérez.
Clínica San Lucas: Martín Odone.
Clínica Zavala: Claudia Bruno.
Corporación San Martín: Fernando Guardiani.
Fundación Favaloro: Ernesto Duronto.
Hospital Argerich: Maximiliano Mascarello.
Hospital Austral: Jorge Bilbao, José Bonorino y Nicolás Torres.
Hospital de la Universidad Abierta Interamericana: Ricardo Levín e Ignacio Vaca.
Hospital Durán: Leandro Parrilla.
Hospital Fernández: Andrea Tufo Pereyra.
Hospital Naval: Sofía Binder.
Hospital Posadas: Natalia Carli.
Hospital Santojanni: Carlos Ruano.
ICBA: Juan P Costabel, Cristian M Garmendia, Rosina Arbucci y Roberto Campos.
Sanatorio Anchorena sede San Martín: Leandro Rodriguez.
Sanatorio Anchorena sede Recoleta: Paz Domínguez y Nicolás Lalor.
Sanatorio Finochietto: Miguel Gonzalez y Guido Damianich.
Sanatorio Güemes: Ezequiel José Zaidel e Iván Gómez.
Sanatorio la Trinidad Palermo: Andrea Tufo Pereyra.
Sanatorio la Trinidad Quilmes: Christian Musante.