Instituto Nacional Cardiovascular

Archivos Peruanos de Cardiología y Cirugía Cardiovascular
Arch Peru Cardiol Cir Cardiovasc. 2023;4(3):96-101. doi: 10.47487/apcyccv.v4i3.322.

Sociedad Científica de Medicina Cardiovascular del Perú

Original article

Impact of pretreatment with P2Y12 inhibitors in patients with non-ST-elevation acute coronary syndromes. Analysis of two multicenter registries

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Received: August 5, 2023
Accepted: September 22, 2023
Online: Setiembre 30, 2023

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Funding
Self-financed

Conflicts of Interest
The authors declare no conflict of interest.

Cite as
Sigal AR, Rivero M, Meza M, Filippa G, Procopio G, Abud CM, *et al.* Impact of pretreatment with P2Y12 inhibitors in patients with non-ST-elevation acute coronary syndromes. Analysis of two multicenter registries. Arch Peru Cardiol Cir Car-diovasc. 2023;4(3):96-101.doi: 10.47487/apcyccv.v4i3.322.

ABSTRACT

Objective. To evaluate the rate of use of antiplatelet pretreatment in patients with non-ST elevation acute coronary syndrome (NSTE-ACS) and its association with adverse events in two Argentine registries. **Materials and methods.** We retrospectively analyzed two Argentine acute coronary syndrome (ACS) registries from 2017 and 2022. We explored the incidence of pretreatment and the drug used. We evaluated the relationship between this strategy and a combined endpoint of in-hospital events: death + myocardial infarction + stent thrombosis + post-infarction angina + transient ischemic event/stroke, and with bleeding events (Bleeding Academic Research [BARC] 2 or higher). Subsequently, we performed a multivariate analysis using logistic regression with other clinical variables**. Results.** A total of 1297 patients were included; 75.6% were men, 25.6% had diabetes, 27.1% were smokers, 70.3% had hypertension, and 23.1% had a previous ACS. The median of age was 55.3 years. The median GRACE score was 113.5, and the CRUSADE was 23.8. 44% of the patients received pretreatment, most with clopidogrel (93.5%). Pretreatment was significantly associated with a higher incidence of the combined endpoint (10.1% vs. 6.9%) (Odds Ratio [OR]: 1.56; 95% confidence interval [CI]: 1.06-2.30; p=0.020). Bleeding events were numerically more frequent with pretreatment (8.7% vs. 5.9%) (OR: 1.51; 95% CI: 0.99-2.30; p=0.054). In the multivariate analysis, pretreatment was no longer associated with a higher incidence of ischemic outcomes (OR: 1.40; 95% CI: 0.89-2.33; p=0.130). **Conclusions.** Pretreatment was used in almost half of the patients, mainly with clopidogrel, and did not show a reduction in ischemic events in patients with NSTE-ACS.

Keywords: NSTEMI; Treatment; Clopidogrel (source: MeSH-NLM).

Introduction

Pretreatment in non-ST elevation acute coronary syndrome (NSTE-ACS) refers to the administration of a loading dose of a P2Y12 inhibitor (clopidogrel, ticagrelor, or prasugrel) before knowing the coronary anatomy. This strategy is based on achieving a higher level of antiplatelet aggregation [1] prior to cardiac catheterization and stent placement, with the aim of reducing the risk of stent thrombosis.

However, pretreatment has not systematically demonstrated a reduction in ischemic events, and both ticagrelor [2] and prasugrel [3] have an earlier onset of action than clopidogrel [4], making early administration unnecessary for their effective use. Furthermore, it is associated with a potential increase in bleeding risk, especially demonstrated with prasugrel [5], and in the case of patients with multi-vessel disease requiring surgical intervention, it will result in a longer hospital stay before surgery or a higher risk of bleeding during surgery [6-9].

We do not have information about the frecuency of pretreatment use in our region, nor the characteristics of patients to whom it was administered. The incidence of ischemic or hemorrhagic events in relation to the pretreatment strategy is also unknown. Therefore, the primary objective of the study was to evaluate the rate of pretreatment use in the Argentine population and the type of drug used for this strategy. As a secondary objective, we explored whether the use of pretreatment was associated with the incidence of in-hospital ischemic events and mortality through a combined endpoint that included: death, myocardial infarction, stent thrombosis, post-infarction angina, and transient ischemic attack/stroke (TIA/Stroke). In addition, an association was sought between the use of pretreatment and the presence of Bleeding Academic Research Consortium (BARC) 2 or greater, during hospitalization.

Materials and Methods

Design and study population

A retrospective analysis was conducted using data from two prospective multicenter registries of ACS in Argentina: Buenos Aires I [10] and the Acute Coronary Syndrome Registry in Centers of Argentina (RESCAR) [11]. Both registries included patients from high-volume complex centers, in the metropolitan area of Buenos Aires, and were designed and carried out by the Emergency and Critical Cardiology Council of the Argentine Society of Cardiology.

The Buenos Aires I registry was a prospective observational study that enrolled patients from December 2017 to July 2018. It included 1100 consecutive patients with NSTE-ACS from 21 centers.

RESCAR was a prospective multicenter observational registry that enrolled patients from January to August 2022. It included 984 patients with ACS with or without ST-segment elevation from 15 centers.

For the current analysis, patients from both registries who had a diagnosis of NSTE-ACS were included, and those who had used thienopyridines upon admission for the index event and those who did not undergo invasive treatment were excluded.

Data analysis

For this analysis, IBM SPSS Statistics for Windows, version 25.0, was used. Continuous variables were expressed as mean and standard deviation or median and interquartile range (IQR) according to the characteristics of their distribution. Normality was assessed using the Kolmogorov-Smirnov or Shapiro-Wilk test, as appropriate. Categorical variables were analyzed using the chi-square test or Fisher's exact test, while numerical variables were analyzed using the Student's t-test or Mann-Whitney U test, based on their distribution.

Following the univariate analysis of both secondary objectives, a multivariate analysis was conducted using logistic regression, including all variables that had a p-value < 0.10 in the univariate analysis. Results were reported as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was considered when the Type I error was less than or equal to 5% ($p < 0.05$, two-tailed).

Ethical aspects

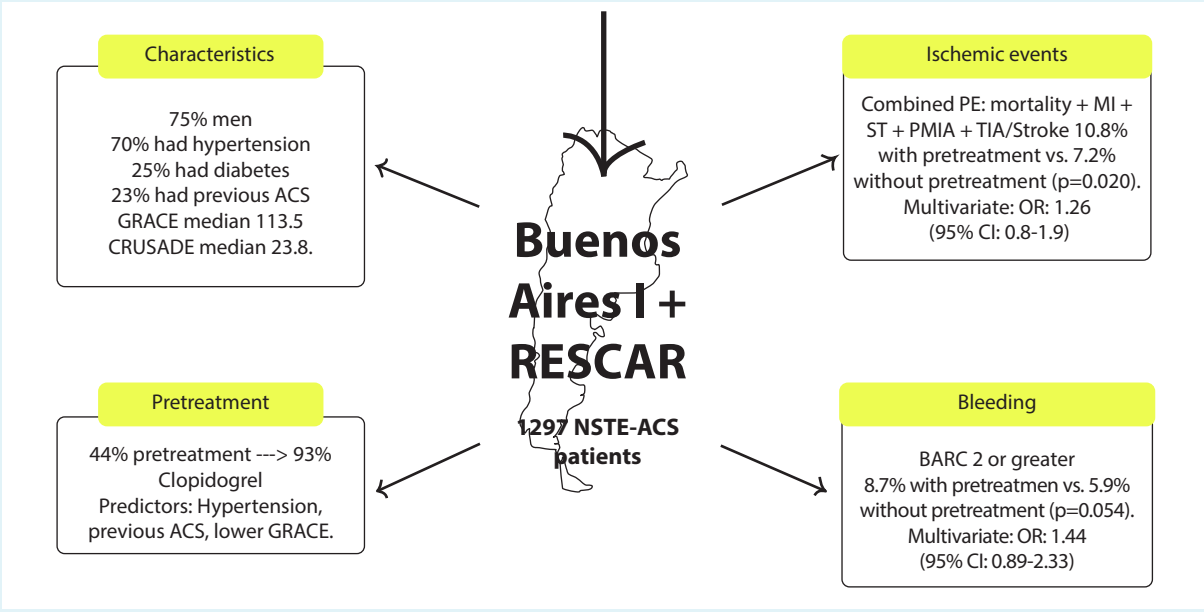
This secondary data study was conducted in compliance with the National Personal Data Protection Law No. 25326. The study was carried out in accordance with national ethical standards (CABA Law No. 3301, National Law on Clinical Research in Human Beings, Declaration of Helsinki, and others).

Results

A total of 1297 patients with a median age of 55.3 years were included. 75.6% were men, 25.6% had diabetes, 27.1% were smokers, 70.3% had hypertension, and 23.1% had a previous history of ACS **(Figure 1)**.

Of the NSTE-ACS cases, 70% were infarctions, and the remaining 30% were unstable angina. The median GRACE (Global Registry of Acute Coronary Events) score was 113.5 (IQR: 94-136), and the median CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) score was 23.8 (IQR: 13-33). The in-hospital event rate was 8.3%.

Forty-four percent patients received pre-treatment, 93.5% with clopidogrel and 6.5% with ticagrelor. The rate of pretreatment use varied significantly between centers, ranging from 10-60%. The median time to cinecoronary angiography was 18 hours (IQR: 12-23). 12% (155 patients) required coronary surgery within the index hospitalization.



RESCAR: the Acute Coronary Syndrome Registry in Centers of Argentina, NSTE-ACS: non-ST elevation acute coronary syndrome, ACS: acute coronary syndrome, PE: primary endpoint, PIA: post-infarction angina, MI: myocardial infarction, ST: stent thrombosis, TIA: transient ischemic attack, BARC: Bleeding Academic Research Consortium, OR: odds ratio, CI: confidence interval.

Figure 1. Central figure summarising the findings of the work.

The patients who received pretreatment were more frequently hypertensive (73.8% vs. 67%; p=0.010), less likely to have dyslipidemia (54.2% vs. 63.9%; p=0.001), had a higher incidence of previous ACS (27% vs. 19%; p=0.002), and were younger (median age of 57 vs. 64 years; p=0.001). They also less frequently received oral anticoagulation (4.7% vs. 7.4%; p=0.040). The rest of the baseline characteristics of the patients were similar between those who received pretreatment and those who did not **(Table 1)**.

As for the secondary objectives, in the univariate analysis, the use of pretreatment was associated with a higher incidence of the combined in-hospital endpoint, occurring in 10.8% of patients who received pretreatment and 7.2% of those who did not (OR: 1.56; 95% CI: 1.06-2.03; p=0.020). Regarding bleeding events according to the BARC criteria grade 2 or greater, there was a trend toward a higher incidence, which did not reach statistical significance, with rates of 8.7% in those who received pretreatment and 5.9% in those who did not (OR: 1.51; 95% CI: 0.99-2.30; p=0.054).

In the multivariate logistic regression analysis, the use of pretreatment did not demonstrate a statistically significant association with the in-hospital ischemic endpoint (OR: 1.26; 95% CI: 0.82-1.92) **(Table 2)**. Similarly, regarding the BARC grade 2 or higher bleeding endpoint, the use of pretreatment did not show a statistically significant association with a higher incidence after multivariate analysis (OR: 1.44; 95% CI: 0.89-2.33) **(Table 3)**.

Discussion

In this retrospective observational study, based on prospectively collected data from two national multicenter ACS registries, the use of pretreatment with clopidogrel in patients with NSTE-ACS did not result in an improvement in in-hospital ischemic events or an increase in BARC 2 or higher bleeding, although there was a trend in the latter. We would like to highlight some aspects of our findings.

First, the rate of pretreatment strategy use was 44%, which is relatively high, considering that current clinical practice guidelines generally assign a Class III recommendation for routine use or a Class IIb recommendation in selected circumstances. The reasons for this high rate may be related to the widespread use of clopidogrel as a P2Y12 inhibitor, given that the in-hospital treatment strategy is pharmacologically more appealing when more potent inhibitors like ticagrelor or prasugrel are used.

Second, pretreatment was more commonly indicated in hypertensive patients and those with a history of previous ACS. In relation to the first factor, it is challenging to find a relationship that justifies this finding, in terms of whether it is a variable considered by physicians when prescribing pretreatment and could be explained by the biases inherent to a non-randomized observational study. On the other hand, previous ACS significantly increases the risk of recurrent ischemic events in patients, and these patients are more likely to require coronary angioplasty and therefore, could have been a situation considered by physicians to indicate it. Additionally, the younger age of patients who received pretreatment could be associated with the risk of bleeding and the need for coronary surgery.

Third, the analysis by centers revealed significant variability, with rates of pretreatment ranging from 10% to 60%, which could reflect differences in institutional protocols rather than

Table 1. Baseline characteristics of the population according to whether they received pre-treatment or not.

Variable	no pretreatment n=724	with pretreatment n=573	p-value
Male - n (%)	543 (75)	438 (76)	0.540
Age – years, median (IQR)	64 (47-75)	57 (35-72)	0.001
BMI - kg/m^2, median (IQR)	28,1 (25-33.1)	28,7 (26-35.2)	0.660
Hypertension - n (%)	489 (67.5)	423 (73.8)	0.010
Diabetes - n (%)	173 (23.8)	159 (27.7)	0.110
Dyslipemia - n (%)	463 (63.9)	311 (54.2)	0.001
Smoking - n (%)	212 (29.3)	140 (24.4)	0.051
Ejection fraction - %, median (IQR)	50 (20-60)	48 (18-55)	0.150
CRUSADE – value, median (IQR)	24 (13-33)	22 (13.7-32)	0.530
GRACE – value, median (IQR)	114 (94-136)	111,5 (90-131)	0.930
Previous bleeding - n (%)	8 (1.1)	7 (1.2)	0.840
Previous ACS- n (%)	144 (19.8)	155 (27)	0.002
Remote CTA- n (%)	153 (21.1)	124 (21.6)	0.820
Previous CABS - n (%)	65 (8.9)	53 (9.2)	0.860
Previous AF - n (%)	60 (8.3)	39 (6.8)	0.320
Previous stroke - n (%)	41 (5.6)	30 (5.2)	0.730
Previous PVD- n (%)	45 (6.2)	35 (6.1)	0.930
Previous aspirin use - n (%)	296 (40.1)	252 (43.9)	0.262
Previous OA use - n (%)	54 (7.4)	27 (4.7)	0.040
KK			0.460
I	672 (92.8)	528 (92.1)	
II	36 (4.9)	37 (6.4)	
III	13 (1.8)	7 (1.2)	
IV	3 (0.5)	1 (0.1)	

BMI: Body Mass Index, ACS: Acute Coronary Syndrome, CTA: Coronary Transluminal Angioplasty, CABS: Coronary Artery Bypass Surgery, AF: Atrial Fibrillation, PVD: Peripheral Vascular Disease, OA: Oral Anticoagulation, KK: Killip and Kimbal, IQR: interquartile range.

individualized patient-by-patient decision-making. This could be related to the rate of surgeries performed at each center, the availability of coronary angiography, or the level of conviction regarding the benefits or risks of this practice. It is worth noting that the rate of patients requiring surgery during their hospital stay was 12%, which is relatively high compared to other registries, such as the European Society of Cardiology (ESC) registry, which reported a surgery rate of 9.2% for low and middle-income countries [12], this occurrence being one of the concerns when considering the use of pretreatment.

Fourth, pretreatment was not associated with a reduction in ischemic events, which is consistent with findings in international literature. For example, a Swedish cohort study [13] of nearly 65,000 patients did not find a survival benefit at 30 days or 1 year or a decrease in stent thrombosis incidence with pretreatment, but it did show a 50% increase in the relative risk of in-hospital bleeding events. The trials that favored pretreatment are mostly older, primarily involving clopidogrel, and reflect a practice that is less commonly used today, especially in the context of decreasing reperfusion times for non–ST-segment elevation myocardial infarction (NSTEMI). For instance, the CREDO [14] study found that pretreatment with clopidogrel provided benefits in events at 28 days only when its use preceded angioplasty by at least 15 hours. In a sub-analysis of the CURE study [15], pretreatment with clopidogrel showed a benefit in reducing ischemic events at 30 days, but the median time between its use and catheterization was 6 days. In our study, the pretreatment time was relatively short, which could have influenced the lack of benefit from the strategy. The ARMYDA-5 study, which included stable patients and 39% of acute cases, also did not find a benefit from this strategy, nor did it show benefits in the subgroup analysis of patients with ACS [16]. A systematic review from 2014 [17], involving a total of 38,000 patients, found a reduction in major adverse cardiovascular events (MACE), primarily driven by the CREDO and CURE studies, but no benefit in patients undergoing angioplasty. It also did not find a reduction in overall mortality or in the cohort of patients who underwent invasive treatment. Moreover, it identified a 30-40% increase in bleeding risk according to the studies analyzed. Another more recent meta-analysis, including the DUBIUS and ISAR-REACT studies, did not find a benefit from pretreatment in the primary endpoint of MACE at 30 days, nor in secondary endpoints such as death or infarction at 30 days, but it did show an increase in major bleeding, with a number needed to harm (NNH) of 63 [18].

Table 2. Result of multivariate analysis of the combined endpoint of in-hospital ischemic events.

Variable	OR (95% CI)	p-value
Use of pretreatment	1.26 (0.82-1.92)	0.277
Age/year	0.99 (0.99-1.01)	0.905
Male	1.03 (0.62-1.72)	0.889
Diabetes	1.31 (0.83-2.07)	0.243
Hypertension	1.00 (0.60-1.60)	0.980
Dyslipemia	0.66 (0.42-1.01)	0.055
Prior bleeding	2.58 (0.61-10.76)	0.193
Previous ACS	2.51 (1.55-4.07)	0.001
Previous aspirin use	0.85 (0.53-1.36)	0.497
Previous OA	0.73 (0.36-1.48)	0.390
KK	2.63 (1.83-3.79)	0.001
LVEF	1.00 (0.99-1.01)	0.414

OR: odds ratio, CI: confidence Interval, ACS: Acute Coronary Syndrome, OA: Oral Anticoagulation, KK: Killip and Kimbal, LVEF: left ventricular ejection fraction

It is reasonable that, in line with these findings, the AHA/ACC clinical practice guidelines [19] do not recommend the routine use of pretreatment, while the ESC 2020 guidelines [20] recommend it as a Class IIB indication for patients at low risk of bleeding who do not have a planned early invasive strategy. The ESC guidelines also contraindicate the use of prasugrel for this strategy based on the results of the ACCOAST study, where pretreatment with prasugrel led to increased bleeding without benefit in ischemic events. In the 2023 ESC ACS guidelines [21], this recommendation drops to Class III for patients undergoing revascularization within 24 hours, while it remains as Class IIB for those with an expected delay of more than 24 hours and low bleeding risk, adding the information from the DUBIUS study [22] which was terminated prematurely due to the futility of the pretreatment strategy in patients scheduled for catheterization within 72 hours of admission for NSTE-ACS.

Table 3. Result of multivariate analysis of the combined endpoint of in-hospital hemorrhagic events.

Variable	OR (95% CI)	p-value
Use of pretreatment	1.44 (0.89-2.33)	0.131
Age/year	0.99 (0.98-1.00)	0.817
Male	0.71 (0.41-1.21)	0.211
Diabetes	0.84 (0.47-1.47)	0.546
Hypertension	2.15 (1.13-4.1)	0.020
Dyslipemia	0.83 (0.52-1.3)	0.470
Prior bleeding	4.16 (1.01-17.16)	0.048
Previous ACS	0.98 (0.54-1.76)	0.954
Previous aspirin use	1.57 (0.94-2.64)	0.084
Previous OA	0.92 (0.43-1.95)	0.830
KK	2.60 (1.76-3.83)	0.001
LVEF	0.99 (0.97-1.00)	0.105

OR: odds ratio, CI: confidence Interval, ACS: Acute Coronary Syndrome, OA: Oral Anticoagulation, KK: Killip and Kimbal, LVEF: left ventricular ejection fraction.

In Argentina, the registry of acute coronary syndromes by the Argentine Council of Cardiology Residents (CONAREC) in 2013 found that 85% of patients diagnosed with NSTEMI received clopidogrel upon hospital admission [23]. An analysis of the Buenos Aires I registry, conducted before the RESCAR registry, revealed that of the patients who received P2Y12 receptor inhibitors, 75% did so as pretreatment. However, this did not result in a reduction of events at 6 months or an increase in bleeding [24]. Expert reviews and the international literature concur on the lack of benefit from the systematic use of this strategy [25].

The limitations of our study include the biases associated with the absence of randomization, making it challenging to establish a direct cause-and-effect relationship between pretreatment and events. Therefore, the conclusions remain in the realm of hypotheses, despite adjusting for certain known variables.

In conclusion, the findings align with the current international literature, with nearly half of the patients receiving pretreatment, and the study does not provide evidence of a systematic benefit from pretreatment with clopidogrel in NSTE-ACS.

Author contributions

AS, MZ, and JPC participated in the conceptualization of the article, methodology, data collection, formal data analysis, original manuscript writing, editing, and revision. MM, GF, GP, CA, SN, MO, and ED contributed to data collection and review.

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