European Journal of Internal Medicine 137 (2025) 83–89

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

# NT-proBNP to guide risk stratification after cardiac rehabilitation in patients with ST-segment elevation myocardial infarction

Nerea Pérez-Solé [a,b,1], Elena de Dios [b,*], José Gavara [a,b], César Ríos-Navarro [a,b,d], Víctor Marcos-Garces [a,b,c], Héctor Merenciano [a,b,c], Josefina I Climent [e], Laura López-Bueno [e], Alfonso Payá [e], Rafael de la Espriella [a,b,c], Antoni Bayés-Genís [b,g,h], Manuel Jiménez-Navarro [b,i,j,k], Francisco Marín [b,l], Julio Núnez [a,b,c,f], Juan Sanchis [a,b,c,f], Vicente Bodí [a,b,c,f,*]

[a] Instituto de Investigación Sanitaria INCLIVA, Valencia, , España
[b] Centro de Investigación Biomédica en Red - Cardiovascular (CIBER-CV), Madrid, España
[c] Servicio de Cardiología, Hospital Clínico Universitario de Valencia, Valencia, España
[d] Departamento de Patología, Facultad de Medicina y Odontología, Universidad de Valencia, Valencia, España
[e] Servicio de Rehabilitación, Hospital Clínico Universitario de Valencia, Valencia, España
[f] Departamento de Medicina, Facultad de Medicina y Odontología, Universidad de Valencia, Valencia, España
[g] Servicio de Cardiología y Unidad de Insuficiencia Cardiaca, Hospital Universitari Germans Trias i Pujol, Badalona, España
[h] Departamento de Medicina, Universitat Autonoma de Barcelona, Barcelona, España
[i] Servicio de Cardiología y Cirugía Cardiovascular-Área del Corazón, Hospital Universitario Virgen de la Victoria, Málaga, España
[j] Instituto de Investigación Biomédica de Málaga y Plataforma en Nanomedicina (IBIMA Plataforma BIONAND), Málaga, España
[k] Departamento de Medicina y Dermatología, Facultad de Medicina, Universidad de Málaga, Málaga, España
[l] Servicio de Cardiología, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, España

ARTICLE INFO

*Keywords:*
St-segment elevation myocardial infarction
N-terminal pro-brain natriuretic peptide
Cardiovascular magnetic resonance
Prognosis
Rehabilitation

ABSTRACT

*Introduction and objectives:* The use of N-terminal pro-brain natriuretic peptide (NT-proBNP) after ST-segment elevation acute myocardial infarction (STEMI) is unclear. We evaluated its prognostic significance after post-STEMI cardiac rehabilitation.

*Methods:* The prognostic significance of NT-proBNP was tested upon completion of cardiac rehabilitation (median, 45 days post-STEMI) in an exploratory group ($n = 105$ patients with the researchers blinded to NT-proBNP values) and validated in the following 276 patients. Baseline and cardiac imaging variables including cardiovascular magnetic resonance (CMR) parameters were recorded. The primary endpoint was the occurrence of a first major adverse cardiac event (MACE: cardiac death, myocardial infarction, or re-admission for heart failure).

*Results:* In the exploratory group, a cut-off value of NT-proBNP >400 pg/mL emerged as a potent MACE predictor (37 % vs.17 %; hazard ratio [HR]: 6.8 [1.5–30.3], $p = 0.01$). In the study group, during a 203-week median follow-up, 88 (32 %) first MACEs were detected. NT-proBNP >400 pg/mL ($n = 168$, 61 %) associated with a higher MACE rate (46 % vs. 10 %, HR: 4.6 [2.3–8.9], $p < 0.001$) and, separately, with more cardiac deaths, myocardial infarctions, and re-admissions for heart failure ($p < 0.05$ for all comparisons). NT-proBNP improved the multivariate model for MACE prediction (area under the curve 0.81 vs. 0.72, $p < 0.001$).

*Conclusions:* Even after comprehensive adjustment, NT-proBNP emerges as a potent, accessible and inexpensive tool for risk stratification of STEMI patients after completion of rehabilitation programs.

## 1. Non-standard abbreviations and acronyms

ACEi = Angiotensin-converting enzyme inhibitors
ARAII = Angiotensin II receptor antagonists
ARNi = Angiotensin receptor neprilysin inhibitors
AUC = Area under the curve

* Correspondence author.
*E-mail address:* vicente.bodi@uv.es (V. Bodí).
[1] These authors contributed equally.

https://doi.org/10.1016/j.ejim.2025.04.027
Received 29 January 2025; Received in revised form 25 March 2025; Accepted 18 April 2025
Available online 1 May 2025

BARI = Bypass Angioplasty Revascularization Investigation
CMR = Cardiovascular magnetic resonance
DAPT = Dual antiplatelet therapy
DM = Diabetes mellitus eGFR = Estimated glomerular filtration rate
GRACE = Global Registry of Acute Coronary Events
HDL = High density lipoprotein
HR [95 % CI] = Hazard ratio [95 % confidence interval]
IDI = Integrated Discrimination Improvement
ICD = Implantable cardioverter defibrillator
IS = Infarct size
LDL = Low-density lipoprotein
LV = Left ventricular
LVEF = Left ventricular ejection fraction
MACE = Major adverse cardiac event
MVO = Microvascular obstruction
NRI = Net Reclassification Improvement
NT-proBNP = *N*-terminal pro-brain natriuretic peptide
STEMI = ST-segment elevation myocardial infarction

## 2. Introduction

N-terminal pro-brain natriuretic peptide (NT-proBNP) is the reference biomarker for risk stratification of subsequent events in heart failure [1]. However, in the context of patients with ST-segment elevation myocardial infarction (STEMI), its use is much less established [2,3]. Although studies, particularly in the acute phase, have linked higher NT-proBNP levels with worse clinical outcomes [4–6], current guidelines scarcely include specific recommendations regarding the routine analysis of this parameter following an infarction.

Patients with STEMI should be referred to a cardiac rehabilitation program after hospital discharge [2]. At the conclusion of this program, it is crucial to predict the likelihood of subsequent events as reliably as possible [2,3]. This is important, among other reasons, to define individualized life expectations for each patient, including their possibilities and circumstances for returning to work. Currently, this risk stratification process is usually based on clinical variables derived from complementary examinations and imaging techniques, which in some cases include cardiovascular magnetic resonance (CMR) [2,3,7]. At this stage, the analysis of NT-proBNP could provide objective, easily accessible, and cost-effective information. However, data regarding the utility of this biomarker for this specific purpose are not available.

In the present study, we analyze the prognostic value of NT-proBNP determination after completing cardiac rehabilitation in predicting subsequent major adverse cardiac events (MACE: cardiac death, myocardial infarction, or rehospitalization due to heart failure), beyond clinical variables and cardiac imaging, in a homogeneous series of STEMI patients treated with primary angioplasty, evaluated with CMR, and who have completed a phase 2 cardiac rehabilitation program.

## 3. METHODS

### 3.1. Study group

The study population included a registry of consecutive patients who, after hospitalization for STEMI treated with primary angioplasty, were referred to a cardiac rehabilitation program at a tertiary hospital and completed phase 2 of the program. Patients were treated, in the acute phase and during the rehabilitation process, at the same center. In all cases, a CMR study was performed prior to the start of phase 2 (median 7 days), and NT-proBNP values (pg/mL) were measured at the end of phase 2 (median 45 days) using an immunoassay (Elecsys NT-proBNP assay, Roche Diagnostics, Indianapolis, USA).

The study adhered to the Declaration of Helsinki. Approval was obtained from the local ethics committee, and all patients provided written informed consent for their inclusion in the registry. Clinical and complementary testing information was collected prospectively. Authorized personnel, including cardiologists and research nurses, recorded the occurrence of MACE during follow-up visits or through the electronic health record system of the regional healthcare system.

The study was conducted in two phases. An exploratory cohort of 105 STEMI patients treated between January and December 2015 was analyzed. NT-proBNP samples were sent to an external laboratory, and the researchers did not have access to NT-proBNP results during this phase. After patient follow-up, the biomarker's association with subsequent MACE and the optimal predictive threshold were determined. The flowchart of patients is shown in Supplementary Figure 1, and the cohort characteristics are in Supplementary Table 1.

The definitive cohort comprised 276 STEMI patients treated between January 2018 and October 2020, whose NT-proBNP samples were analyzed in the institution's central laboratory. Cardiologists had access to NT-proBNP results in this phase. The flowchart of patients and exclusion reasons are shown in Supplementary Figure 1, while the cohort characteristics are presented in Table 1.

Baseline clinical characteristics, the "Global Registry of Acute Coronary Events (GRACE)" risk score [2,3], and basic angiographic data including the "Bypass Angioplasty Revascularization Investigation (BARI)" disease burden score were recorded (Table 1).

All patients underwent echocardiography and CMR studies (5±2 and 7±2 days post-STEMI, respectively). Patients participated in a post-STEMI phase 2 cardiac rehabilitation program involving successive visits and personalized training for 45 days post-discharge. NT-proBNP levels obtained at this point were used to evaluate the biomarker's utility in predicting a subsequent first MACE. Detailed descriptions of imaging procedures [7] and rehabilitation protocols [8] are provided in the References and Supplementary Materials.

### 3.2. Objective

The study aimed to analyze the prognostic value of NT-proBNP measured at the end of phase 2 cardiac rehabilitation in predicting a first subsequent MACE (cardiac death, myocardial infarction, or heart failure rehospitalization) in STEMI patients treated with percutaneous reperfusion.

### 3.3. Statistical analysis

Data normality was assessed using the Kolmogorov-Smirnov test. Continuous normally distributed data were expressed as mean ± standard deviation and compared using the Student's *t*-test for unpaired samples. Non-parametric data were expressed as median [quartile 1 – quartile 3] and compared using the Mann-Whitney U test. Percentages were compared using the Chi-square test or Fisher's exact test when appropriate. A p-value for trend was used to compare more than two percentages.

In the exploratory group, the best NT-proBNP cutoffs values for predicting subsequent MACE were determined using the Youden's index and were 395 pg/mL and 407 pg/mL (with equal precision). For simplicity in routine application, a cutoff value of 400 pg/mL, aligning with the upper normal limit for the immunoassay used in our institution's central laboratory, was prospectively tested in the definitive study group. Kaplan-Meier survival curves and log-rank tests were used to assess the associations between NT-proBNP (categorized by the 400 pg/mL cutoff and by the respective quartiles) and the time to first MACE occurrence.

Multivariate Cox regression models were used for MACE prediction (Table 2) following a hierarchical approach. 1) Baseline model: Included patient presentation characteristics, excluding echocardiography and CMR-derived variables. Variables significantly associated with MACE ($p < 0.05$, Table 1) were evaluated. 2) Final model without NT-proBNP: Included independent variables from the baseline model, along with echocardiography and CMR variables significantly associated with MACE. 3) Final model with NT-proBNP: Included all independent

**Table 1**
Baseline, echocardiographic, and CMR characteristics of the study group and of patients with and without MACE.

| | Total $n = 276$ | MACE | | p-value |
|---|---|---|---|---|
| | | Yes ($n = 88$) | No ($n = 188$) | |
| **Age (years)** | 61±12 | 65±13 | 60±12 | 0.009 |
| **Male sex (%)** | 215 (78) | 64 (73) | 151 (81) | 0.11 |
| **DM (%)** | 71 (26) | 33 (37) | 38 (20) | 0.002 |
| **Hypertension (%)** | 135 (49) | 45 (51) | 90 (48) | 0.67 |
| **Hypercholesterolemia (%)** | 128 (47) | 38 (43) | 90 (48) | 0.42 |
| **Current smoker (%)** | 134 (49) | 41 (47) | 93 (50) | 0.63 |
| **GRACE score** | 126±37 | 145±40 | 118±33 | <0.001 |
| **Proximal LAD** | 96 (36) | 30 (35) | 66 (37) | 0.78 |
| **BARI score** | 27 [24–30] | 28 [24–32] | 26 [21–30] | 0.45 |
| **Multivessel disease (%)** | 116 (42) | 41 (47) | 75 (40) | 0.29 |
| **Atrial fibrillation (%)** | 37 (13) | 25 (28) | 12 (6) | <0.001 |
| **Echo indices** | | | | |
| **LVEF (%)** | 49±12 | 45±13 | 51±10 | <0.001 |
| **LV end-diastolic volume (mL)** | 111±40 | 121±46 | 103±33 | 0.06 |
| **LV end-systolic volume (mL)** | 60±32 | 72±36 | 48±24 | 0.003 |
| **E wave velocity (m/s)** | 3±13 | 4±12 | 3±13 | 0.88 |
| **A wave velocity (m/s)** | 4±14 | 5±17 | 3±12 | 0.58 |
| **Left atrium diameter (mm)** | 36±5 | 38±5 | 35±5 | 0.01 |
| **CMR indices** | | | | |
| **LVEF (%)** | 49±13 | 45±14 | 51±12 | <0.001 |
| **LV end-diastolic volume ($mL/m^2$)** | 81±22 | 85±29 | 79±18 | 0.03 |
| **LV end-systolic volume ($mL/m^2$)** | 43±21 | 50±27 | 39±16 | <0.001 |
| **IS (% of LV mass)** | 26±15 | 29±17 | 24±14 | 0.05 |
| **MVO (n of segments)** | 2.6±3.8 | 3.2±4.7 | 2.3±3.2 | 0.14 |
| **Treatment** | | | | |
| **Acetylsalicylic acid (%)** | 268 (97) | 86 (98) | 182 (97) | 0.67 |
| **DAPT (%)** | 268 (97) | 86 (98) | 182 (97) | 0.67 |
| **Statins (%)** | 271 (98) | 88 (100) | 183 (97) | 0.12 |
| **ACEi (%)** | 158 (57) | 48 (54) | 110 (58) | 0.53 |
| **ARAII (%)** | 51 (18) | 20 (23) | 31 (16) | 0.3 |
| **Beta-blockers (%)** | 252 (91) | 78 (89) | 174 (93) | 0.28 |
| **Diuretics (%)** | 49 (18) | 24 (27) | 25 (13) | 0.005 |
| **Anticoagulants (%)** | 46 (17) | 19 (22) | 27 (14) | 0.13 |
| **Mineralocorticoid receptor antagonist (%)** | 65 (26) | 26 (34) | 39 (22) | 0.04 |
| **Sacubitril- Valsartan (%)** | 18 (8) | 6 (8) | 12 (7) | 0.78 |
| **ICD (%)** | 31 (11) | 20 (23) | 11 (6) | <0.001 |
| **Biochemistry** | | | | |
| **Creatinine (mg/dL)** | 1.3±4.7 | 1±0.4 | 1.4±5.7 | 0.56 |
| **eGFR ($mL/min/1.73m^2$)** | 84±45 | 82±45 | 85±46 | 0.54 |
| **Haemoglobin (g/dL)** | 14±2.7 | 13±1.8 | 14±3 | 0.003 |
| **Cholesterol (mg/dL)** | 131±36 | 134±40 | 129±34 | 0.24 |
| **HDL cholesterol (mg/dL)** | 41±12 | 41±14 | 41±11 | 0.87 |
| **LDL cholesterol (mg/dL)** | 76±27 | 79±29 | 74±26 | 0.14 |
| **Triglycerides (mg/dL)** | 124±58 | 132±59 | 120±58 | 0.12 |
| **NTproBNP (pg/mL)** | 578 [221–1383] | 1419 [739–3538] | 368 [137–838] | <0.001 |

**Abbreviations:** ACEi: Angiotensin-converting enzyme inhibitors; ARAII: Angiotensin II receptor antagonists; ARNi: Angiotensin receptor neprilysin inhibitors; BARI: Bypass Angioplasty Revascularization Investigation; CMR: Cardiovascular magnetic resonance; DAPT: Dual antiplatelet therapy; DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; GRACE: Global Registry of Acute Coronary Events; HDL: High density lipoprotein; ICD: Implantable cardioverter defibrillator; IS: Infarct size; LAD: Left anterior descending; LDL: Low-density lipoprotein; LV: Left ventricular; LVEF: Left ventricular ejection fraction; MVO: Microvascular obstruction; MACE: Major adverse cardiac event; NT-proBNP: N-terminal pro-brain natriuretic peptide.
For patients with atrial fibrillation at the time of echocardiography, the respective velocities of the E and A waves were not included in the analyses.

variables plus NT-proBNP tested as a categorical variable (both using the pre-defined cutoff value of 400 pg/mL and the categorization in quartiles) and a continuous variable (log-transformed due to its non-parametric distribution).

Hazard ratios (HR) with 95 % confidence intervals (CI) for independent variables ($p < 0.05$) were calculated. Proportional hazards assumptions were validated using Schoenfeld residuals ($p > 0.05$), and collinearity was regarded as statistical tolerance <0.20 or variance inflation factor >5.

The areas under the curve (AUC) for MACE prediction of the final models "with" and "without" NT-proBNP were calculated and compared. Risk reclassification improvement by the inclusion of NT-proBNP in the predictive model was assessed using the Integrated Discrimination Improvement (IDI) and Net Reclassification Improvement (NRI) tests.

Additionally, three exploratory objectives (not pre-specified) were analyzed. 1) Associations between NT-proBNP levels (above or below 400 pg/mL) and the number/duration of hospitalizations due to acute coronary syndrome, heart failure, and non-cardiac causes. 2) Associations between NT-proBNP levels and cumulative incidences of cardiac death, myocardial infarction, and heart failure as separate events (analyzed using the Pepe and Mori test for competing events). 3) Association of the dynamics of NT-proBNP (above/below 400 pg/mL) from pre-discharge to post-phase 2 cardiac rehabilitation in the 233 patients with available pre-discharge NT-proBNP values.

Statistical significance was set at a bilateral $p < 0.05$. Analyses were performed using SPSS (v15.0, SPSS Inc., Chicago, IL) and STATA (v9.0, StataCorp, College Station, TX).

## 4. Results

### 4.1. Exploratory group

The flowchart of the 105 patients included is shown in

**Table 2**
Predictors of MACE: Multivariate analysis of the "baseline", "final without NT-proBNP", and "final with NT-proBNP" models in the study group.

| Baseline Model | | |
|---|---|---|
| | **HR [95 % IC]** | **p-value** |
| **DM (%)** | 1.7 [1.1–2.7] | 0.01 |
| **GRACE score** | 1.01 [1.01–1.02] | <0.001 |
| **Final Model without NT-proBNP** | | |
| | **HR [95 % IC]** | **p-value** |
| **DM (%)** | 1.9 [1.2–2.9] | 0.005 |
| **GRACE score** | 1.01 [1.01–1.02] | <0.001 |
| **LVEF (%)** | 0.97 [0.95–0.98] | <0.001 |
| **Final Model with NT-proBNP** | | |
| | **HR [95 % IC]** | **p-value** |
| **DM (%)** | 1.6 [1–2.5] | 0.03 |
| **GRACE score** | 1 [0.99–1.01] | 0.21 |
| **LVEF (%)** | 1 [0.98–1] | 0.38 |
| **$Log_{10}$ NT-proBNP** | 4.2 [2.9–5.9] | <0.001 |
| **DM (%)** | 1.6 [1.04–2.5] | 0.03 |
| **GRACE score** | 1 [1–1.01] | 0.06 |
| **LVEF (%)** | 1 [0.97–1] | 0.13 |
| **NTproBNP quartiles** | | |
| **Quartile 2 vs quartile 1** | 2.9 [1.1–8.0] | 0.03 |
| **Quartile 3 vs quartile 1** | 6.8 [2.8–16.3] | <0.001 |
| **Quartile 4 vs quartile 1** | 13.3 [5.6–31.6] | <0.001 |
| **DM (%)** | 1.9 [1.1–2.9] | 0.004 |
| **GRACE score** | 1 [1–1.01] | 0.02 |
| **LVEF (%)** | 0.98 [0.96–0.99] | 0.01 |
| **NT-proBNP >400 pg/mL** | 4.6 [2.3–8.9] | <0.001 |

**Abbreviations:** DM: Diabetes mellitus; GRACE: Global Registry of Acute Coronary Events; HR [95 % CI] = Hazard ratio [95 % confidence interval]; LVEF: Left ventricular ejection fraction; MACE: Major adverse cardiac event; NT-proBNP: N-terminal pro-brain natriuretic peptide.
The LVEF refers to the one derived from CMR. The LVEF derived from echocardiography was excluded due to collinearity.

Supplementary Figure 1. During a median follow-up of 138 weeks [101–155 weeks], 31 first MACE (30 %) were detected: 3 cardiac deaths (3 %), 13 myocardial infarctions (12 %), and 15 readmissions for heart failure (15 %).

The characteristics of the group and the differences between patients with and without MACE are presented in Supplementary Table 1. Patients who experienced MACE had higher NT-proBNP levels. In the analysis of the AUC of NT-proBNP in predicting MACE, an NT-proBNP level >400 pg/mL emerged as the best cutoff (37 % vs. 17 %, $p$ = 0.03) and was independently associated (Supplementary Table 2) with a higher risk of experiencing a first MACE (HR: 6.8 [1.5–30.3], $p$ = 0.01).

### 4.2. Study group: univariate analysis

The flowchart of the 276 patients included is exposed in Supplementary Figure 1. During a median follow-up of 203 weeks [159–298 weeks], 88 first MACE (32 %) were detected: 8 cardiac deaths (3 %), 22 myocardial infarctions (8 %), and 58 hospital readmissions for heart failure (21 %). The characteristics of the group and the differences between patients with and without MACE are summarized in Table 1.

Patients with MACE had significantly higher NT-proBNP levels (1419 [739–3538] pg/mL vs. 368 [137–838] pg/mL, $p$ < 0.001) (Table 1, Fig. 1). The rate of first MACE across NT-proBNP quartiles was: 9 % in quartile 1 [17–221 pg/mL], 17 % in quartile 2 [223–573 pg/mL], 36 % in quartile 3 [584–1380 pg/mL], and 67 % in quartile 4 [1384–35,000 pg/mL] ($p$ < 0.001) (Fig. 1). Detection of NT-proBNP >400 pg/mL, as predefined in the exploratory group ($n$ = 168, 61 %), was associated with a higher likelihood of experiencing a first MACE (46 % vs. 10 %, $p$ < 0.001) (Fig. 1).

Separately, NT-proBNP >400 pg/mL was associated with: a higher cumulative incidence of cardiac deaths (5 % vs. 0 %, $p$ = 0.004), myocardial infarctions (13 % vs. 6 %, $p$ = 0.02), and heart failure readmissions (38 % vs. 5 %, $p$ < 0.001) (Supplementary Figure 2). NT-proBNP >400 pg/mL was also related to more severe structural cardiac impairment as assessed by imaging techniques (Supplementary Table 3).

Additionally, NT-proBNP >400 pg/mL was associated with a higher number of hospital admissions and more total days of hospitalization, both overall and specifically due to acute coronary syndrome, heart failure, and non-cardiac causes (Fig. 4, Supplementary Table 4).

### 4.3. Multivariate analysis

The results of the multivariate analyses are presented in Table 2. In the "Final model without NT-proBNP", which included all variables except NT-proBNP, the independent predictors identified were a history of diabetes mellitus (DM), the GRACE risk score, and the left ventricular ejection fraction (LVEF) as derived from CMR imaging (Table 2).

In the "Final model with NT-proBNP", NT-proBNP was found to be an independent predictor of MACE, whether analyzed as a categorical variable (both using the predefined cutoff of 400 pg/mL and the categorization in quartiles) or as a continuous variable ($Log_{10}$ NT-proBNP). This is detailed in Table 2 and Fig. 1.

The "Final model with NT-proBNP", which incorporated $Log_{10}$ NT-proBNP, showed improved predictive capacity for a first MACE compared to the "Final model without NT-proBNP" (AUC: 0.81 [0.75–0.86] vs. 0.72 [0.65–0.78], $p$ < 0.001), as shown in Fig. 2.

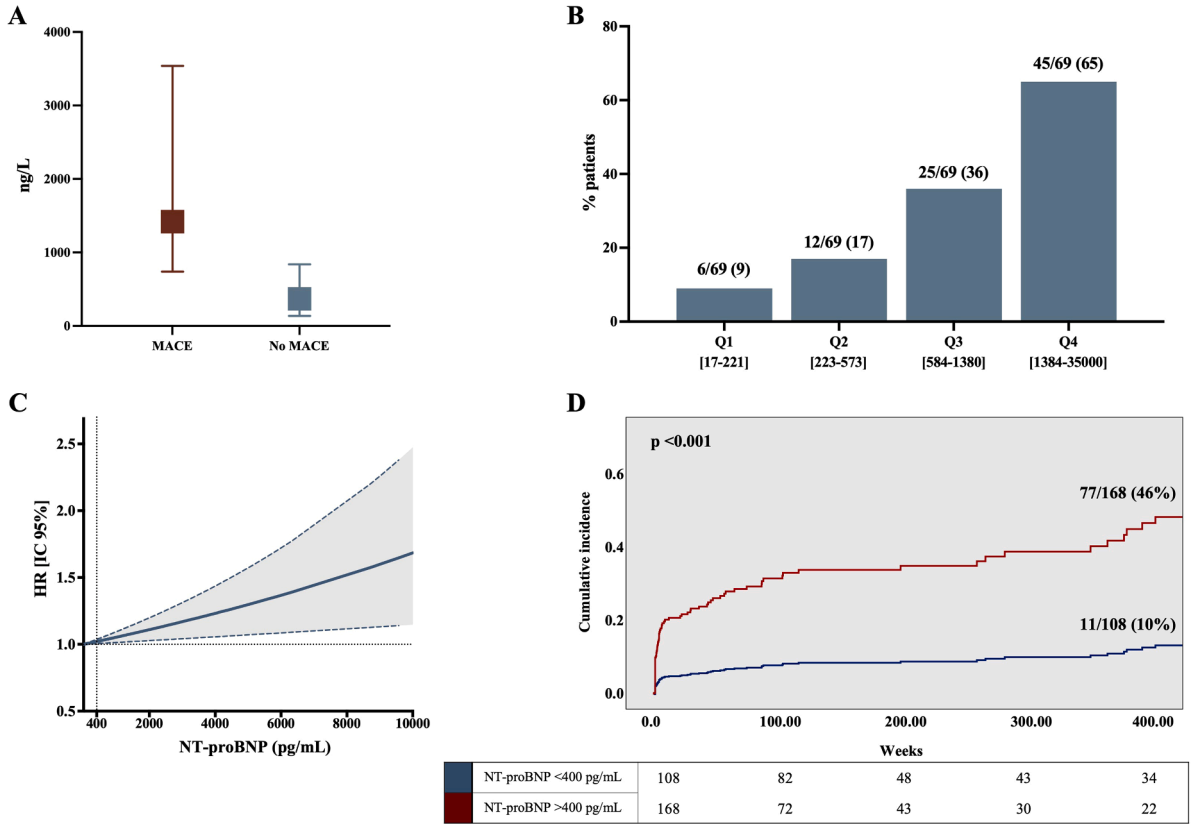



**Fig. 1.** Association of NT-proBNP with MACE.
A. Patients with subsequent MACE had higher NT-proBNP levels.
B. The MACE rate progressively increased from quartile 1 to quartile 4 of NT-proBNP.
C. When analyzed as a continuous variable, higher NT-proBNP levels were independently associated with an increased risk of MACE, adjusted for variables identified as independent predictors in the final predictive model presented in Table 2.
D. NT-proBNP levels above the predefined cutoff value (>400 pg/mL) were associated with a higher risk of MACE.
**Abbreviations:** MACE: Major adverse cardiac event; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Furthermore, the model including $Log_{10}$ NT-proBNP enhanced risk reclassification for a first MACE, as demonstrated by the IDI test (0.11 [0.004–0.19], $p < 0.001$) and the NRI test (0.75 [0.48–1.01], $p < 0.001$) (Fig. 2).

Interestingly, $Log_{10}$ NT-proBNP alone, when analyzed separately, improved the predictive value of the entire "Final model without NT-proBNP" for a first MACE (AUC: 0.79 [0.73–0.85] vs. 0.72 [0.65–0.78], $p < 0.05$), as depicted in Fig. 3.

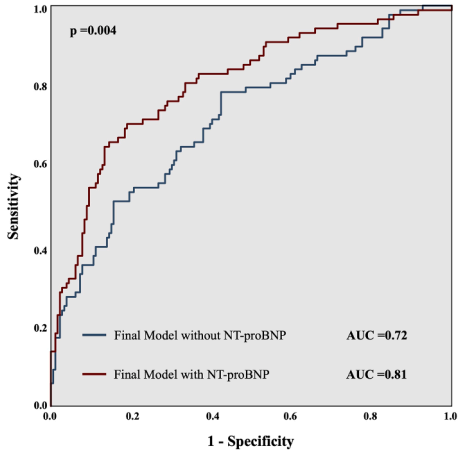
In a not pre-specified analysis, pre-discharge NT-proBNP values had been obtained in 233 patients from the study cohort. Patients with MACE had significantly higher pre-discharge NT-proBNP levels, and pre-discharge NT-proBNP >400 pg/mL associated with a higher risk of subsequent MACE (Supplementary Figure 3). It was observed that (from pre-discharge to the index post-rehabilitation measurement) the transition from NT-proBNP >400 pg/mL to NT-proBNP <400 pg/mL was significantly more frequent than the reverse transition. Regardless of the state of NT-proBNP at pre-discharge, the occurrence of MACE was significantly higher in patients with NT-proBNP >400 pg/mL at post-rehabilitation (Supplementary Figure 4). In the separate multivariate analysis of this subset, after adjustment for pre-discharge NT-proBNP values, only the post-rehabilitation measurement independently associated with MACE occurrence (Supplementary Table 5).

## 5. Discussion

The main finding of this study is that measuring NT-proBNP at the conclusion of phase 2 of cardiac rehabilitation in STEMI patients represents a powerful, accessible, and cost-effective tool for predicting subsequent MACE. This tool could complement and enhance current risk stratification strategies in this setting.

### 5.1. Study rationale

After a STEMI, the highest risk of events occurs within the initial hours and days. Once this critical period is overcome, management has been bolstered by rehabilitation programs that have proven effective in improving quality of life, risk factor control, and even MACE-free survival [2,3,8]. Subsequent risk stratification is particularly relevant due to the significant personal, familial, and professional implications of this process. Simple, economical, and widely available tools are needed to personalize the future risk of MACE in STEMI patients who have surpassed the acute phase of the disease and are preparing to resume an active life [2,3,9].




| NRI | p-value | IDI | p-value |
|---|---|---|---|
| 0.75 [0.48-1.01] | <0.001 | 0.11 [0.04-0.19] | <0.001 |

**Fig. 2.** Added value of NT-proBNP in multivariate models for predicting and reclassifying the risk of MACE.
The inclusion of NT-proBNP (greater or <400 pg/mL) in the multivariate model significantly improved prediction (AUC) and reclassification of MACE risk ("IDI" and "NRI" indexes).
**Abbreviations:** AUC: Area under the curve; IDI: Integrated Discrimination Improvement; MACE: Major adverse cardiac event; NRI: Net Reclassification Improvement; NT-proBNP: N-terminal pro-brain natriuretic peptide.

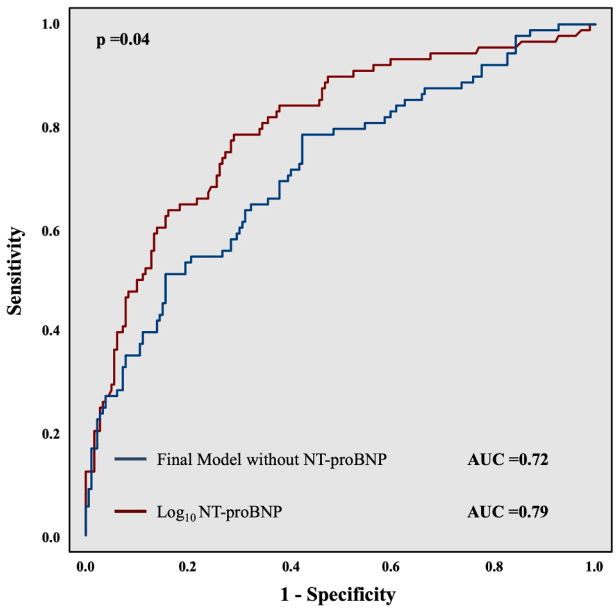



**Fig. 3.** Comparison of NT-proBNP alone analyzed separately versus the "Final Multivariate Model without NT-proBNP" for predicting MACE risk.
NT-proBNP ($Log_{10}$) analyzed separately significantly improved the prediction (AUC) of MACE compared to the "Final Multivariate Model without NT-proBNP," which includes all variables independently associated with MACE, except NT-proBNP (Table 2).
**Abbreviations:** AUC: Area under the curve; MACE: Major adverse cardiac event; NT-proBNP: N-terminal pro-brain natriuretic peptide.

### 5.2. NT-proBNP and MACE prediction after STEMI

Although post-rehabilitation STEMI represents a paradigm of stage B systolic dysfunction in heart failure, evidence supporting the use of NT-proBNP to stratify subsequent risk in this context is scarce [4–6]. Its routine use for this purpose has not been defined [1–3,10], and the predictive value of this biomarker beyond the information provided by clinical presentation characteristics and imaging techniques, such as echocardiography and CMR, is unknown.

Three prior studies by Li et al. [5], Wolsk et al. [6], and Jering et al. [4] demonstrated that NT-proBNP elevation within the first days after an acute event is associated with higher risk of adverse events in selected post-infarction populations (not exclusively STEMI). However, NT-proBNP dynamics during the early days and weeks post-event are highly variable due to factors such as ventricular remodeling and administered therapies [5]. Studies are needed to analyze its prognostic value in a more stable phase of the disease, in a homogeneous population that received the best treatment according to guideline standards.

This study confirms the prognostic value of NT-proBNP for predicting subsequent MACE after STEMI and provides two original contributions compared to previous series: 1) It demonstrates the value of NT-proBNP in a homogeneous series of patients, all of whom had reperfused STEMI and completed phase 2 of rehabilitation. At the conclusion of this phase, with patients and biomarkers stabilized, individualizing risk and defining the additional predictive value of tools like NT-proBNP are crucial for active life resumption. 2) The study highlights the prognostic value of NT-proBNP even after adjustment for data derived from advanced imaging techniques like CMR, which allows for precise characterization of the structural damage caused by STEMI [7,11,12].

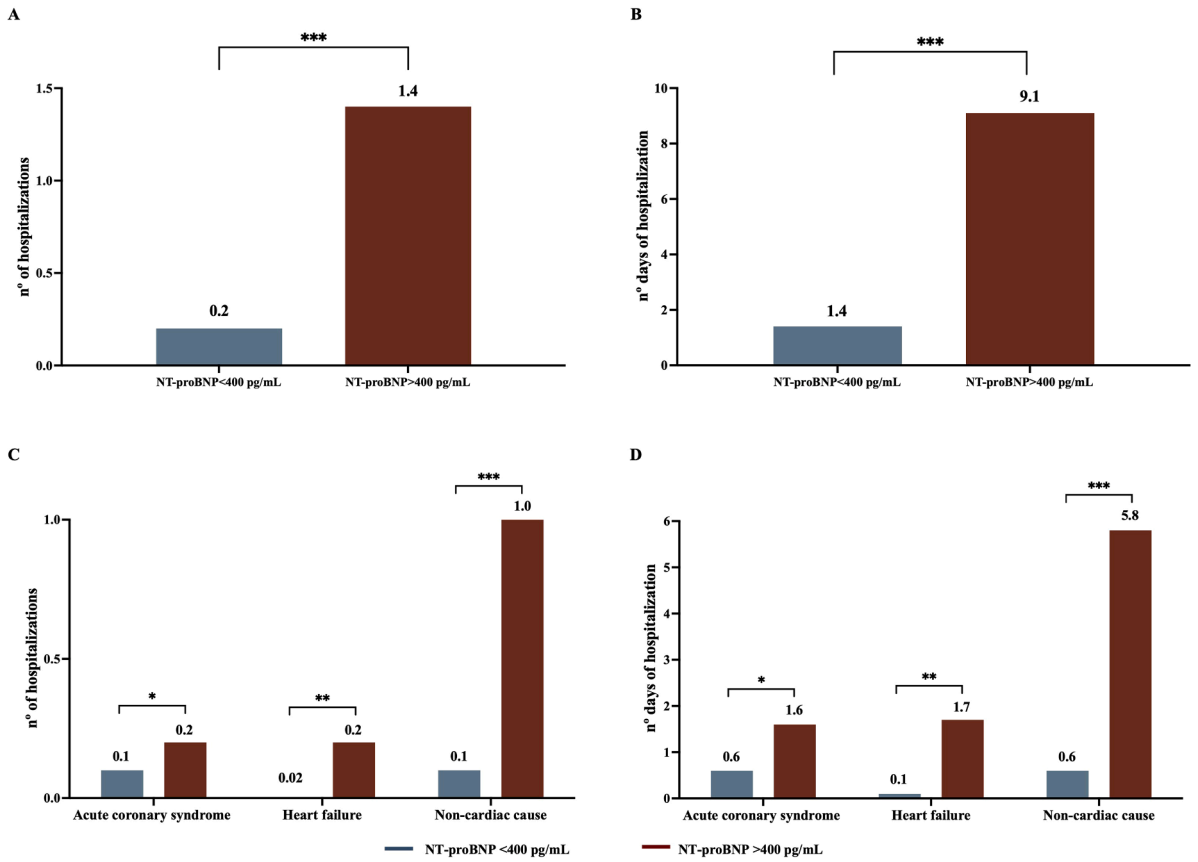



**Fig. 4.** Association of NT-proBNP with the number of hospitalizations and days of hospitalization.
The number of hospitalizations and days of hospitalization, both total (A and B) and separately for acute coronary syndrome, heart failure, and non-cardiac causes (C and D), was significantly higher in patients with NT-proBNP >400 pg/mL.
**Abbreviations:** NT-proBNP: N-terminal pro-brain natriuretic peptide
The analyzed variables are non-parametric. Therefore, the p-values shown are derived from non-parametric tests. The median values are 0 in many of the analyses, so for illustrative purposes, the bars correspond to the mean values.
(*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

In the exploratory phase and in the subsequent analysis of the 276 STEMI patients in the study group, NT-proBNP (analyzed continuously, by quartiles, or using the pre-defined cutoff value of 400 pg/mL) was an independent predictor of MACE, even after exhaustive adjustment for baseline clinical variables and cardiac imaging. Elevated NT-proBNP levels were associated with more than a fourfold increase in the adjusted risk of MACE. Furthermore, similar to findings by Wolsk et al. [6] in patients with acute coronary syndrome shortly after the event, the predictive power of a single NT-proBNP measurement at the end of phase 2 rehabilitation (based on its AUC for MACE prediction) surpassed that of a model including all baseline clinical and imaging variables.

CMR is currently the imaging technique of choice for an accurate and comprehensive non-invasive assessment of the structural damage derived from STEMI [11]. As expected and consistent with previous findings [13], elevated NT-proBNP values were associated with worse systolic function, greater remodeling, and larger infarct and microvascular obstruction (MVO) areas. However, no prior data demonstrated the additional prognostic value of NT-proBNP beyond CMR after post-infarction cardiac rehabilitation.

The results of this study suggest that in this context, the utility of NT-proBNP remains robust even after adjustment for CMR data. In fact, incorporating NT-proBNP significantly improved predictive models and risk reclassification. This underscores that beyond clinical evaluation and imaging-derived structural damage, NT-proBNP reflects the physiological impact of this damage, which is crucial for optimal risk prediction.

In a non-pre-specified analysis, it was observed that, from pre-discharge to the index post-rehabilitation measurement, transitioning from elevated to reduced NT-proBNP was much more frequent than the reverse, and the MACE risk was significantly higher when NT-proBNP levels were elevated at the stable phase. Although these results suggest that periodic NT-proBNP measurements in STEMI patients could aid in individualized management, they should be interpreted as merely exploratory because our study was designed for assessing the prognostic value of NT-proBNP levels at the end of post-STEMI phase 2 rehabilitation but not for evaluating a therapeutic strategy guided by NT-proBNP levels in this scenario.

While cost-effectiveness studies and larger external validation series are needed for routine NT-proBNP use post-rehabilitation, the biomarker's low cost (€10–15) and its high prognostic value suggest its potential for risk stratification. Probably, patients with high levels of NT-proBNP after a post-STEMI rehabilitation cycle should be directed to more frequent clinical monitoring, more frequent verification of therapy compliance, and careful evaluation of the indication for ICD implantation.

### 5.3. *Limitations*

The study is limited by the small number of patients, which implies a certain patients' selection. However, the high event rate detected illustrates that the study group was made up of high risk patients, who are those in whom this risk stratification is needed.

Although the results of the initial exploratory group and the definitive study group coincided, the findings obtained undoubtedly need to be validated externally in a larger series of patients.

Availability of NT-proBNP values for the cardiologist in charge of patients in the study group but not in the exploratory group could have exerted a certain influence on patients' outcomes.

Our study suggests that the information provided by post-rehabilitation NT-proBNP values persists beyond the study of this biomarker in the acute phase. However, our study was not designed for an in-depth analysis of this issue.

The utility of a management strategy focused on guiding treatment based on NT-proBNP levels would need to be evaluated in a randomized study comparing patient outcomes with and without the use of this biomarker. The implications identified in this regard are purely hypothesis-generating.

### *5.4. Conclusions*

The findings of this study suggest that NT-proBNP is a powerful, accessible, and cost-effective tool for risk stratification in STEMI patients after completing phase 2 of cardiac rehabilitation.

## Funding statement

This work was supported by the 'Instituto de Salud Carlos III' and FEDER (grant numbers PI23/01150, CB16/11/00486, CB16/11/00420, CB16/11/00403, CB16/11/00360, CB16/11/00261, CB16/11/00385) and "Conselleria de Educación de la Generalitat Valenciana y Fondo Social Europeo Plus" (grant numbers PROMETEO/2021/008, CIAPOS/2023/247, CIAPOS/2023/248).

## Author contributions

NPS and ED contributed equally to this work.

Conceptualization: V.B; data collection: NPS, ED and VB; formal analysis: NPS, ED, JG and VB; research: NPS, ED, JG, CRN, VMG, HM, JIC, LLB, AP, RDL, ABG, MJN, FM, JN, JS and VB; writing-original draft preparation: NPS, ED and VB; review and editing the final manuscript: NPS, ED, JG, CRN, VMG, HM, JIC, LLB, AP, RDL, ABG, MJN, FM, JN, JS and VB; funding acquisition, JG, CRN, ABG, MJN, FM, JS and VB. All authors have read and agreed to the published version of the manuscript.

## Declaration of competing interest

The authors declare no conflicts of interest.

## Acknowledgments

We thank the physicians Francisco J. Chorro, Joaquim Cánoves, Gema Miñana, Clara Bonanad and Carlos Bertolin of the Hospital Clínico Universitario de Valencia for their help and support during the study. We also thank Luis Martínez Dolz of the Hospital Universitario y Politécnico La Fe and Jorge Rodríguez-Capitán of the Hospital Universitario Virgen de la Victoria for their support of this research.

Additionally, we would like to thank José V. Monmeneu and María P. López-Lereu of the ASCIRES Biomedical Group for their invaluable assistance in the data collection process.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2025.04.027.

## References

[1] McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2022;24:4–131.

[2] Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC guidelines for the management of acute coronary syndromes. Eur Heart J 2023;12(44):3720–826.

[3] Vrints C, Andreotti F, Koskinas KC, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes: developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC) endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2024;45(36):3415–537.

[4] Jering KS, Claggett BL, Pfeffer MA, et al. Prognostic importance of NT-proBNP (N-terminal pro-B-type natriuretic peptide) following high-risk myocardial infarction in the PARADISE-MI trial. Circ Heart Fail 2023;16:e010259.

[5] Li N, Chen R, Li J, et al. Prognostic significance of serial N-terminal pro-B type natriuretic peptide levels in patients with acute myocardial infarction: a prospective study. Am Heart J 2023;262:90–9.

[6] Wolsk E, Claggett B, Pfeffer MA, et al. Role of B-type natriuretic peptide and N-terminal prohormone BNP as predictors of cardiovascular morbidity and mortality in patients with a recent coronary event and type 2 diabetes mellitus. J Am Heart Assoc 2017;29(6):e004743.

[7] Ríos-Navarro C, Gavara J, de Dios E, et al. Effect of serum from patients with ST-segment elevation myocardial infarction on endothelial cells. Rev Esp Cardiol 2024;77:254–64.

[8] Marcos-Garcés V, Merenciano-González H, Martínez Mas ML, et al. Short-course high-intensity statin treatment during admission for myocardial infarction and LDL-cholesterol reduction-impact on tailored lipid-lowering therapy at discharge. J Clin Med 2023;13:127.

[9] Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. Lancet 2017;14(389):197–210.

[10] Mueller C, McDonald K, de Boer RA, et al. Heart failure association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail 2019;21:715–31.

[11] Reinstadler SJ, Thiele H, Eitel I. Risk stratification by cardiac magnetic resonance imaging after ST-elevation myocardial infarction. Curr Opin Cardiol 2015;30:681–9.

[12] Ríos-Navarro C, Gavara J, Bodí V. Microvascular injury after acute myocardial infarction. Focus on the catheterization laboratory. Rev Esp Cardiol 2022;75:777–9.

[13] Mayr A, Mair J, Schocke M, et al. Predictive value of NT-pro BNP after acute myocardial infarction: relation with acute and chronic infarct size and myocardial function. Int J Cardiol 2011;17(147):118–23.