ORIGINAL ARTICLE

Antiplatelet Strategies in Non-ST-Segment Elevation Acute Coronary Syndromes

Estrategias de antiagregación en síndromes coronarios agudos sin elevación del segmento ST

CRISTIAN M. GARMENDIA, MIRZA RIVERO, ERNESTO DURONTO, JAVIER N. GUETTA, SEBASTIÁN NANI, CARLOS RUANO, ANDREA TUFO PEREYRA, MARÍA PAZ DOMÍNGUEZ, NATALIA CARLI, JUAN P. COSTABEL

ABSTRACT

Background: There is limited real life information on treatment strategies with P2Y12 receptor inhibitors (P2Y12i) in non-ST-segment elevation acute coronary syndromes (NSTEACS).
Objectives: The aim of this study was to determine the incidence of major adverse cardiac events (MACE) and BARC bleeding ≥2, according to the treatment strategy with P2Y12i at 6 months.
Methods: The study used the pre-specified subanalysis of the BUENOS AIRES I registry (n=1100). The cohort was stratified according to P2Y12i "pretreatment" (before knowing the coronary anatomy), or "cath lab treatment" (after knowing the coronary anatomy), and the incidence of clinical events was analyzed according to pretreatment or cath lab treatment with clopidogrel/ticagrelor.
Results: Mean age was 65.4±11.5 years and 77.2% were male patients. In 79.72% of cases patients received P2Y12i, 75% as pretreatment and 25% as cath lab treatment. Pretreatment patients were younger and with greater prevalence of acute myocardial infarction (AMI) compared with the cath lab treatment subgroup. At 6 months, there were no significant differences in the incidence of MACE (16.4% vs. 14.4%; p=0.508), or BARC bleeding ≥2 (14.7% vs. 11.1%; p=0.205), between the different times of P2Y12i administration. Treatment with ticagrelor presented reduced MACE compared with clopidogrel (p=0.044), with no difference in bleeding. No MACE differences were observed between pretreatment or in cath lab treatment with ticagrelor (p=0.893).
Conclusions: The subgroup of patients selected to receive P2Y12i pretreatment did not present differences in MACE or bleeding relative to those treated in cath lab. Patients selected for ticagrelor treatment in cath lab presented a beneficial balance between ischemic and hemorrhagic events.

Key words: Acute coronary syndrome - Non-ST elevation myocardial infarction - Platelet aggregation inhibitors / therapeutic use - Ticagrelor - Clopidogrel.

RESUMEN

Introducción: Existe información limitada sobre estrategias de tratamiento con inhibidores del receptor P2Y12 (iP2Y12) en síndromes coronarios agudos sin elevación del segmento ST (SCASEST) en la vida real.
Objetivos: Determinar la incidencia de eventos cardíacos adversos mayores (MACE)y sangrado BARC ≥ 2, según la estrategia de tratamiento con iP2Y12 a 6 meses.
Material y métodos: Subanálisis preespecificado del registro BUENOS AIRES I (n = 1100). Se estratificó la cohorte según "pretratamiento" con iP2Y12 (antes de conocer la anatomía coronaria), o "tratamiento en sala" (luego de conocer la anatomía coronaria) y se analizó la incidencia de eventos clínicos, según: pretratamiento con clopidogrel/ticagrelor, tratamiento en sala con clopidogrel/ticagrelor.
Resultados: La edad media fue 65,4 ± 11,5 años, con 77,2% de sexo masculino. El 79,72% recibió iP2Y12, el 75% como pretratamiento y 25% como tratamiento en sala. Los pacientes con pretratamiento fueron más jóvenes y con más infarto agudo de miocardio (IAM), en comparación con el subgrupo de tratamiento en sala. A los 6 meses, no hubo diferencias significativas en la incidencia de MACE (16,4% vs. 14,4%; p = 0,508), o sangrado BARC ≥ 2 (14,7% vs. 11,1%; p = 0,205), entre los distintos momentos de administración del iP2Y12. El tratamiento con ticagrelor presentó menos MACE en comparación con el clopidogrel (p = 0,044), sin diferencias en sangrados. No se observaron diferencias en MACE entre ticagrelor en pretratamiento o tratamiento en sala (p = 0,893).
Conclusiones: El subgrupo de pacientes seleccionados para recibir pretratamiento con iP2Y12 no presentó diferencias en MACE ni sangrado en relación con los tratados en sala. Los pacientes seleccionados para su tratamiento con ticagrelor en sala presentaron un balance beneficioso entre eventos isquémicos y hemorrágicos.

Palabras clave: Síndrome coronario agudo - Infarto del miocardio sin elevación de ST - Inhibidores de agregación plaquetaria/uso terapéutico - Ticagrelor - Clopidogrel.

REV ARGENT CARDIOL 2021;89:209-216. http://dx.doi.org/10.7775/rac.v89.i3.20191

Received: 12/14/2020 – *Accepted:* 03/08/2021

Address for reprints: Dr. Juan Pablo Costabel - Av. Del Libertador 6302 - 1428- CABA, Argentina - Tel: +54 11 4787-7500 - E-mail: jpcostabel@icba.com.ar

On behalf of the Buenos Aires I researchers. (See list)

Abbreviations

ACS	Acute coronary syndrome	**CV**	Cardiovascular
AMI	Acute myocardial infarction	**MACE**	Major adverse cardiac events
UA	Unstable angina	**NSTEACS**	Non-ST segment elevation acute coronary syndrome
BARC	Bleeding Academic Research Consortium	**NSTEMI**	Non-ST segment elevation acute myocardial infarction
CA	Coronary angiography	**TCA**	Transluminal coronary angioplasty
CABG	Coronary artery bypass grafting	**TIA**	Transient ischemic attack
CKD	Chronic kidney disease		

INTRODUCTION

Non-ST-segment elevation acute coronary syndromes (NSTEACS) represent a wide variety of conditions from a diagnostic, treatment, and prognostic point of view, and share common pathophysiological mechanisms. (1)

In the last decades, a variety of clinical trials evaluating new coronary revascularization strategies and antiplatelet treatments with P2Y12 receptor inhibitors (P2Y12i) have been developed, thereby achieving a reduction in NSTEACS morbidity and mortality. (2-4) However, there is currently limited information about how these therapeutic strategies are incorporated into clinical practice in our population. (5, 6)

The recently published BUENOS AIRES I registry presented updated information on the demographic characteristics, therapeutic strategies for coronary revascularization and prescribed medical treatment of patients with NSTEACS in our setting. (7)

The aim of this pre-specified subanalysis of the BUENOS AIRES I registry was to determine the clinical impact of different antiplatelet strategies in terms of ischemic and hemorrhagic events, 6 months after the index ACS.

OBJECTIVES

Primary objective

To determine the incidence of major adverse cardiac events (MACE) in patients with NSTEACS, 6 months after the index coronary event, according to the prescribed antiplatelet strategy.

Co-primary objective

To determine the incidence of BARC bleeding ≥2 in patients with NSTEACS, 6 months after the index coronary event, according to the prescribed antiplatelet strategy.

METHODS

This is a pre-specified subanalysis of the prospective BUENOS AIRES I registry, describing the treatment strategy of patients with NSTEACS in high complexity medical centers of the Autonomous City of Buenos Aires (CABA) and the Province of Buenos Aires (PBA). For more information, please refer to the BUENOS AIRES I registry. (7)

Definition of events and antiplatelet strategies analyzed
The following antiplatelet strategies were analyzed:

- Pretreatment: P2Y12i pretreatment was considered when it was administered before knowing the coronary anatomy by coronary angiography (CA).
- Cath lab treatment: In cath lab P2Y12i treatment was considered when it was administered after knowing the coronary anatomy, both at the time of CA and during the course of hospitalization.
- A total of 4 antiplatelet P2Y12i strategies was analyzed, excluding prasugrel pretreatment, since it was part of the hospitalized patient's previous medication, and in cath lab treatment due to the low number of reported cases (2.6%, n = 29):
  1. Pretreatment with clopidogrel.
  2. Pretreatment with ticagrelor.
  3. Cath lab treatment with clopidogrel.
  4. Cath lab treatment with ticagrelor.

The following clinical events were analyzed:

- Non-ST-segment elevation acute myocardial infarction (NSTEMI): defined according to the Fourth Universal Definition of Infarction. (1)
- Unstable angina (UA).
- ACS: composed of NSTEMI and UA.
- Stroke: ischemic and hemorrhagic.
- Transient ischemic attack (TIA).
- Cardiovascular (CV) death: death due to AMI, stroke, ventricular arrhythmia or sudden death of unknown cause.
- All-cause death.
- MACE: composite of CV death, ACS and stroke/TIA.
- Bleeding: ≥2 according to the Bleeding Academic Research Consortium (BARC) classification.

Medical centers

The centers of CABA and PBA participating in the BUENOS AIRES I registry were required to have a coronary care unit, 24 hour-hemodynamics service, cardiac surgery and affiliation to the Argentine Society of Cardiology.

Follow-up

Patients were followed up for 6 months after index NSTEACS.

Statistical analysis

SPSS 25.0 software (IBM, Armonk, USA) was used for statistical analysis. The Kolmogorov-Smirnov test or the Shapiro-Wilk test was used for the analysis of normality, as appropriate. Quantitative variables were expressed as mean and standard deviation, or median and interquartile range, and were compared using Student's t test or the Mann-Whitney U test, according to their distribution. Categorical variables were expressed as frequency and percentage, and were analyzed using the chi square test or Fisher's exact test. Event-free survival was analyzed with the Kaplan-Meier estimator, expressed by the Log-Rank test. A type I error ≤5% was considered statistically significant (two-tailed $p < 0.05$).

Ethical considerations

All study participants were asked to sign the written informed consent before inclusion. The consent was submitted for approval by the ethics committees of each medical center, which verified that it complied with the regulations of the Central Ethics Committee.

This study was carried out in compliance with the National Law on Protection of Personal Data No. 25,326. Thus, patients' identity and personal data will remain anonymous and only researchers and members of the teaching and research committee and ethics on research committee will have access to these data, if required.

The study was conducted according to national ethical regulations (Law No. 3301, National Law on Clinical Research in Human Beings, Declaration of Helsinki and others).

RESULTS

The BUENOS AIRES I registry included a total of 1100 patients for analysis, with a 6-month follow-up of 88.3% of the initial cohort (n=971). Mean age was 65.4 ±11.5 years, and 77.2% were male patients. Baseline prevalence of hypertension was 74.6%, diabetes mellitus 27.6%, dyslipidemia 60.1%, chronic kidney disease 21.0% and active smoking 21.8%, (Table 1).

On hospital admission, the mean GRACE score was 133.83±52.1, and the mean CRUSADE score 24.31±13.9. Among all NSTEACS events, 62.6% were classified as NSTEMI and 37.4% were UA events (Table 1).

Therapeutic management was through an invasive strategy in 86.7% of the cases, with CA in 91.5% of patients, transluminal coronary angioplasty (TCA) in 62.1%, and coronary artery bypass grafting (CABG) in 14.4%. Median time to CA was 18 h (IQR 7-27.7).
In 79.72% of cases (n=877), P2Y12i treatment was administered during the course of hospitalization, in 75% (n=658) of patients as pretreatment, and in 25% (n=219) as cath lab treatment (Table 1).

Patient characteristics according to the treatment scheme with P2Y12i received

Pretreatment versus cath lab treatment

When comparing patient characteristics according to the time of P2Y12i administration, patients who received P2Y12i pretreatment were younger, predominantly female, and with higher prevalence of hypertension than the subgroup of patients who received P2Y12i treatment in the cath lab. In turn, the prevalence of a history of AMI and TCA was higher in the subgroup of patients who received P2Y12i, compared with the subgroup who received P2Y12i treatment in the cath lab, without statistically significant differences in terms of risk of ischemic (GRACE score) or hemorrhagic (CRUSADE score) events between the groups analyzed, as well as no differences in relation to time to CA performance (Table 1).

Table 1. Baseline characteristics

Variables	Pretreatment (n=658, 75%)					Cath lab treatment (n=219, 25%)				
	Total (n = 1100)	Total (n = 658)	Clopidogrel (n = 555)	Ticagrelor (n = 91)	*p**value	Total (n = 219)	Clopidogrel (n = 112)	Ticagrelor (n = 95)	*p**value	*p*†
Age - years±SD	65.45±11.47	65.45±11.43	**66.37±11.45**	**60.92 ± 9.37**	**<0.001**	67.55±11.41	**71.61±11.51**	**63.69±9.80**	**<0.001**	**0.021**
Male gender - n(%)	849 (77.2)	515 (78.3)	**425 (76.6)**	**79 (86.8)**	**0.029**	187 (85.4)	**88 (78.6)**	**88 (92.6)**	**0.005**	**0.022**
Hypertension - n(%)	821 (74.6)	514 (78.1)	438 (78.9)	68 (74.7)	0.368	154 (70.3)	**87 (77.7)**	**58 (61.1)**	**0.009**	**0.019**
Diabetes mellitus - n(%)	304 (27.6)	199 (30.2)	**181 (32.6)**	**14 (15.4)**	**0.001**	53 (24.2)	**33 (29.5)**	**14 (14.7)**	**0.012**	0.087
Smoking - n(%)	240 (21.8)	149 (22.6)	129 (23.2)	18 (19.8)	0.465	48 (21.9)	21 (18.8)	24 (25.3)	0.258	0.823
Dyslipidemia - n(%)	661 (60.1)	390 (59.3)	330 (59.5)	52 (57.1)	0.677	146 (66.7)	75 (67.0)	63 (66.3)	0.921	0.052
CKD - n/tot(%)	223/1060 (21.0)	132/631 (20.9)	**119/531 (22.4)**	**11/88 (12.5)**	**0.035**	50/211 (23.7)	**35/106 (33.0)**	**15/93 (16.1)**	**0.006**	0.396
Cardiovascular history										
AMI - n(%)	347 (31.5)	256 (38.9)	218 (39.3)	31 (34. 1)	0.344	50 (22.8)	31 (27.7)	18 (18.9)	0.141	**<0.001**
TCA - n(%)	361 (32.8)	263 (40.0)	220 (39.6)	33 (36.3)	0.541	57 (26.0)	34 (30.4)	23 (24.2)	0.324	**<0.001**
CABG - n(%)	121 (11.0)	77 (11.7)	64 (11.5)	13 (14.3)	0.452	27 (12.3)	15 (13.4)	11 (11.6)	0.695	0.804
Stroke /TIA - n(%)	63 (5.7)	41 (6.2)	34 (6.1)	7 (7.7)	0.570	9 (4.1)	7 (6.3)	2 (2.1)	0.145	0.241
PVD - n(%)	70 (6.4)	40 (6.1)	39 (7.0)	1 (1.1)	**0.030**	17 (7.8,)	13 (11.6)	4 (4.2)	0.053	0.381
COPD - n(%)	43 (3.9)	27 (4.1)	21 (3.8)	6 (6.6)	0.214	9 (4.1)	3 (2.7)	5 (5.3)	0.336	0.997
Atrial fibrillation - n(%)	75 (6.8)	45 (6.8)	43 (7.7)	2 (2.2)	0.054	20 (9.1)	**19 (17.0)**	**1 (1.1)**	**<0.001**	0.262
Index cardiovascular event										
NSTEMI - n(%)	689 (62.6)	444 (67.5)	374 (67.4)	63 (69.2)	0.728	143 (65.3)	70 (62.5)	66 (69.5)	0.292	0.552
UA - n(%)	411 (37.4)	214 (32.5)	181 (32.6)	28 (30.8)	0.728	76 (34.7)	42 (37.5)	29 (30.5)	0.292	0.552
GRACE - m ± DE	133.83±52.09	138.81±52.09	139.96±51.93	133.86±51.99	0.281	136.30±50.65	**142.90±55.80**	**130.47±43.68**	**0.041**	0.498
CRUSADE - m±DE	24.31±13.99	24.41±14.17	**25.26±14.45**	**19.78±11.26**	**0.002**	24.05±13.21	**28.76±14.24**	**19.63±10.15**	**<0.001**	0.928

* p value for the difference between clopidogrel vs. ticagrelor.
† p value for the difference between pretreatment vs. cath lab treatment.
SD = Standard deviation; CKD = Chronic kidney disease (creatinine clearance <60 mL/min/m²); AMI = Acute myocardial infarction; TCA = Transluminal coronary angioplasty; CABG = coronary artery bypass grafting; TIA = Transient ischemic attack; PVD = Peripheral vascular disease; COPD = chronic obstructive pulmonary disease; NSTEMI = Non-ST-segment elevation acute myocardial infarction; UA = unstable angina. Patients treated with prasugrel, either in pretreatment or in the cath lab, are not presented in the table due to their small number.

Pretreatment: clopidogrel versus ticagrelor

Within the subgroup of patients that received P2Y12i pretreatment, those pretreated with ticagrelor were younger, predominantly male and had a lower prevalence of diabetes mellitus and chronic kidney disease (CKD), compared with patients pretreated with clopidogrel. No statistically significant differences were found in the prevalence of previous coronary history, or in the GRACE score between the groups analyzed. In turn, patients pretreated with clopidogrel had a higher CRUSADE score compared with those pretreated with ticagrelor (Table 1).

Cath lab treatment: clopidogrel vs. ticagrelor

Within the subgroup of patients who received cath lab P2Y12i treatment, those treated with ticagrelor were younger, with male predominance, lower prevalence of hypertension, diabetes mellitus and CKD, in relation to those treated with clopidogrel, without statistically significant differences. In turn, patients who received cath lab treatment with ticagrelor had lower GRACE and CRUSADE scores compared with those that received clopidogrel (Table 1).

Clinical evolution of patients according to the treatment strategy received

At 6-month follow-up, the overall incidence of MACE was 16.4% in the subgroup of patients with P2Y12i pretreatment, and 14.4% in the subgroup of patients with cath lab P2Y12i treatment, with no significant differences between the groups analyzed (p=0.508) (Table 2).

No statistically significant differences were observed in terms of BARC bleeding ≥2 events between pretreatment or cath lab treatment P2Y12i strategies (14.7% vs. 11.1%; p = 0.205) (Table 2).

Treatment with ticagrelor, regardless of the time of administration (pretreatment or cath lab treatment), demonstrated greater freedom from MACE, in relation to clopidogrel treatment, in its different strategies (pretreatment or cath lab treatment) at 6-month follow-up, with a statistically significant difference between both drugs (Log-Rank p=0.044) (Figure 1).

No differences were observed in terms of MACE between ticagrelor administration in pretreatment and cath lab treatment (Log-Rank p=0.893). (Figure 2)

No statistically significant differences were found in the incidence of BARC ≥2 bleeding events between ticagrelor and clopidogrel (Log-Rank p=0.237) (Figure 3).

DISCUSSION

The BUENOS AIRES I registry is a multicenter registry that offers the possibility of analyzing current real-world data in terms of therapeutic strategies implemented and associated clinical complications in patients with NSTEACS, belonging to high complexity centers in CABA and PBA. At present, the evidence in the medical literature that supports P2Y12i pretreatment in NSTEACS is scarce and, many times, contradictory, in relation to its benefits, in light of the emergence of new therapeutic approaches. Based on the results obtained in the present study, we can infer the following conclusions:

First, the choice of antiplatelet treatment strategy in the sample population of the present registry does not seem to be associated with the ischemic or hemorrhagic risks observed with scores validated for

Table 2. Cardiovascular events at 6 months

Variables	Total (n = 1100)	Pretreatment (n=658, 75%)			p*value	Cath lab treatment (=219, 25%)			p*value	p†
		Total (n = 658)	Clopidogrel (n = 555)	Ticagrelor (n = 91)		Total (n = 219)	Clopidogrel (n = 112)	Ticagrelor (n = 95)		
Follow-up - n/tot(%)	971/1100 (88.3)	572/658 (86.9)	479/555 (86.3)	82/91 (90.1)	0.320	197/219 (90.0)	97/112 (86.6)	88/95 (92.6)	0.161	0.238
Adherence - n/tot(%)	668/873 (76.5)	403/528 (76.3)	**327/440 (74.3)**	**67/77 (87.0)**	**0.016**	139/172 (80.8)	62/81 (76.5)	69/79 (87.3)	0.076	0.221
MACE - n/tot(%)	146/983 (14.9)	95/579 (16.4)	83/485 (17.1)	10/83 (12.0)	0.249	29/201 (14.4)	19/101 (18.8)	10/88 (11.4)	0.156	0.508
Death - n/tot(%)	55/971 (5.7)	29/572 (5.1)	27/479 (5.6)	2/82 (2.4)	0.227	14/197 (7.1)	9/97 (9.3)	5/88 (5.7)	0.356	0.283
CV death - n/tot(%)	34/966 (3.5)	19/570 (3.3)	18/477 (3.8)	1/82 (1.2)	0.238	8/196 (4.1)	3/96 (3.1)	5/88 (5.7)	0.396	0.624
ACS - n/tot(%)	105/963 (10.9)	73/568 (12.9)	65/474 (13.7)	6/83 (7.2)	0.102	19/197 (9.6)	**16/99 (16.2)**	**3/86 (3.5)**	**0.005**	0.233
TCA - n/tot(%)	47/946 (5.0)	32/558 (5.7)	26/465 (5.6)	5/82 (6.1)	0.855	12/191 (6.3)	6/94 (6.4)	5/85 (5.9)	0.889	0.781
CABG - n/tot(%)	9/946 (1.0)	6/558 (1.1)	4/465 (0.9)	2/82 (2.4)	0.206	0/191 (0.0)	0/94 (0.0)	0/85 (0.0)	-	0.15
AMI - n/tot(%)	81/963 (8.4)	55/568 (9.7)	45/474 (9.5)	8/83 (9.6)	0.967	16/197 (8.1)	9/99 (9.1)	7/86 (8.1)	0.818	0.515
STROKE/TIA - n/tot(%)	5/947 (0.5)	2/559 (0.4)	2/466 (0.4)	0/82 (0.0)	0.552	2/191 (1.0)	1/94 (1.1)	1/85 (1.2)	0.943	0.259
CHF	105/960 (10.9)	59/567 (10.4)	55/474 (11.6)	4/82 (4.9)	0.068	19/193 (9.8)	**15/94 (16.0)**	**3/87 (3.4)**	**0.005**	0.824
AF - n/tot(%)	91/955 (9.5)	56/564 (9.9)	52/471 (11.0)	4/82 (4.9)	0.088	12/191 (6.3)	8/94 (8.5)	3/85 (3.5)	0.166	0.128
Bleeding - n/tot(%) ‡	133/979 (13.6)	85/578 (14.7)	72/485 (14.8)	11/82 (13.4)	0.735	22/198 (11.1)	14/98 (14.3)	8/88 (9.1)	0.273	0.205

* P value for the difference between clopidogrel vs. ticagrelor.
† P value for the difference between pretreatment vs. cath lab treatment.
‡ BARC bleeding ≥2
MACE = Major adverse cardiac event; CV = Cardiovascular; ACS = Acute coronary syndrome; TCA = Transluminal coronary angioplasty; CABG = Coronary artery bypass grafting; AMI = Acute myocardial infarction; TIA = Transient ischemic attack; CHF = Congestive heart failure; AF = Atrial fibrillation; BARC = Bleeding Academic Research Consortium.
Patients treated with prasugrel, either in pretreatment or in the cath lab, are not presented in the table due to their small number..

this purpose. When considering the time of P2Y12i administration, two conditions usually influence the decision: the risk of presenting hemorrhagic events and the probability of multi-vessel atherosclerotic coronary artery disease requiring CABG. While in the first situation, P2Y12i pretreatment increases the risk of bleeding due to a longer exposure to antiplatelet therapy, in the second one it could delay the appropriate therapeutic approach. In the present cohort of patients with NSTEACS belonging to our setting, it is possible that other variables, such as access to pharmacological medication, could have played a considerable role at the time of selection. (8)

Second, no differences were observed in terms of patient clinical evolution according to the time of P2Y12i administration. In this context, several studies have explored the benefit of P2Y12i pretreatment, with the disadvantage of presenting a longer time from P2Y12i administration to CA than that reported in patients belonging to the real world. (9, 10) A systematic review and meta-analysis that included studies of patients with NSTEACS (n=32 383) demonstrated that P2Y12i pretreatment was not associated with a decrease in total mortality [OR 0.90 (95% CI 0.71-1.14); p=0.39], but with an associated increase in major bleeding events [OR 1.32 (95% CI 1.16-1.49); p <0.001]. (11) In turn, a subgroup analysis of the ACCOAST study (n=4001) has shown that no net clinical benefit was observed with P2Y12i pretreatment, regardless of the time of administration. This was associated with an increased risk of bleeding events without benefit in terms of ischemic events, even in patients included in the upper quartiles of time from P2Y12i to CA (>12.25 h),

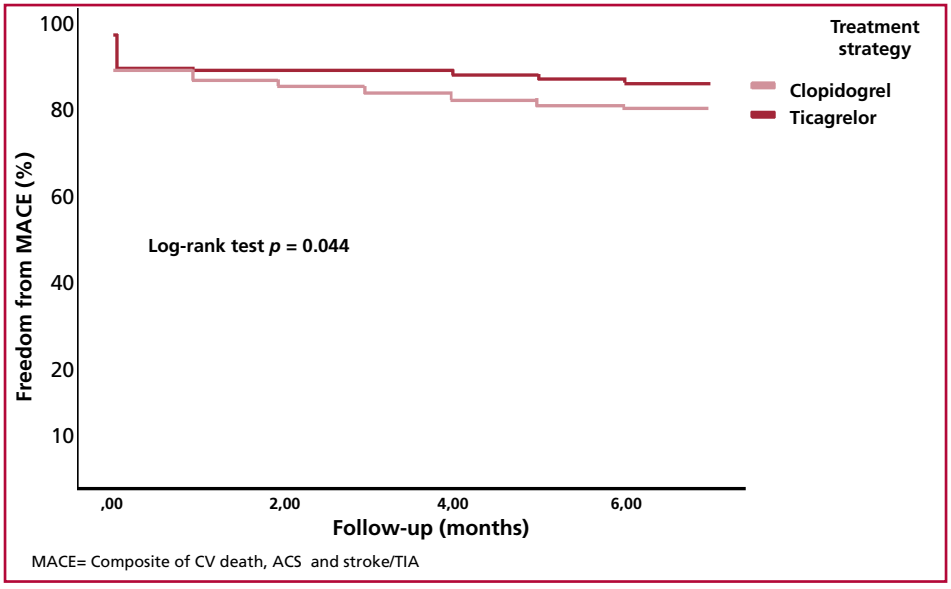

Fig. 1. Freedom from MACE with ticagrelor vs. clopidogrel

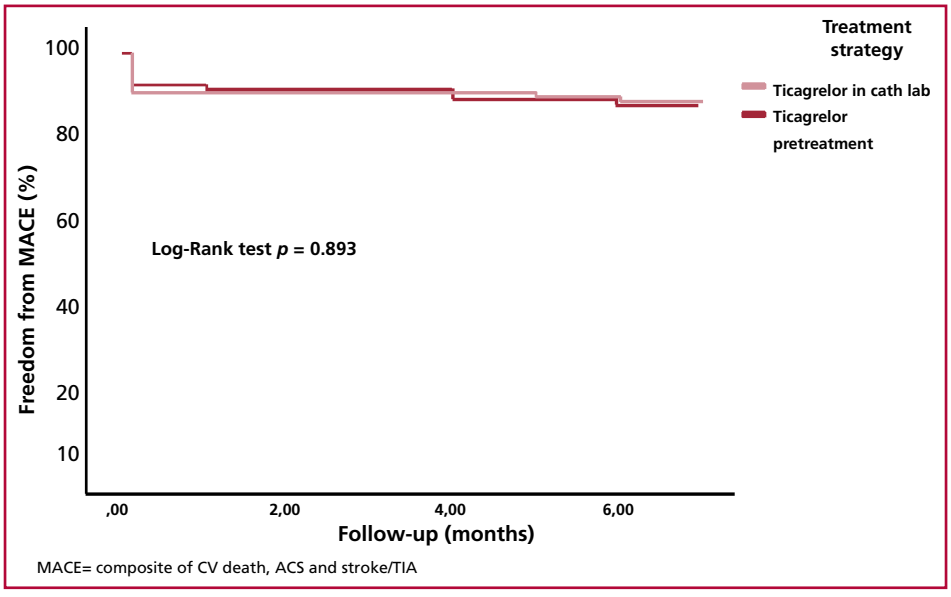

Fig. 2. Freedom from MACE with ticagrelor according to time of administration

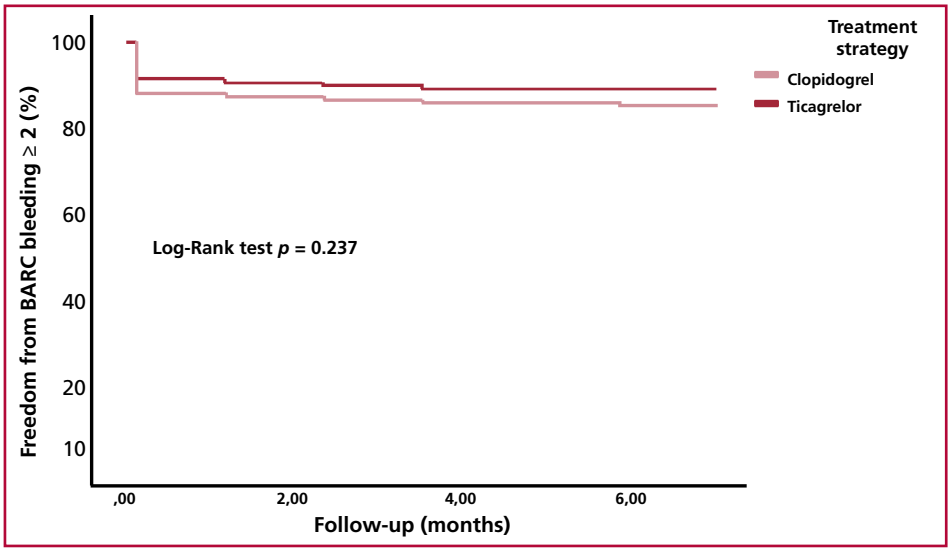

Fig. 3. Freedom from BARC bleeding ≥ 2 with ticagrelor vs. clopidogrel

which coincides with the results obtained. (12) In the present registry, a median time from P2Y12i administration to CA of 18 h was observed (IQR 7-27.7), which would indicate that most of the patients included received P2Y12i pretreatment within a period of 24 h from hospital admission to CA. This is contrary to the current recommendations of ACS clinical management guidelines, which suggest not performing routine P2Y12i pretreatment in patients who will undergo CA within 24 h, and to consider the ischemic and hemorrhagic risk present in each case. (13) In this context, it must be considered that the patients in this cohort were included as of 2017, at a time in which P2Y12i pretreatment was recommended as soon as it was available.

Third, treatment with ticagrelor, regardless its administration time, showed a considerable benefit in terms of adverse clinical events at follow-up in the subgroup of selected patients. This finding coincides with that evidenced in other studies. The PLATO study (n=18 624), which included 42% of NSTEMI patients (n=6792), demonstrated benefit by pretreatment with ticagrelor over clopidogrel in terms of ischemic event reduction, with no differences in major bleeding events between the groups analyzed. (3) According to a post hoc analysis of the PLATO study, the benefit of ticagrelor over clopidogrel remained constant at 7 days, 30 days and 1 year after the index coronary event, regardless of the time from P2Y12i administration to CA, which was defined as "early" (<3 h), or "late" (≥3 h). An increased risk of bleeding was observed with ticagrelor pretreatment in the "late" CA subgroup [HR 1.51 (95% CI 1.12-2.04); interaction p=0.002]. (14) To date, the pretreatment strategy of ticagrelor has not been evaluated in a randomized study compared with cath lab treatment in the context of NSTEACS, whereas in the setting of STEMI (ATLANTIC study, n=1862), pretreatment with ticagrelor has not shown benefits in terms of MACE and bleeding episodes, with a definitive decrease in stent thrombosis at 30-day follow-up (0.2% vs. 1.2%; p=0.02). (15)

Fourth, the advantages that are potentially associated with P2Y12i pretreatment are based on the maximum antiplatelet effect at the time of an eventual TCA with stent implantation, protection against ischemic events during the waiting period before performing the procedure, a lower percentage of associated thrombotic complications, and lower requirement of rescue glycoprotein IIb/IIIa inhibitors. But, on the other hand, P2Y12i pretreatment is associated with an increased risk of bleeding, prolonged hospital length of stay and a potential delay in case of requiring a surgical therapeutic approach. (16) According to the results obtained in the present study, the cath lab treatment strategy with P2Y12i appears to be an interesting option, since it does not translate into an increase in MACE during follow-up and allows knowing the coronary anatomy in order to select the most appropriate therapeutic approach.

Limitations

Since this is a multicenter study, the criteria considered to define the timing of P2Y12i administration may not be uniform. On the other hand, the number of patients did not allow for propensity score matching in order to reduce potential selection biases.

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 consider it vitally important to have a perspective of what happens in real life with patients who are "selected" for one strategy or another.

CONCLUSIONS

In this registry, the subgroup of patients selected to receive P2Y12i pretreatment did not show benefits

in terms of MACE and bleeding events in relation to those treated in the cath lab. On the other hand, the subgroup of patients treated with ticagrelor in the cath lab presented a considerable balance between ischemic and hemorrhagic events.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material)

Funding

The present work did not receive any scholarship or funding.

REFERENCES

1. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth Universal Definition of Myocardial Infarction. Circulation 2018;138:e618-51. https://doi.org/10.1161/CIR.0000000000000617

2. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. 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. https://doi.org/10.1056/NEJMoa010746

3. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57. https://doi.org/10.1056/NEJMoa0904327

4. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15. https://doi.org/10.1056/NEJMoa0706482

5. Aurelio MJ, Arazi HC, Higa C, Gómez Santa María HR, Mauro VM, Fernández H, et al. Infarto agudo de miocardio con supradesnivel persistente del segmento ST. Registro multicéntrico SCAR (síndromes coronarios agudos en Argentina) de la Sociedad Argentina de Cardiología. Rev Argent Cardiol 2014;82:259-67. https://doi.org/10.7775/rac.es.v82.i4.2169

6. Pérez GE, Costabel JP, González N, Zaidel E, Altamirano M, Schiavone M, et al. Infarto agudo de miocardio en la República Argentina. Registro CONAREC XVII. Rev Argent Cardiol 2013;81:365-73. https://doi.org/10.7775/rac.v81.i5.1391

7. Costabel JP, Zaidel E, Rivero M, Gómez I, Pérez GE, Garmendia CM, et al. Registro multicéntrico prospectivo de pacientes hospitalizados por síndrome coronario agudo sin elevación del segmento ST en centros de alta complejidad. Resultados intrahospitalarios y evolución a 6 meses (BUENOS AIRES I). Rev Argent Cardiol. 2020;88:308-16. https://doi.org/10.7775/rac.es.v88.i4.18501

8. Shafiq A, Valle J, Jang JS, Qintar M, Gosch K, Cohen DJ, et al. Variation in practice regarding pretreatment with dual antiplatelet therapy for patients with non-ST elevation myocardial infarction. J Am Heart Assoc 2016;5:e003576. https://doi.org/10.1161/JAHA.116.003576

9. Mehta SR, Yusuf S, Peters RJG, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: The PCI-CURE study. Lancet 2001;358:527-33. https://doi.org/10.1016/S0140-6736(01)05701-4

10. Montalescot G, Bolognese L, Dudek D, Goldstein P, Hamm C, Tanguay JF, et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. N Engl J Med 2013;369:999-1010. https://doi.org/10.1056/NEJMoa1308075

11. Bellemain-Appaix A, Kerneis M, O'Connor SA, Silvain J, Cucherat M, Beygui F, et al. Reappraisal of thienopyridine pretreatment in patients with non-ST elevation acute coronary syndrome: A systematic review and meta-analysis. BMJ 2014;349: g6269. https://doi.org/10.1136/bmj.g6269

12. Silvain J, Rakowski T, Lattuca B, Liu Z, Bolognese L, Goldstein P, et al. Interval From Initiation of Prasugrel to Coronary Angiography in Patients With Non–ST-Segment Elevation Myocardial Infarction. J Am Coll Cardiol 2019;73:906-14. https://doi.org/10.1016/j.jacc.2018.11.055

13. Collet J-P, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2020;ehaa575. https://doi.org/10.1093/eurheartj/ehaa575

14. Pollack CV, Davoudi F, Diercks DB, Becker RC, James SK, Lim ST, et al. Relative efficacy and safety of ticagrelor vs clopidogrel as a function of time to invasive management in non-ST-segment elevation acute coronary syndrome in the PLATO trial. Clin Cardiol 2017;40:390-8. https://doi.org/10.1002/clc.22733

15. Montalescot G, van 't Hof AW, Lapostolle F, Silvain J, Lassen JF, Bolognese L, et al. Prehospital Ticagrelor in ST-Segment Elevation Myocardial Infarction. N Engl J Med 2014;371:1016-27. https://doi.org/10.1056/NEJMoa1407024

16. Sibbing D, Kastrati A, Berger PB. Pre-treatment with P2Y12 inhibitors in ACS patients: who, when, why, and which agent? Eur Heart J 2016;37:1284-95. https://doi.org/10.1093/eurheartj/ehv717

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 Rodríguez.
Sanatorio Anchorena sede Recoleta: Paz Domínguez y Nicolás Lalor.
Sanatorio Finochietto: Miguel González y Guido Damianich.
Sanatorio Güemes: Ezequiel José Zaidel e Iván Gómez.
Sanatorio la Trinidad Palermo: Andrea Tufo Pereyra.
Sanatorio la Trinidad Quilmes: Christian Musante.