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High medium-term incidence of major cardiovascular events in discharged patients with unstable angina

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ABSTRACT

The introduction of high-sensitivity troponin (hsTn) assays has reduced the diagnosis of unstable angina (UA) in favor of non-ST elevation myocardial infarction (NSTEMI) in the context of non-ST elevation acute coronary syndrome (NSTEACS). It is unclear whether the detection of these hsTn levels affects the prognosis and therefore whether a different therapeutic approach is warranted. This study aims to determine whether using hsTn results in medium-term prognostic differences in patients with UA and NSTEMI.

Methods: This multicenter, prospective registry study included consecutive patients who underwent hsTn assays and were discharged with a diagnosis of NSTEACS. Patients were followed for two years. Outcomes were the occurrence of major adverse cardiovascular events (MACE: cardiovascular death, non-fatal myocardial infarction, and non-fatal ischemic stroke), major bleeding, and all-cause mortality.

Results: Patients with UA and NSTEMI did not show differences in terms of the invasive interventions received, the coronary artery disease diagnosed, the type of revascularization performed, or the proportion presenting MACE (UA 18.1% vs. NSTEMI 18.9%; $p = 0.79$). However, patients with NSTEMI had higher cardiovascular mortality at two years (UA 4% vs. NSTEMI 9.2%; $p = 0.012$), as well as, all-cause mortality (UA vs. 7.9% vs. NSTEMI 16.4%; $p = 0.002$).

Conclusions: Medium-term incidence of MACE was similar in patients with UA and NSTEMI, but cardiovascular and all-cause mortality in NSTEMI patients was over twice that of patients with UA.

1. Introduction

Cardiovascular disease is the main cause of morbidity and mortality worldwide, with acute coronary syndrome (ACS) standing out as one of the most important manifestation. Its three phenotypes are acute ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA). The latter two, encompassed under non-ST elevation acute coronary syndrome (NSTEACS), are considered similar entities, often sharing pathophysiology and prognosis, although NSTEMI differs from UA by the presence of acute myocardial necrosis, associated with a clinical context suggestive of myocardial ischemia [1–3].

The advent of hsTn assays in recent years has enabled the measurement of troponin concentrations that were previously undetectable

Abbreviations: ACS, acute coronary syndrome; NSTEMI, non-ST-elevation myocardial infarction; STEMI, elevation myocardial infarction; UA, unstable angina; NSTEACS, non-ST-segment-elevation acute coronary syndrome; HsTn, high-sensitivity troponin T; MACE, major adverse cardiovascular events; BARC, Bleeding Academic Research Consortium; PCI, percutaneous coronary intervention; ASA, acetylsalicylic acid; AMI, acute myocardial infarction.

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with conventional tests. This ultra-high sensitivity allowed earlier diagnosis and increased the proportion of patients with suspected ACS who are diagnosed with NSTEMI, with a corresponding reduction in diagnoses of UA [1–5].

The European Society of Cardiology's 2020 NSTEACS clinical practice guidelines establish that patients with UA have a substantially lower risk of death and benefit less from intense antiplatelet therapy and invasive treatment in the first 72 h [6]. Recent studies using the hsTnT found prognostic differences between NSTEMI and UA, with higher all-cause mortality at 30 days and at one year in people with NSTEMI [1–6].

However, it is unclear whether the detected hsTnT levels affect patients' short- and medium-term prognosis and in turn whether a different therapeutic approach may be warranted [1–3,5]. The primary aim of this study is to determine if the use of hsTnT results in medium-term prognostic differences in patients with UA versus NSTEMI.

2. Material and methods

2.1. Study design

This is a post-hoc analysis of the ACHILLES registry (AntiagregaCión en HospitaLes del Levante Español), whose design has been described elsewhere [8–10]. Briefly, ACHILLES is an observational, prospective, multicenter, consecutive registry, which analyzed therapeutic management and the use of different treatment strategies and antiplatelet drugs in patients discharged following an ACS.

All adults (≥18 years) discharged with a diagnosis of ACS from participating hospitals over a period of almost two years were consecutively included. Patients who presented ACS during the course of another extracardiac pathology (stroke, sepsis, surgery, or trauma) and those who died during hospitalization were excluded.

Upon inclusion in the registry, data were collected on demographic characteristics, medical history, laboratory parameters, risk estimation, use of antiplatelet agents during admission and after discharge, and therapeutic management. Researchers explained to patients that participation involved the collection of data from their clinical history and face-to-face or telephone check-ups for two years from the date of inclusion. Participants had to sign informed consent to be included in the registry; refusal to do so implied no change in the patients' therapeutic approach, hospital management, or follow-up. The most appropriate treatment strategy (invasive vs. conservative treatment) and pharmacological therapy were established at the discretion of the attending physician.

2.2. Study population

The present analysis included only patients from the ACHILLES registry with a diagnosis of NSTEACS at discharge in whom systematic measurement of hsTn was performed upon admission and serially at least 3 h later.

The final diagnosis of UA or NSTEMI was established according to hsTn levels. Diagnosis of NSTEMI was based on evidence of acute myocardial necrosis, that is, an increase or decrease in hsTn levels with at least one determination in the 99th percentile, in association with symptoms consistent with myocardial ischemia at the discretion of a clinical cardiologist. UA was diagnosed in patients with symptoms consistent with myocardial ischemia at the discretion of a clinical cardiologist but without acute myocardial necrosis, that is, with normal or slightly elevated hsTn levels secondary to other chronic processes, such as heart failure or chronic kidney disease, but without dynamic changes at these levels.

2.3. Ethical considerations

The research protocol is aligned with the Declaration of Helsinki and was approved by the Research Ethics Committees of the three participating hospitals. The Department of Medicines for Human Use, part of the National Agency for Medicines and Medical Devices, also approved this study as an observational, post-authorization study (reference: JRN-NAG-2014–01). An external independent audit of the registry was performed to evaluate the correct inclusion of patients, the analyzed data, and the possible existence of patients not included during the recruitment period in all participating hospitals.

Table 1
Baseline characteristics.

		Unstable angina n (%)*	NSTEMI n (%)*	p value
N		227 (30.4)	519 (69.6)	
Age in years, mean ± SD		66.9 ± 11.5	67.0 ± 13.0	0.93
Male sex		168 (74.0)	363 (69.9)	0.26
Cardiovascular risk factors	Arterial hypertension	179 (79.2)	351 (67.6)	0.001
	Dyslipidemia	165 (72.7)	302 (58.2)	<0.001
	Diabetes mellitus	99 (43.6)	224 (43.2)	0.91
	Body mass index, kg/m^2, mean ± SD	28.9 ± 4.8	28.3 ± 4.5	0.12
	Active tobacco use	61 (27)	182 (35.1)	0.031
	Family history	14 (6.2)	39 (7.5)	0.51
Medical history	Coronary revascularization	100 (40.1)	124 (22.8)	<0.001
	Atrial fibrillation	27 (11.9)	39 (7.5)	0.037
	Stroke or transient ischemic attack	25 (11)	54 (10.4)	0.80
	Peripheral arteriopathy	22 (9.7)	64 (12.3)	0.30
	Renal failure**	49 (21.6)	138 (26.6)	0.09
Prior treatment	Acetylsalicylic acid	128 (56.4)	180 (34.7)	<0.001
	Dual anti-platelets	55 (24.3)	86 (16.6)	0.013
	Oral anticoagulant	36 (15.9)	41 (7.9)	0.001
	ACE inhibitor/ARB	196 (86.3)	443 (85.4)	0.72
	Beta-blockers	199 (87.7)	461 (88.8)	0.65
	Calcium channel blockers	44 (19.4)	71 (13.7)	0.047
	Statins	214 (94.3)	494 (95.2)	0.60
Killip class 3–4		5 (2.2)	29 (5.6)	0.027
Usage of inotropic agents		1 (0.4)	5 (1.0)	0.41

ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; NSTEMI: non-ST-elevation myocardial infarction.
* Unless otherwise noted.
** eGFR < 60 ml/min per 1.73 m^2 by MDRD-4.

2.4. Clinical follow-up and study outcomes

Following patient discharge, follow-up was carried out through personal interviews, telephone calls with patients and family members, and medical records review, over a two-year period.

The primary outcome was the occurrence of major adverse cardiovascular events (MACE), i.e. a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal ischemic stroke. Major bleeding (according to the Bleeding Academic Research Consortium [BARC] classification [7]) and all-cause mortality were also recorded. In all cases, the investigators identified, recorded and classified these endpoints.

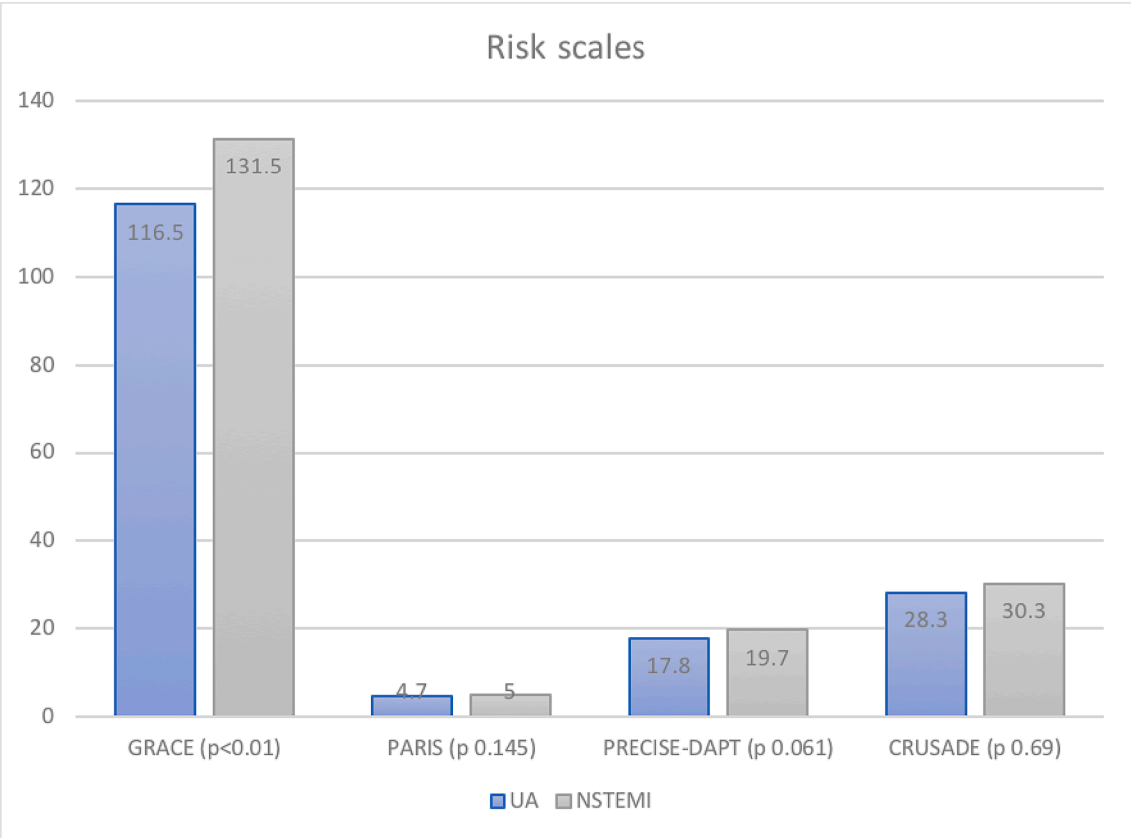

Fig. 1. Risk of in-hospital and long-term mortality, as estimated by GRACE, PARIS, and PRECISE-DAPT scales, in patients with unstable angina versus NSTEMI; plus risk of in-hospital bleeding, estimated using the CRUSADE scale.

2.5. Statistical analysis

Categorical variables were expressed as absolute and relative frequencies and compared using the χ^2 test. For continuous variables, the Kolmogorov-Smirnov test was used to determine the normality of the distribution; values were expressed as mean (standard deviation [SD]) or median (interquartile range [IQR]), as appropriate. Groups were compared according to continuous variables using the student's *t*-test for unpaired data, and the Mann-Whitney *U* test in case of a non-parametric distribution.

Kaplan-Meier survival curves were used to compare time to event, and the log-rank test to compare the survival in patients with UA versus NSTEMI. P values of<0.05 were considered statistically significant. SPSS software (version 25.0, SPSS Inc., Chicago, Illinois, USA) was used for all analyses.

3. Results

Overall, 1717 patients were included in the registry. After excluding STEMI patients and patients from hospitals not using hsTnT assays during the recruitment period, 746 patients met the criteria for NSTEACS and underwent serial hsTnT measurement. Participants were predominantly male (71.2%) with a mean age of 66.9 ± 12.6 years. The diagnosis at discharge was UA in 227 (30.4%) patients and NSTEMI in 519 (69.9%). The treatment approach was mainly invasive, with catheterization performed in 682 patients (91.4%).

3.1. Baseline characteristics

Table 1 describes patients' baseline characteristics according to the diagnosis of UA or NSTEMI. Patients with UA had a higher prevalence of hypertension and dyslipidemia and a lower prevalence of active tobacco use, but there were no differences in terms of diabetes, body mass index, or familiar history of ischemic heart disease. Patients with UA had more previous coronary involvement, while the atherosclerotic involvement of other regions was similar. Regarding patients' baseline treatment, those with UA were more likely to take antiplatelets and oral anticoagulants, but the use of other drugs, such as angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers, beta-blockers, and statins, was similar in both groups.

The estimated risk of mortality according to the GRACE score was significantly lower in patients with UA compared to NSTEMI (116.5 ± 33.9 vs. 131.5 ± 39.8; $p < 0.001$; Fig. 1). Bleeding risk, as quantified with the CRUSADE score, did not show significant differences (28.3 ± 13.5 vs. 30.3 ± 15.4; $p = 0.690$). The PARIS or PRECISE-DAPT score likewise did not show significant differences between patients with UA versus NSTEMI.

3.2. Invasive management and type of revascularization

Regarding the therapeutic approach, we did not find substantial differences between patients with UA versus NSTEMI. Similarly, high proportions underwent coronary angiography (90.7% vs 91.7%; $p = 0.670$; Table 2). The main reasons for not performing this procedure were: already known anatomy (27.1%), patient comorbidity (23.7%), advanced age (18.6%), patient refusal (10.2%), negative ischemia test (6.8%), atypical or low-risk pain (6.8%), and other causes (6.8%). The prevalence of coronary heart disease was also similar (p = ns).

The treatment received (percutaneous coronary intervention [PCI], coronary artery bypass surgery, or medical treatment) was also similar in both groups, as was the number of revascularized arteries and stents implanted. Revascularization was complete in a similar proportion of patients (71.3% in UA vs. 71.9% in NSTEMI; $p = 0.900$).

Table 2
Invasive treatments.

Intervention	Unstable angina (N = 227) n (%)*	NSTEMI (N = 519) n (%)*	p value
Coronary angiography	206 (90.7)	476 (91.7)	0.67
Early coronary angiography (<24 h)	12 (5.3)	58 (11.2)	0.011
Radial artery access	186 (82.3)	429 (82.8)	0.86
Findings of coronary angiography			
Normal /no significant lesions	35 (16.9)	66 (13.8)	0.30
1 vessel	62 (30)	146 (30.7)	0.85
2 vessels	46 (22.2)	112 (23.7)	0.67
3 vessels	48 (23.2)	125 (26.3)	0.40
Involvement of left common trunk	16 (7.7)	26 (5.5)	0.26
Type of revascularization			
PCI	132 (58.1)	310 (59.7)	0.69
Coronary artery bypass surgery	18 (7.9)	52 (10)	0.37
Medical treatment	77 (33.9)	157 (30.3)	0.32
N revascularized arteries	1.51 ± 0.7	1.57 ± 0.7	0.36
Complete revascularization	107 (71.3)	258 (71.9)	0.90
PCI			
≥ 1 pharmacoactive stents	114 (87)	259 (84.9)	0.57
Total N stents implanted, mean ± SD	1.73 ± 1.2	1.75 ± 1	0.90
Total length of implanted stents, mm, mean ± SD	5.97 ± 5.2	6.37 ± 5.1	0.88

PCI: percutaneous coronary intervention; NSTEMI: non-ST-elevation myocardial infarction; SD: standard deviation.
* Unless otherwise noted.

Table 3
Medical treatment on discharge.

Treatment	Unstable angina (N = 227) n (%)	NSTEMI (N = 519) n (%)	p value
Acetylsalicylic acid	219 (96.5)	494 (95.2)	0.43
Clopidogrel	125 (55.1)	274 (52.7)	0.57
Ticagrelor/prasugrel	55 (24.2)	176 (34.0)	0.008
Dual anti-platelet	180 (79.3)	450 (86.7)	0.01
Oral anticoagulant	37 (16.3)	69 (13.3)	0.28
ACE inhibitors/ARBs	182 (80.2)	403 (77.6)	0.44
Beta-blockers	196 (86.3)	433 (83.6)	0.34
Calcium channel blockers	45 (19.8)	93 (17.9)	0.54
Statins	215 (94.7)	483 (93.1)	0.40

ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blockers; NSTEMI: non-ST-elevation myocardial infarction.

3.3. Medical treatment upon discharge

Medical treatment at discharge was similar in terms of the indication for acetylsalicylic acid (ASA), ACE inhibitors, beta-blockers, and statins (Table 3). A lower proportion of patients with UA received dual antiplatelet agents (79.3% vs. 86.7%; p = 0.010) or the more potent $P2Y_{12}$ inhibitors, ticagrelor and prasugrel. (24.2% vs. 34.0%; p = 0.008).

3.4. Medium-term prognosis

Clinical follow-up was performed in 96.3% of the patients, with a median duration of 2.7 years (IQR 1.6–3.7). At two years, all-cause mortality and cardiovascular mortality rates in the UA group were roughly half of those compared to patients with NSTEMI (all-cause: 7.9% vs 16.4%, p = 0.002; cardiovascular mortality: 4.0% vs 9.2%, p = 0.012; Table 4). However, no differences were observed in terms of MACE (18.1% vs 18.9%; p = 0.790), non-fatal acute myocardial infarction (11.0% vs 9.1%; p = 0.410), non-fatal stroke (4.0% vs 3.3%; p = 0.640; Fig. 2) or unplanned revascularization (6.2% vs 7.6; p = 0.350).

Table 4
Events at two-year follow-up.

	Unstable angina (N = 227) n (%)	NSTEMI (N = 519) n (%)	p value
Ischemic events			
Total MACE	41 (18.1)	98 (18.9)	0.79
Cardiovascular death	9 (4.0)	48 (9.2)	0.012
Non-fatal myocardial infarction	25 (11.0)	47 (9.1)	0.41
Non-fatal stroke	9 (4.0)	17 (3.3)	0.64
Unplanned revascularization	13 (6.2)	36 (7.6)	0.35
All-cause mortality	18 (7.9)	85 (16.4)	0.002
Bleeding events			
BARC 1–5	36 (15.9)	67 (12.9)	0.28
BARC 2–5	30 (13.2)	50 (9.6)	0.15
BARC 3–5	10 (4.4)	15 (2.9)	0.29

BARC: Bleeding Academic Research Consortium; MACE: major adverse cardiovascular events; NSTEMI: non-ST-elevation myocardial infarction.

Causes of cardiovascular death were similar in both groups: heart failure (33.3% vs 35.4%; p = NS), fatal ischemic events (44.4% vs 33.4%; p = NS) and sudden death (22.3% vs 31.2%; p = NS).

Bleeding events were also similar between groups (15.9% vs. 12.9%; p = 0.280 for BARC 1–5 bleeding; 13.2% vs. 9.6%; p = 0.150 for BARC 2–5 bleeding; and 4.4% vs. 2.9%; p = 0.290 for BARC 3–5 bleeding).

4. Discussion

The main findings of this prospective registry study, in patients hospitalized for NSTEACS with medium-term follow-up, were as follows: a) patients diagnosed with UA show the same prevalence of coronary artery disease as patients with NSTEMI; b) they are managed in a similar way in terms of invasive management and revascularization, but with a lower proportion of dual antiplatelet agents or new antiplatelet agents; c) the incidence of major cardiovascular events in the medium term is similar in both groups, although cardiovascular and all-cause mortality from NSTEMI is over twice that of patients diagnosed with UA.

In a current population hospitalized for NSTEACS, patients diagnosed with UA show the same prevalence of coronary artery disease as patients with NSTEMI. The incidence of major cardiovascular events in the medium term is similar in both groups, although cardiovascular and all-cause mortality from NSTEMI is over twice that of patients diagnosed with UA.

Our findings corroborate previous studies, which determined that the more sensitive the TnT used for diagnosing the ACS, the less likely it is to misclassify an NSTEMI as a UA, which leads to a lower incidence of UA [1,4]. Shah et al. observed that the use of hsTn led to a reclassification of some patients from UA to NSTEMI, without any decrease in the incidence of AMI or cardiovascular death at one year [3]. In our study, we found a ratio of UA to NSTEMI of approximately 1:2 (30.1% vs 69.9%).

In line with the literature, our UA patients generally presented a higher prevalence of cardiovascular risk factors and prior coronary involvement, including prior coronary revascularization. When applying the different risk stratification schemes, patients with UA did not present differences in long-term mortality risk according to the PARIS and PRECISE-DAPT score or in bleeding risk according to CRUSADE. The only difference observed at this level was a lower risk of

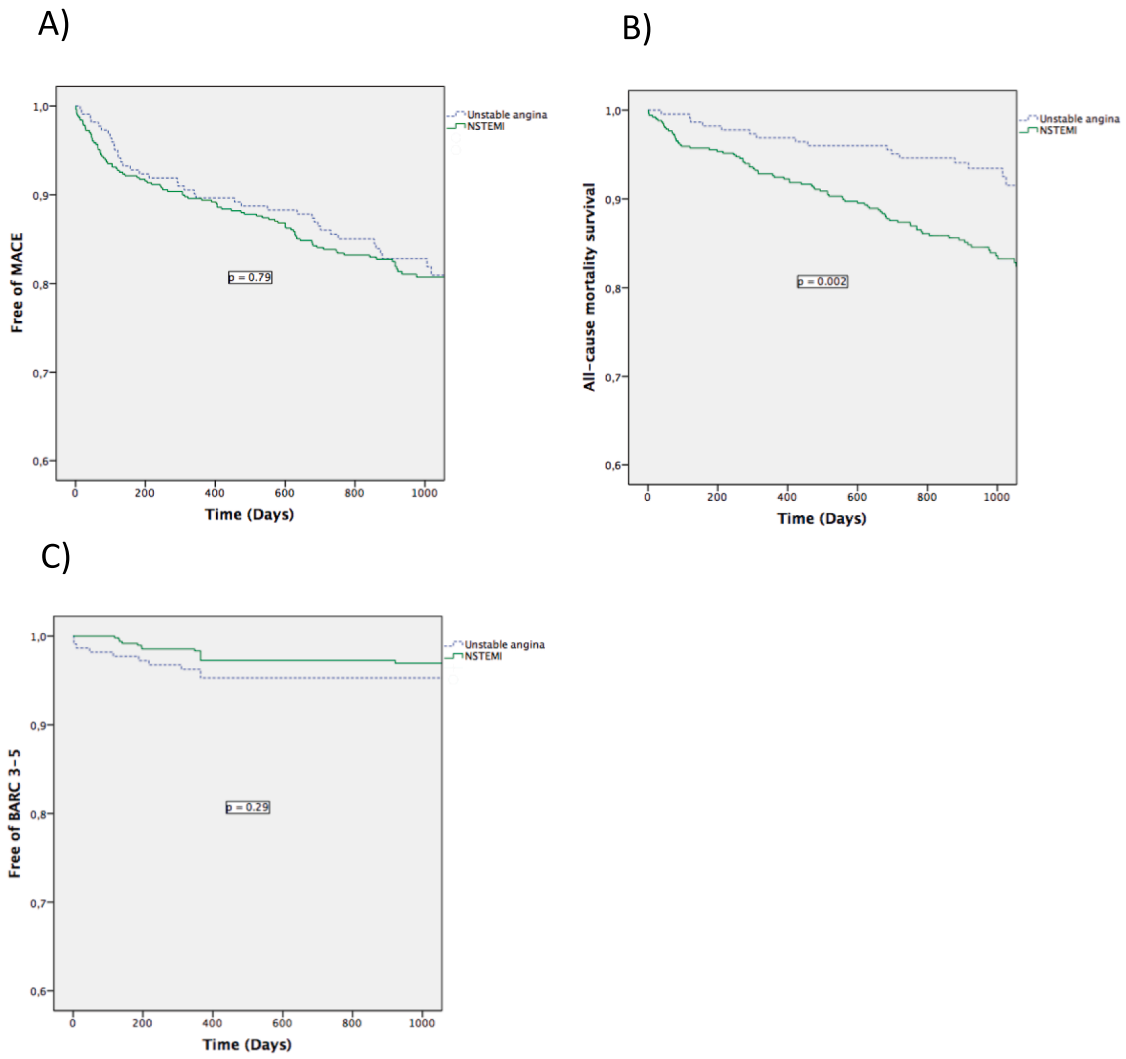

Fig. 2. Kaplan-Meier survival curves in the two predefined subgroups. A: Kaplan-Meier survival curve for major adverse cardiovascular events (MACE: cardiovascular death, non-fatal stroke and acute non-fatal myocardial infarction). Log-rank test (Mantel-Cox); p = 0.79. B: Kaplan Meier survival curve for all-cause mortality. Log-rank test (Mantel-Cox); p = 0.002. C: Kaplan Meier survival curve for BARC 3–5 bleeding events. Log-rank test (Mantel-Cox); p = 0.29.

in-hospital mortality, as determined by the GRACE score.

Assessing prognostic differences in people with UA and NSTEMI requires an examination of how these entities have been managed. In our population, no differences were observed between patient groups with regard to the treatment received (PCI, coronary artery bypass surgery, or medical treatment), the coronary disease found, the number of revascularized arteries, the number and total length of stents implanted, or the type of stents implanted. There was less use of dual antiplatelet therapy upon discharge in patients with UA, as well as less use of the new antiplatelet agents, ticagrelor and prasugrel, compared to patients with NSTEMI. This could reflect a more favorable prognosis in patients with UA and therefore the use of less aggressive therapies.

At two years, patients with NSTEMI showed twice the cardiovascular mortality of patients with UA. This finding corroborates the results of previous studies. Reichlin et al. also observed higher all-cause mortality at 30 months in NSTEMI compared to UA (16% vs. 5%; $p < 0.001$).[4] Likewise, in the Thrombolysis in Myocardial Infarction 3 trial, mortality at 42 days was over twice as high in patients with NSTEMI compared to patients with UA [2].

However, the incidence of MACE, AMI and acute stroke was similar between groups. These findings are consistent with other studies observing a high rate of non-fatal AMI at one year follow-up in patients with UA (11.0%), similar to that seen in patients with NSTEMI [1]. These results underline that UA is not a benign pathology, and although incidence and mortality is lower than with NSTEMI, the risk of MACE, AMI, and acute stroke is similar.

The observed differences in prognosis raise questions about whether clinical management should actually be different. In an observational study, Eggers et al. found that the benefit of performing invasive management of patients with NSTEACS depended on hsTn levels, with the reduction in the risk of cardiovascular events starting at hsTn levels of more than 30 ng/L [11]. Thus, there may be room for improvement in the prognosis of UA, justifying new studies to clarify whether less use of intense antiplatelet therapy and early invasive treatment in patients with UA, as indicated by the latest guidelines of the European Society of Cardiology guidelines, may affect patients' prognosis in the medium and long term.

5. Limitations

Our study has some limitations. First, it is a substudy of an observational registry, designed primarily to analyze the therapeutic management of patients discharged after an ACS and taking antiplatelet drugs. Second, in the absence of objective criteria, the diagnosis of UA

continues to pose challenges. Thus, some patients with chest pain of non-coronary origin may have been classified as having UA, especially those with a known history of coronary disease, and vice versa. Third, there were some baseline differences between groups, such as the prevalence of cardiovascular risk factors, treatments, and therapeutic approach. No analysis was performed to determine whether these differences may have affected the results. Lastly, we did not evaluate whether the rate of MACE and AMI may be influenced by less aggressive medical management in patients with UA, who were less likely to receive dual antiplatelet therapy or new antiplatelet agents.

6. Conclusions

In a current population hospitalized for NSTEACS, patients diagnosed with UA show the same prevalence of coronary artery disease as patients with NSTEMI. The incidence of major cardiovascular events in the medium term is similar in both groups, although cardiovascular and all-cause mortality from NSTEMI is over twice that of patients diagnosed with UA.

Declaration of Competing Interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: 'This study has been partially supported by a Research Grant from the Spanish Society of Cardiology (SEC).'

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