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ORIGINAL ARTICLE

Pretreatment antithrombotic strategies in non-ST elevation acute coronary syndromes in contemporaneous clinical practice

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ABSTRACT

BACKGROUND Pretreatment antithrombotic strategies in non-ST elevation acute coronary syndromes (NSTE-ACS) during hospitalization is still a matter of contention within the cardiology community. Our aim was to analyze in-hospital and one-year follow-up outcomes of patients with NSTE-ACS pretreated with dual antiplatelet therapy (DAPT) versus single antiplatelet therapy (SAPT).

METHODS A retrospective study was carried out with NSTE-ACS patients who planned to undergo an invasive strategy and were included in the Portuguese Registry of ACS between 2018 and 2021. A composite primary outcome (in-hospital re-infarction, stroke, heart failure, hemorrhage, death) was compared regarding antiplatelet strategy (DAPT versus SAPT). Secondary outcomes were defined as one-year all-cause mortality and one-year cardiovascular rehospitalization.

RESULTS A total of 1469 patients were included, with a mean age of 66 $\pm$ 12 years, and 73.9 % were male. The DAPT regime was used in 38.2 % of patients and SAPT in 61.8 % of patients. NSTE myocardial infarction was the most frequent presentation (88.5 %). Revascularization was performed within 24 h in 55.2% of patients. Time until revascularization $>$24 h occurred in 44.8% of patients, with 16.5% of these between [24 h–48 h], 10.6% in [48 h–72 h] and 17.6% $>$ 72 h. The primary outcome was more frequently observed in the SAPT group (10.4 %, $p = 0.033$), mainly driven by more ischemic events. Time until revascularization $>$72 h and the SAPT regime were independent predictors of the primary outcome (OR 3.09, $p = 0.005$, and OR 2.03, $p = 0.008$, respectively).

CONCLUSION NSTE-ACS patients pretreated with SAPT had worse in-hospital outcomes. This difference can probably be explained by time until revascularization delay. (Hellenic Journal of Cardiology 2024;80:12-20) © 2023 Hellenic Society of Cardiology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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1. INTRODUCTION

The role of antithrombotic (ATT) pretreatment in non-ST elevation acute coronary syndromes (NSTE-ACS) has been widely studied in the last decade, and the optimal antiplatelet and anticoagulation strategy is still a matter of debate within the international cardiology community. The European guidelines do not recommend routine pretreatment with P2Y12 inhibitors in NSTE-ACS patients whose coronary anatomy is not known and for whom an early invasive management is planned. As such, pretreatment may only be considered in patients who are not planned to undergo an early invasive strategy and those who do not have a high bleeding risk.[1-3]

In 2003, Peters et al. showed the benefits (mainly ischemic) of adding clopidogrel to different doses of aspirin in NSTE-ACS patients, despite excluding the timing of treatment (pre or post-revascularization), the low rates of percutaneous coronary intervention (PCI), and being based on a post hoc observational analysis.[4] Later, Wallentin et al. showed that treatment with ticagrelor as compared to clopidogrel in patients with ACS with or without ST-segment elevation significantly reduced mortality, myocardial infarction, and stroke, although they also did not take into consideration the timing and the use of PCI.[5]

One randomized study suggested that pretreatment with clopidogrel could reduce the rate of ischemic events at the cost of an increase in bleeding.[6] Subsequently, the ACCOAST trial was designed to compare systematic pretreatment with prasugrel at the time of diagnosis of an NSTE-ACS with prasugrel given selectively after coronary angiography (CA) to patients undergoing PCI. Among these patients, pretreatment with prasugrel did not reduce the rate of major ischemic events, but it increased the rate of major bleeding.[7] More recently, Tarantini et al. showed that the primary composite endpoint (ischemic and hemorrhagic) of NSTE-ACS patients pretreated with ticagrelor did not differ from a downstream strategy (no pretreatment).[8]

The current study aimed to understand the benefits of different pretreatment ATT strategies in NSTE-ACS patients during hospitalization and in medium-term follow-up, in contemporaneous clinical practice where ideal time delay to PCI is often difficult to achieve.

2. METHODS

This was a nationwide retrospective cohort study. All consecutive patients included in the *Portuguese Registry on ACS* (ProACS) between January 1, 2018 and December 31, 2021 were included. The ProACS is a multicenter, continuous, prospective observational registry that is under the aegis of the Portuguese Society of Cardiology and is coordinated by the National Center for Data Collection in Cardiology. All Portuguese cardiology departments were invited to participate and subsequently assist with recruiting eligible hospitalized adult patients.

2.1. PATIENT SELECTION. Patients were eligible for the study if they had a diagnosis of NSTE-ACS and planned to undergo an invasive strategy. Patients with established ST elevation ACS (STEMI), previous atrial fibrillation (AF) or AF at the time of diagnosis, and on oral anticoagulation for other reasons were excluded. Baseline patient demographic data, cardiovascular risk (CVR) factors, clinical, laboratory, echocardiographic, and angiographic data were recorded. Patients were divided into two groups regarding antiplatelet pretreatment strategy: DAPT (dual antiplatelet therapy) or SAPT (single antiplatelet therapy).

The study abides by the ethical principles set by the 1975 Declaration of Helsinki.

2.2. OUTCOMES. The primary (composite) outcome was defined as in-hospital re-infarction, stroke, heart failure (HF), hemorrhage, and/or death. In-hospital re-infarction was defined based on the fourth universal definition of myocardial infarction[9]: the diagnosis of re-infarction required a >20 % increase of the cardiac troponins (cTn) compared with the baseline (elevated but stable or decreasing) with new clinical signs and symptoms or electrocardiographic changes. Stroke was defined as an acute focal injury of the central nervous system of vascular etiology, including cerebral infarction and intracerebral/subarachnoid hemorrhage. Heart failure was defined as per the European HF guidelines[10]. Hemorrhage was defined as per the definition by the Bleeding Academic Research Consortium (*BARC*)[11].

Secondary outcomes were defined as one-year all-cause mortality and one-year cardiovascular rehospitalization.

2.3. STATISTICAL ANALYSIS. Continuous variables were presented as mean ± standard deviation or median and interquartile ranges. These were compared between groups using independent samples T-test or the Mann-Whitney U test, based on

ABBREVIATIONS

ACS = acute coronary syndrome
AF = atrial fibrillation
ATT = antithrombotic treatment
CA = coronary angiogram
cTN = cardiac troponins
CVR = cardiovascular risk
DAPT = dual antiplatelet therapy
ECG = electrocardiogram
HF = heart failure
KK = Killip-Kimball
MVD = multivessel disease
NSTE-ACS = non-ST elevation acute coronary syndrome
NSTEMI = non-ST elevation myocardial infarction
PCI = percutaneous coronary intervention
SAPT = Single antiplatelet therapy
STEMI = ST elevation myocardial infarction

TABLE 1 Clinical and procedure characteristics of NSTE-ACS patients pretreated according to the antiplatelet regime

			Antiplatelet regime			
			DAPT (n=561, 38,2%)	SAPT (n=908, 61,8%)	Total (n=1469)	P value
Gender	***Male***	n (%)	419 (74,7)	666 (73,3)	1085 (73,9)	
	Female	n (%)	142 (25,3)	242 (26,7)	384 (26,1)	
						0,570
Age	***Mean±SD - years***		65,0±12,2	66,4±12,0	65,8±12,1	
						0,016
BMI	***Mean±SD - years***		27,7±4,10	27,7±4,50	27,7±4,30	
						0,411
Hypertension		n (%)	399 (71,1)	658 (72,9)	1057 (72,2)	
						0,469
Dyslipidemia		n (%)	341 (60,8)	540 (59,9)	881 (60,3)	
						0,746
Type 2 diabetes mellitus		n (%)	189 (34,1)	320 (35,6)	509 (35,0)	
						0,550
Smoker		n (%)	175 (31,3)	265 (29,3)	440 (30,0)	
						0,425
Heart failure history		n (%)	45,0 (8,10)	66,0 (7,30)	111 (7,60)	
						0,611
Valvular disease		n (%)	7,00 (1,30)	23,0 (2,50)	30,0 (2,10)	
						0,089
Ischemic heart disease		n (%)	142 (25,3)	282 (31,1)	424 (28,9)	
						0,110
Chronic renal disease		n (%)	44,0 (8,00)	57,0 (6,40)	101 (7,00)	
						0,240
Chronic lung disease		n (%)	20,0 (3,60)	42,0 (4,70)	62,0 (4,30)	
						0,326
Clinical indication	***NSTEMI***	n (%)	488 (87,0)	812 (89,4)	1300 (88,5)	0,154
	Unstable angina	n (%)	34,0 (6,10)	44,0 (4,80)	78,0 (5,30)	0,313
	ACS with LBBB or RBBB	n (%)	39,0 (7,00)	52,0 (5,70)	91,0 (6,20)	0,344
KK class *	***I***	n (%)	498 (89,7)	807 (89,5)	1305 (89,6)	0,874
	> I (II, III, IV)	n (%)	57,0 (10,3)	95,0 (10,5)	152 (10,4)	0,874
LVEF at baseline	***Mean±SD - %***		53,0±11,0	54,0±11,0	54,0±11,0	
						0,020
Hemoglobin*	***Mean±SD - g/dl***		14,1±1,90	13,9±1,80	14,0±1,80	
						0,062
Creatinine*	***Mean±SD - mg/dl***		1,20±1,00	1,10±0,80	1,10±0,90	
						0,274
Time until revascularization/CA	***≤ 24 h***	n (%)	295 (53,8)	497 (56,1)	792 (55,2)	0,402
	[24 h-48 h]	n (%)	86,0 (15,7)	151 (17,0)	237 (16,5)	0,504
	[48 h-72 h]	n (%)	62,0 (11,3)	90,0 (10,2)	152 (10,6)	0,490
	> 72 h	n (%)	105 (19,2)	148 (16,7)	253 (17,6)	0,236
Nº of vessel with disease	***1 vessel***	n (%)	137 (31,7)	326 (39,8)	463 (37,0)	**0,005**
	Multivessel disease (>1)	n (%)	275 (57,7)	483 (57,5)	758 (57,6)	0,957
	Without lesions	n (%)	64,0 (11,4)	30,0 (3,30)	94,0 (6,40)	**<0,001**
Culprit artery	***LMCA***	n (%)	13,0 (3,60)	23,0 (3,10)	36,0 (3,20)	0,667
	Anterior descendent	n (%)	126 (34,5)	300 (40,1)	426 (38,3)	0,072
	Circunflex artery	n (%)	102 (27,9)	156 (20,9)	258 (23,2)	**0,009**
	Right coronary artery	n (%)	94,0 (25,8)	188 (25,1)	282 (25,3)	0,823
Antipletelet therapy	***AAS***	n(%)	561 (100)	903 (99,4)	1464 (99,7)	**<0,001**
-> *Pretreatment*	***Clopidogrel***	n (%)	134 (90,5)	0,00 (0,00)	134 (47,3)	**<0,001**
	Ticagrelor	n (%)	427 (94,1)	5,00 (1,20)	432 (49,1)	**<0,001**
Anticoagulation therapy	***Unfractionated heparin***	n (%)	186 (33,5)	126 (14,1)	312 (21,6)	**<0,001**
-> *Pretreatment*	***Enoxaparin***	n (%)	277 (49,9)	376 (42,1)	653 (45,1)	**0,003**
	Fondaparinux	n (%)	138 (24,7)	323 (36,1)	461 (31,7)	**<0,001**

AAS, Acetylsalicylic acid; ACS, Acute coronary syndrome; BMI, Body mass index; DAPT, Dual antiplatelet therapy; KK, Killip and Kimball class; LBBB, Left bundle branch block; LMCA, Left main coronary artery; LVEF, Left ventricular ejection fraction; NSTEMI, Non-ST elevation myocardial infarction; RBBB, Right bundle brunch block; SAPT, Single antiplatelet therapy; SD, Standard deviation; * at admission.

TABLE 2 Primary outcome in NSTE-ACS patients, compared by pretreatment antiplatelet regime

		Antiplatelet regime			
		DAPT (n=561, 38,2%)	SAPT (n=908, 61,8%)	Total (n=1469)	p value
Primary outcome (composite):	n (%)	39,0 (7,00)	94,0 (10,4)	133 (9,10)	
-> *Re-MI, Stroke, HF, Hemorrhage, Death**					**0,033**
Components of primary outcome					
-> *Re-MI*	n (%)	2,00 (0,40)	11,0 (1,20)	13,0 (0,90)	**0,008**
-> *Stroke*	n (%)	1,00 (0,20)	4,00 (0,40)	5,00 (0,30)	**<0,001**
-> *HF*	n (%)	32,0 (5,30)	65,0 (7,20)	97,0 (6,70)	0,132
-> Major hemorrhage	n (%)	2,00 (0,40)	3,00 (0,30)	5,00 (0,30)	**<0,001**
-> Death	n (%)	4,00 (0,70)	11,0 (1,20)	15,0 (1,00)	0,357

DAPT, Dual antiplatelet therapy; HF, Heart failure; MI, Myocardial infarction; SAPT, Single antiplatelet therapy; * in-hospital.

their distribution. Categorical variables were presented as frequencies and percentages and were compared using the Chi-square or Fisher's exact tests, as appropriate.

Separate analyses were conducted for in-hospital and 1-year endpoints. The independent predictors of the primary outcome were assessed by multivariable logistic regression analyses using the stepwise forward method. The Hosmer-Lemeshow test was used for the calibration of the regression model. The effect of the variables was assessed by estimating the odds ratio and 95 % confidence intervals. The variables that were entered into the model were gender, age, hypertension, type 2 diabetes mellitus, multivessel disease (MVD), Killip-Kimball (KK) class at admission, time until revascularization, ischemic heart disease, and chronic renal disease. Survival analysis was used to compare secondary outcomes. Cumulative incidences of events were estimated by the Kaplan-Meier method, and the difference was assessed by the log-rank test.

3. RESULTS

3.1. PATIENT'S CHARACTERISTICS. A total of 1469 NSTE-ACS patients were included, with a mean age of 66 ± 12 years, of which 73.9 % were male. Of these, 561 (38.2 %) patients were pretreated with DAPT and 908 (61.8 %) with SAPT during hospitalization. The sample showed high rates of CVR factors, including hypertension (72.2 %), dyslipidemia (60.3 %), type 2 diabetes (35 %), or smoking habits (30 %). NSTE myocardial infarction (NSTEMI) was the most frequent presentation (88.5 %), with KK class = I in 89.6 % of admitted patients. CA/PCI was performed within 24 h in 55.2 % of patients. Time until revascularization >24 h occurred in 44.8 % of patients, with 16.5 % of these between [24 h-48 h], 10.6 % in [48 h-72 h], and 17.6 % > 72 h. MVD was common (57.6 %), and 6.4 % of patients did not have relevant coronary artery disease. The DAPT strategy mostly included aspirin (100 %) and ticagrelor (94.1 %), whereas the SAPT regime usually included aspirin only (99.4 %). Anticoagulation therapy more frequently used was enoxaparin in the DAPT group (49.9 %, p = 0.003) and fondaparinux in the SAPT group (36.1 %, p < 0.001) (Table 1).

3.2. COMPOSITE PRIMARY OUTCOME. The composite primary outcome occurred in 94 patients in the SAPT group and in 39 patients in the DAPT group (10.4 % vs 7.00 %, p = 0.033). The components of primary outcome were re-infarction (SAPT 1.20 %, DAPT 0.40 %, p = 0.008), stroke (SAPT 0.40 %, DAPT 0.20 %, p < 0.001), HF (SAPT 7.20 %, DAPT 5.30 %, p = 0.132), major hemorrhage (SAPT 0.30 %, DAPT 0.40 %, p < 0.001), and death (SAPT 1.20 %, DAPT 0.70 %, p = 0.357) during hospitalization (Table 2).

The composite primary outcome was also analyzed according to time until revascularization: in ≤24 h (SAPT 30.8 %, DAPT 15.8 %, p = 0.628), [24 h-48 h] (SAPT 11.3 %, DAPT 2.60 %, p = 0.071), [48 h-72 h] (SAPT 4.51 %, DAPT 4.51 %, p = 0.553), and >72 h (SAPT 24.8 %, DAPT 6.02 %, p = 0.007) (Table 3). Independent predictors of the composite primary outcome were hypertension (OR 1.91, p = 0.031), MVD (OR 1.69, p = 0.045), time until revascularization >72 h (OR 3.09, p < 0.005), KK class > I (OR 29.4, p < 0.001), and SAPT (OR 2.03, p < 0.008) (Table 4).

3.3. SECONDARY OUTCOMES. One-year all-cause mortality and one-year cardiovascular rehospitalization showed no differences between groups—SAPT (6.28 %, p = 0.494 and 7.24 %, p = 0.063, survival analysis) (Fig. 1, Fig. 2). Secondary outcomes also with no differences between groups and according to time until revascularization (Fig. 3, Fig. 4).

TABLE 3 Primary outcome in NSTE-ACS patients, compared by pretreatment antiplatelet regime taking into account the time until revascularization

		Primary Outcome			
		Without (n=1280, 90,2%)	With (n=133, 9,41%)	Total (n=1413)	P value
Time until revascularizazion					
≤ ***24 h - DAPT***	n (%)	265 (20,7)	21,0 (15,8)	286 (20,2)	p=0,628
≤ ***24 h - SAPT***	n (%)	452 (35,3)	41,0 (30,8)	493 (34,9)	
[24 h-48 h] - DAPT	n (%)	82,0 (6,40)	3,00 (2,26)	85,0 (6,02)	p=0,071
[24 h-48 h] - SAPT	n (%)	134 (10,5)	15,0 (11,3)	149 (10,5)	
[48 h-72 h] - DAPT	n (%)	56,0 (4,37)	6,00 (4,51)	62,0 (4,39)	p=0,553
[48 h-72 h] - SAPT	n (%)	80,0 (6,25)	6,00 (4,51)	86,0 (6,08)	
> ***72 h - DAPT***	n (%)	94,0 (7,34)	8,00 (6,02)	102 (7,22)	**p=0,007**
> ***72 h - SAPT***	n (%)	117 (9,14)	33,0 (24,8)	150 (10,6)	

DAPT, Dual antiplatelet therapy; SAPT, Single antiplatelet therapy.

4. DISCUSSION

This study has found that pretreatment antiplatelet strategy in NSTE-ACS patients with SAPT was associated with higher rates of in-hospital re-infarction, stroke, HF, hemorrhage, and/or death when compared with a DAPT regime in pretreatment fashion. Moreover, SAPT was an independent predictor of the primary composite outcome.

The optimal timing of the administration of oral P2Y12 inhibitors has been largely debated, particularly among patients with NSTE-ACS.[12] Even in STEMI patients, an observational study showed conflicting results when compared to established guideline recommendations.[13] Pretreatment with P2Y12 inhibitors before evaluating coronary anatomy bears a theoretical advantage of ischemic protection while awaiting CA and reduces the risk of periprocedural ischemic complications. However, it may also increase the risk of periprocedural bleeding during PCI or coronary artery bypass graft.[7,14,15]

Based on recent trials, the European guidelines recommend against the routine use of pretreatment with P2Y12 inhibitors in NSTE-ACS patients whose coronary anatomy is not known and for which an early invasive management is planned, although it may be considered in patients who are not planned to undergo an early invasive strategy.[3,7,16] Nevertheless, in NSTE-ACS high-risk patients, the recommendation is to advance to an early invasive strategy (within 24 h).[3] In the current analysis, SAPT strategy was associated with higher rates of primary outcome, mainly driven by more ischemic events during hospitalization (re-infarction and stroke) with a short benefit in bleeding. In addition, in multivariable analysis, SAPT was shown to be an independent predictor of the primary outcome, contradicting the European guideline recommendations. In a more detailed analysis, this can be explained by the waiting time until CA and subsequently PCI. In the present study, at least 88.5 % of patients were classified as high risk (NSTEMI patients), which should have triggered an invasive strategy within 24 h. However, almost half (44.8 %) performed a CA after 24 h, and of these, 10.6 % between [48 h-72 h] and 17.6 % after 72 h. Time until revascularization >72 h was associated with the primary outcome in SAPT (vs DAPT) patients (SAPT 24.8 %, DAPT 6.02 %, p = 0.007) and was an independent predictor of the primary outcome. This delay to revascularization is probably the main driving factor influencing the results of this study. Nevertheless, hard outcomes at one-year follow-up (secondary outcomes) did not show differences between antiplatelet strategy.

In our sample, the parenteral anticoagulation therapy more frequently used was enoxaparin (45.1 % versus fondaparinux in 31.7 %), mainly when the DAPT strategy was adopted (49.9 %, p = 0.003), which is not in concordance with what is recommended in the guidelines.

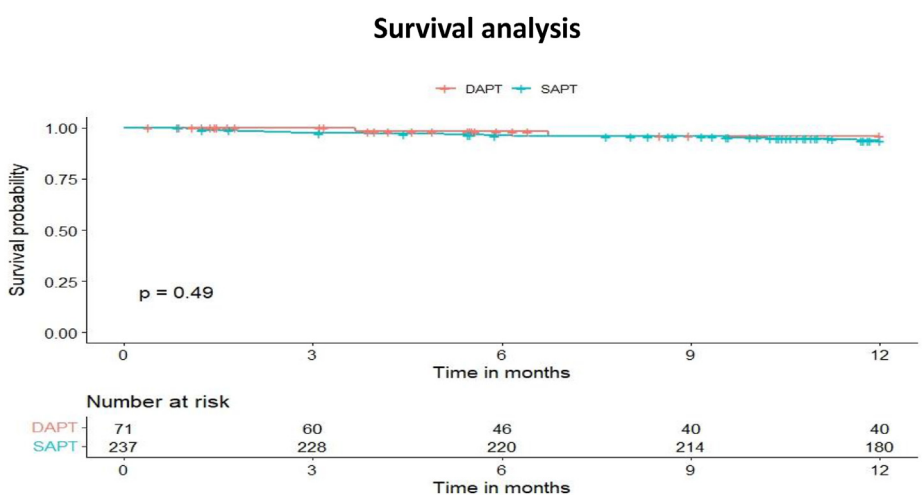
Being able to perform a timely (and thus early) invasive strategy may be challenging, as shown in our data from various Portuguese centers. This may be experienced in other European centers, which highlights the fact that time is of the essence when choosing the ideal antiplatelet regime.

TABLE 4 Multivariable analysis (logistic regression) of predictors of composite primary outcome

	OR (95% CI)	p value
SAPT (vs DAPT)	2,03 (1,20-3,43)	**0,008**
Hypertension	1,91 (1,01-3,59)	**0,031**
Multivessel disease	1,69 (1,02-2,79)	**0,045**
KK class (admission) > I	29,4 (18,1-47,8)	**<0,001**
Time until revascularization > 72 h	3,09 (1,40-6,79)	**0,005**

CI, Confidence interval; DAPT, Dual antiplatelet therapy; KK, Killip and Kimball class; OR, Odds ratio; SAPT, Single antiplatelet therapy.

FIGURE 1 **Kaplan-Meier curve shown time until death (follow-up at 1 year) in NSTE-ACS patients, pretreated with SAPT vs DAPT**



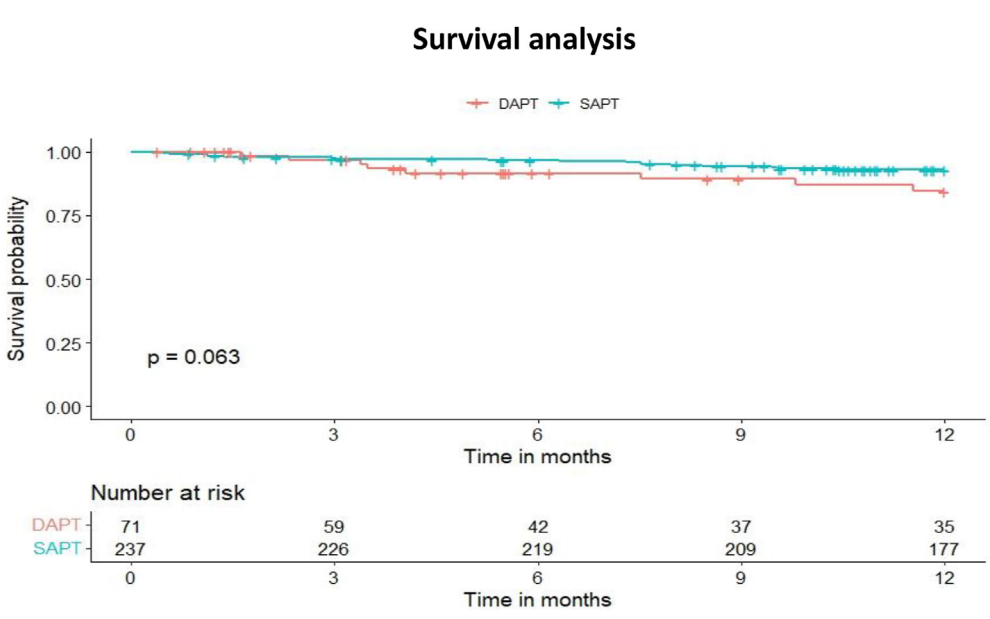
DAPT: Dual antiplatelet therapy; NSTE-ACS: Non-ST elevation acute coronary syndromes; SAPT: Single antiplatelet therapy.

In conclusion, the correct implementation of antiplatelet therapy requires strict adherence to the European guidelines, which include risk stratification of NST-ACS patients for the timing of catheterization.

5. LIMITATIONS

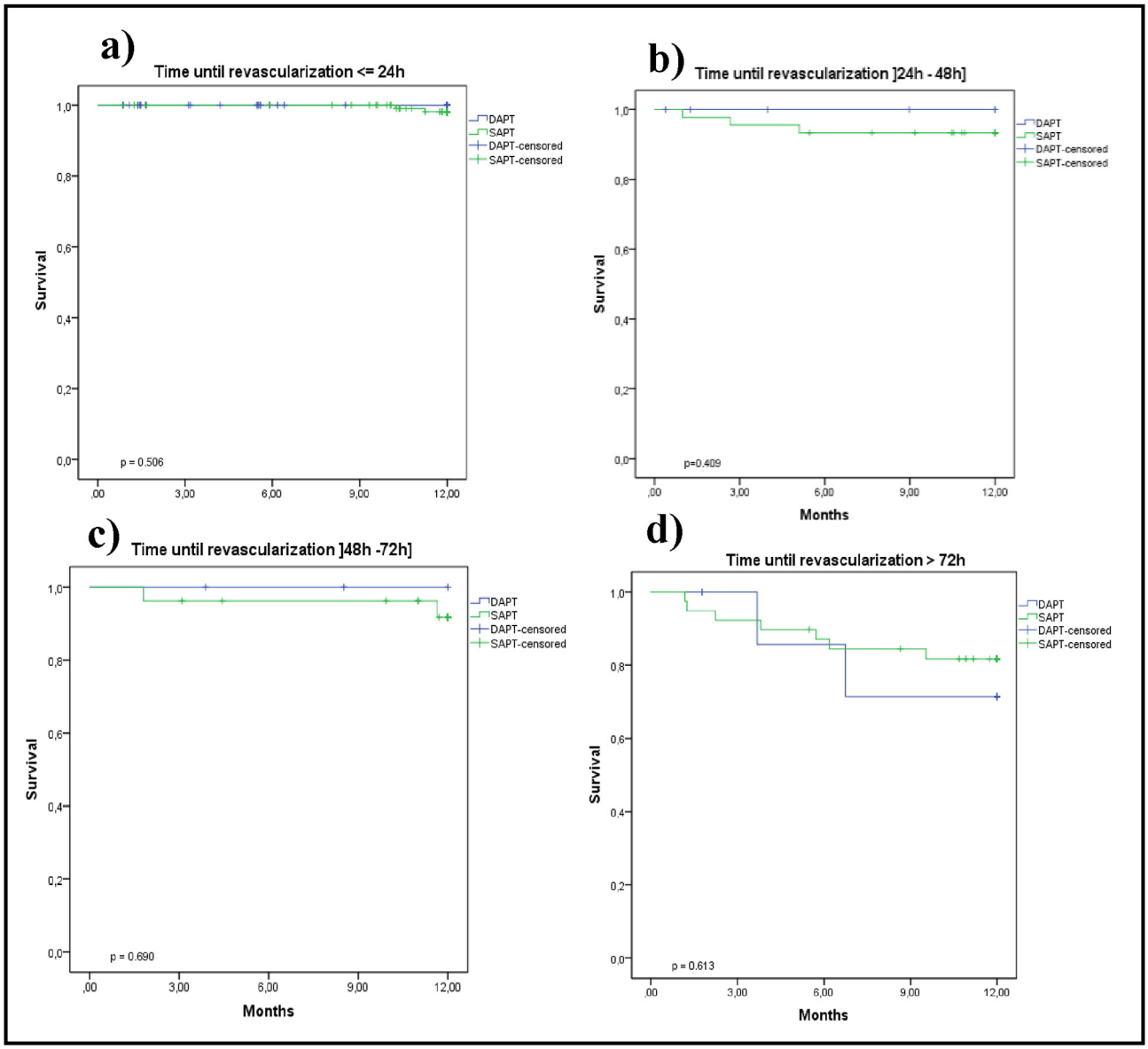
This was a retrospective study in which medical records stored on ProACS were used as the main source

FIGURE 2 **Kaplan-Meier curve shown time until cardiovascular rehospitalization (follow-up at 1 year) in NSTE-ACS patients, pretreated with SAPT vs DAPT**



DAPT: Dual antiplatelet therapy; NSTE-ACS: Non-ST elevation acute coronary syndromes; SAPT: Single antiplatelet therapy.

FIGURE 3 Kaplan-Meier curve shown time until death (follow-up at 1 year) in NSTE-ACS patients, pretreated with SAPT vs DAPT: a) Time until revascularization ≤24 h; b) Time until revascularization [24 h-48 h]; c) Time until revascularization [48 h-72 h]; d) Time until revascularization >72 h. DAPT: Dual antiplatelet therapy; NSTE-ACS: Non-ST elevation acute coronary syndromes; SAPT: Single antiplatelet therapy

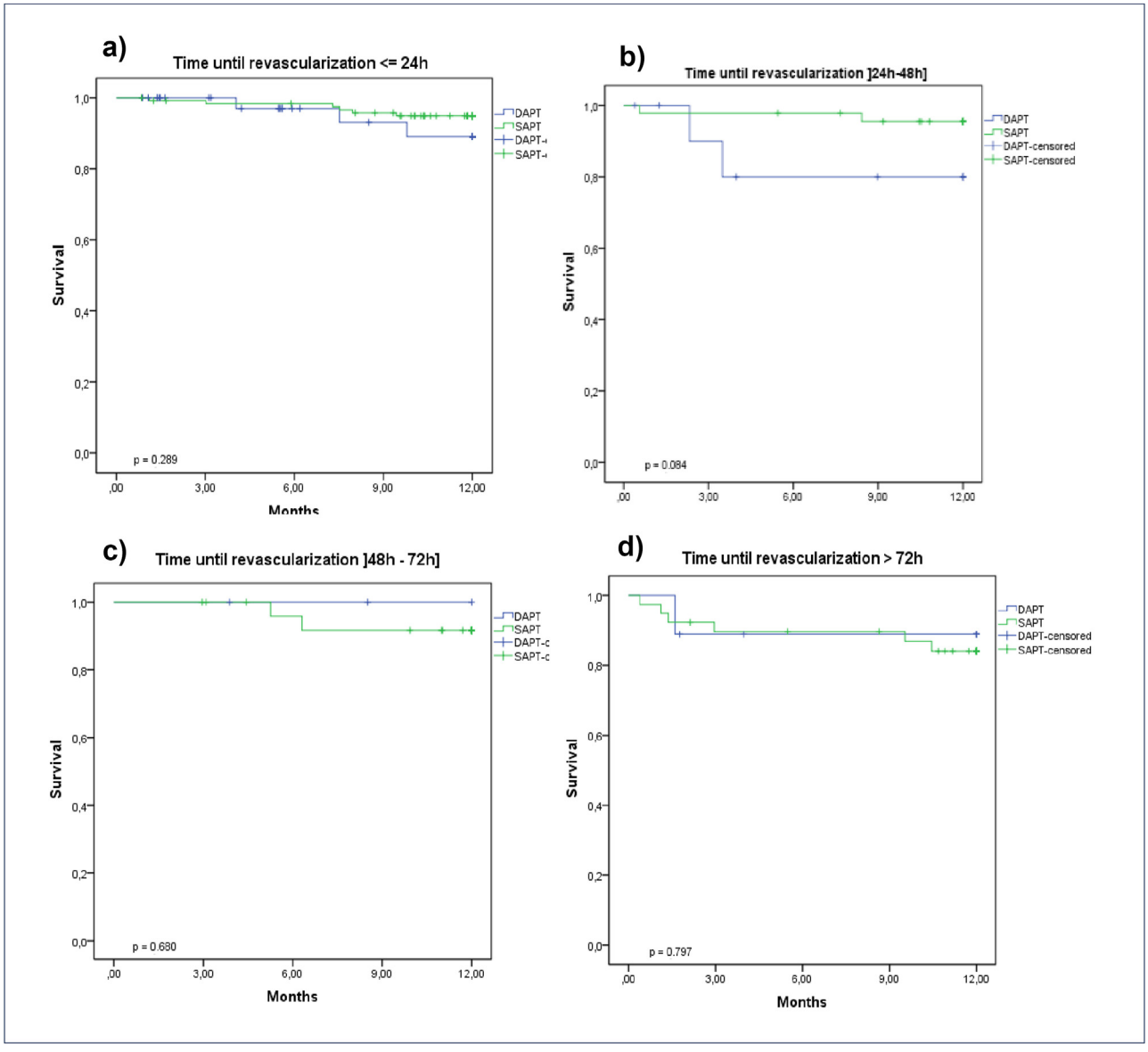


for data collection. The study included data from 2018 to 2021, which in part predates the 2020 guidelines recommending the non-use of routine DAPT in patients for whom an early invasive strategy is planned. Despite including data during the COVID-19 pandemic, data on COVID-19 infection status was not collected but may have influenced the results.

6. CONCLUSIONS

NSTE-ACS patients pretreated with the SAPT strategy had worse in-hospital outcomes, mainly driven by more ischemic events. The study showed a high rate of high-risk patients with an invasive strategy after 24 h, reflecting the difficulty in treating these patients in a timely manner, which may explain our findings.

FIGURE 4 **Kaplan-Meier curve shown time until cardiovascular rehospitalization (follow-up at 1 year) in NSTE-ACS patients, pretreated with SAPT vs DAPT: a) Time until revascularization ≤24 h; b) Time until revascularization [24 h-48 h]; c) Time until revascularization [48 h-72 h]; d) Time until revascularization >72 h. DAPT: Dual antiplatelet therapy; NSTE-ACS: Non-ST elevation acute coronary syndromes; SAPT: Single antiplatelet therapy**



DECLARATION OF COMPETING INTEREST

None.

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