



# Prognostic Implications of N-Terminal Pro-B-Type Natriuretic Peptide in Patients With Non-ST-Elevation Myocardial Infarction

Chang Hoon Kim, MD; Seung Hun Lee, MD, PhD; Hyun Kuk Kim, MD, PhD; Min Chul Kim, MD, PhD; Ju Han Kim, MD, PhD; Young Joon Hong, MD, PhD; Young Keun Ahn, MD, PhD; Myung Ho Jeong, MD, PhD; Seung Ho Hur, MD, PhD; Doo Il Kim, MD, PhD; Kiyuk Chang, MD, PhD; Hun Sik Park, MD, PhD; Jang-Wan Bae, MD, PhD; Jin-Ok Jeong, MD, PhD; Yong Hwan Park, MD, PhD; Kyeong Ho Yun, MD, PhD; Chang-Hwan Yoon, MD, PhD; Yisik Kim, MD, PhD; Jin-Yong Hwang, MD, PhD; Hyo-Soo Kim, MD, PhD; Ki Hong Choi, MD, PhD; Taek Kyu Park, MD, PhD; Jeong Hoon Yang, MD, PhD; Young Bin Song, MD, PhD; Joo-Yong Hahn, MD, PhD; Seung-Hyuk Choi, MD, PhD; Hyeon-Cheol Gwon, MD, PhD; Joo Myung Lee, MD, MPH, PhD; The KAMIR-NIH Investigators

**Background:** Limited data exist regarding the prognostic implications of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in patients with non-ST-elevation myocardial infarction (NSTEMI) who undergo percutaneous coronary intervention (PCI).

**Methods and Results:** Of 13,104 patients in the nationwide Korea Acute Myocardial Infarction Registry-National Institutes of Health, 3,083 patients with NSTEMI who underwent PCI were included in the present study. The primary endpoint was major adverse cardiovascular events (MACE) at 3 years, a composite of all-cause death, recurrent myocardial infarction, unplanned repeat revascularization, and admission for heart failure. NT-proBNP was measured at the time of initial presentation for the management of NSTEMI, and patients were divided into a low (<700 pg/mL; n=1,813) and high (≥700 pg/mL; n=1,270) NT-proBNP group. The high NT-proBNP group had a significantly higher risk of MACE, driven primarily by a higher risk of cardiac death or admission for heart failure. These results were consistent after confounder adjustment by propensity score matching and inverse probability weighting analysis.

**Conclusions:** In patients with NSTEMI who underwent PCI, an initial elevated NT-proBNP concentration was associated with higher risk of MACE at 3 years, driven primarily by higher risks of cardiac death or admission for heart failure. These results suggest that the initial NT-proBNP concentration may have a clinically significant prognostic value in NSTEMI patients undergoing PCI.

**Key Words:** Acute myocardial infarction; Biomarkers; Coronary intervention; Non-ST-elevation myocardial infarction; Prognosis

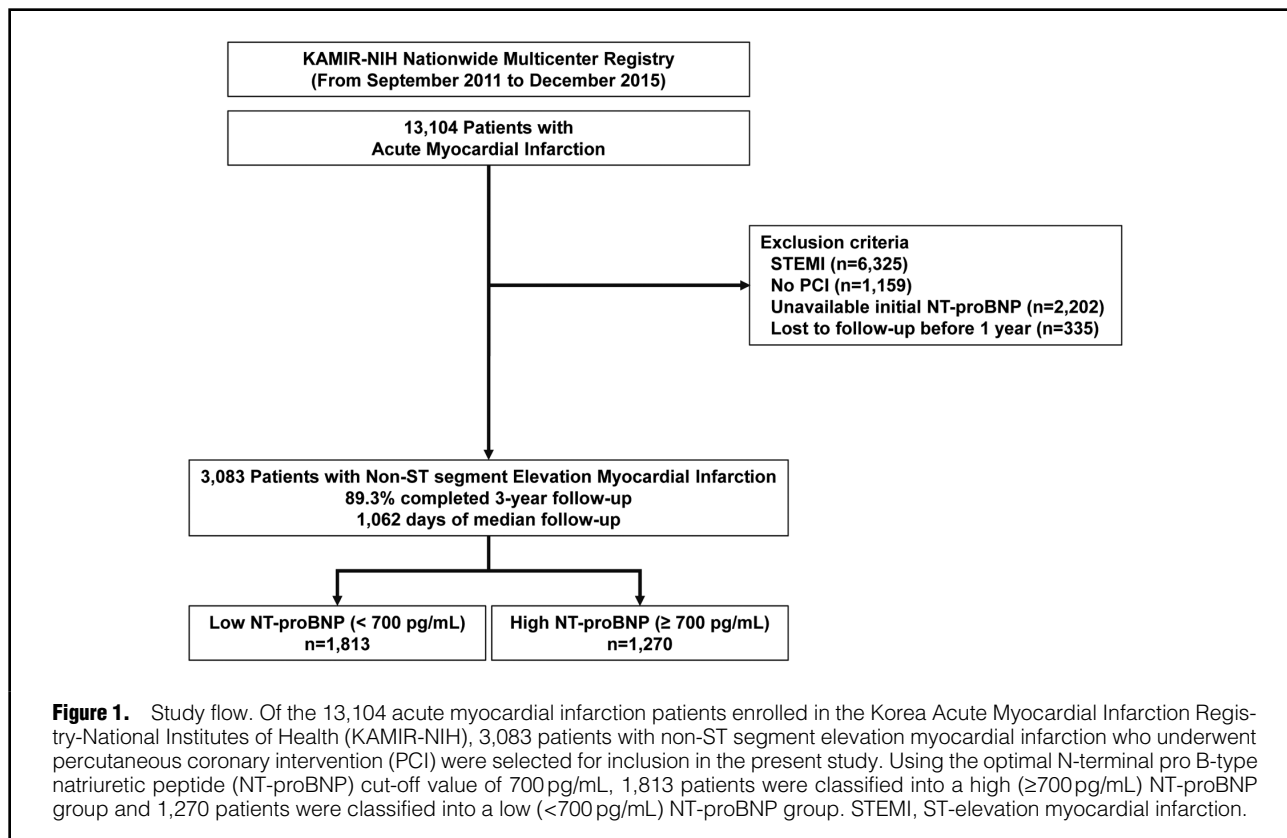
**N**on-ST-elevation myocardial infarction (NSTEMI) results in significant ischemic myocardial damage, caused primarily by a decrease in coronary blood flow, which requires revascularization.<sup>1</sup> One of the treatment options for acute phase management to restore coronary blood flow and minimize ischemic myocardial damage is percutaneous coronary intervention (PCI).<sup>2</sup> With recent advances in biomarker assays, such as high-sensitivity cardiac troponin for a working diagnosis of acute coronary

syndrome (ACS), NSTEMI has become the predominant clinical presentation among the total ACS population.<sup>3,4</sup>

In this regard, there is a growing need to identify reliable prognostic biomarkers for risk stratification and long-term guidance of therapeutic decisions in NSTEMI patients undergoing PCI. Nevertheless, cardiac enzymes such as troponin and creatine kinase-myocardial band (CK-MB), commonly used in the diagnosis of acute myocardial infarction (MI), failed to demonstrate predictive value in long-

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Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul (C.H.K., K.H.C., T.K.P., J.H.Y., Y.B.S., J.-Y. Hahn, S.-H.C., H.-C.G., J.M.L.); Division of Cardiology, Department of Internal Medicine, Heart Center, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju (S.H.L., M.C.K., J.H.K., Y.J.H., Y.K.A., M.H.J.); Department of Internal Medicine and Cardiovascular Center, Chosun University Hospital, University of Chosun College of Medicine, Gwangju (H.K.K.); Keimyung University Dongsan Medical Center, Daegu (S.H.H.); Department of Cardiology, Inje University Haeundae Baek Hospital, Inje University College of Medicine, Busan (D.I.K.); Division of Cardiology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, (Footnote continued the next page.)



term prognosis and risk stratification in NSTEMI patients.<sup>5-7</sup> Although previous studies evaluated novel biomarkers associated with the prognosis of NSTEMI patients, the clinical utility of these biomarkers has not been fully validated as yet.<sup>8-10</sup>

N-terminal pro-B-type natriuretic peptide (NT-proBNP), a prohormone secreted by ventricular myocytes in response to myocardial stress and ventricular stretching, has been recognized as a promising biomarker for various cardiovascular diseases, including congestive heart failure (CHF), valvular heart disease, pulmonary hypertension, and cardiomyopathies.<sup>11-16</sup> Although there have been few studies presenting the prognostic value of NT-proBNP in patients with NSTEMI,<sup>17,18</sup> clinical evidence of NT-proBNP in NSTEMI patients who underwent PCI is still limited due to small sample sizes and limited follow-up durations of previous studies. In this regard, the aim of the present

study was to evaluate the clinical relevance of NT-proBNP for predicting clinical outcomes among NSTEMI patients after PCI using a nationwide multicenter registry.

## Methods

### Study Protocol and Population Selection

The study population was derived from the nationwide multicenter prospective Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH). This dedicated registry consecutively enrolled patients with acute MI from 20 tertiary university hospitals in South Korea from November 2011 to December 2015. A detailed study protocol has been published previously.<sup>19,20</sup> The protocol of KAMIR-NIH was approved by the ethics committees of each participating center and written informed consent was obtained from all participants. The registry protocol

The Catholic University of Korea, Seoul (K.C.); Department of Internal Medicine, Kyungpook National University Hospital, Daegu (H.S.P.); Department of Internal Medicine, College of Medicine, Chungbuk National University, Cheongju (J.-W.B.); Chungnam National University Hospital, Chungnam National University College of Medicine, Daejeon (J.-O.J.); Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon (Y.H.P.); Wonkwang University Hospital, Iksan (K.H.Y.); Seoul National University Bundang Hospital, Seongnam (C.-H.Y.); Chonbuk National University Hospital and Chonbuk National University Medical School, Jeonju (Y.K.); Department of Internal Medicine, Gyeongsang National University Hospital, Gyeongsang National University School of Medicine, Jinju (J.-Y. Hwang); and Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul (H.-S.K.), Republic of Korea

The first two authors contributed equally and are equal first authors (C.H.K., S.H.L.).

Mailing address: Joo Myung Lee, MD, MPH, PhD, Division of Cardiology, Department of Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea. email: drone80@hanmail.net

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adhered to the tenets of the Declaration of Helsinki.

Of the 13,104 patients enrolled in KAMIR-NIH, we selected patients who underwent PCI for NSTEMI, which was defined as acute MI without newly detected ST-elevation in  $\geq 2$  contiguous leads measuring  $\geq 0.1$  mV or a new left bundle branch block on a 12-lead electrocardiogram (ECG), accompanied by an increase of at least 1 cardiac marker of necrosis.<sup>20</sup> Patients with ST-elevation myocardial infarction (STEMI;  $n=6,325$ ), those for whom NT-proBNP concentrations at the time of initial presentation were unavailable ( $n=2,202$ ), those who did not undergo PCI ( $n=1,159$ ), and those lost to follow-up in  $< 1$  year ( $n=335$ ) were excluded from the study (Figure 1). Finally, 3,083 patients were included in the analysis and were classified into a low or high NT-proBNP group using an optimal cut-off value of 700 pg/mL NT-proBNP, as determined by receiver operating characteristic (ROC) curve analysis (Supplementary Figure 1).

### Patient Management, Data Collection, and Follow-up

Patients were treated according to current guidelines and coronary interventions were performed using standard techniques. The choice of treatment strategy, such as the type, diameter, length, and number of stents, the use of intravascular imaging devices, thrombus aspiration, or percutaneous cardiopulmonary support devices, as well as the selection of medications were left to the operator's discretion. PCI was considered successful if the final residual stenosis was  $< 30\%$  with Thrombolysis in Myocardial Infarction (TIMI) Grade 3 flow. Complete revascularization was achieved when successful PCI was performed on all coronary arteries with significant stenosis during the index hospitalization. Following the index procedure, all patients were prescribed aspirin and a P2Y<sub>12</sub> inhibitor for at least 12 months, unless contraindications were present. The choice of P2Y<sub>12</sub> inhibitor was at the operator's discretion in accordance with current guidelines and considering individual patient factors, such as bleeding risk. Additional medications, including renin-angiotensin-aldosterone system blockers,  $\beta$ -blockers, and statins, were also prescribed based on practice guidelines.<sup>21,22</sup>

Demographic features and cardiovascular risk factors were collected by detailed patient interview. NT-proBNP was measured at the time of initial presentation for the management of NSTEMI. During the index hospitalization, features of coronary angiography and specific procedural details of PCI, as well as information about complications and discharge medications, were documented. After discharge, patients were followed up at 6, 12, 24, and 36 months through outpatient clinic visits or telephone contact, and whenever any clinical event occurred. Independent clinical research coordinators collected all data using a web-based case report form on the internet-based Clinical Research and Trial management system (iCReaT), a data management system established by the Centers for Disease Control and Prevention, Ministry of Health and Welfare, Republic of Korea (iCReaT Study No. C110016).

### Study Outcomes

The primary outcome was a major adverse cardiovascular event (MACE), a composite of all-cause death, recurrent MI, unplanned repeat revascularization, and admission for heart failure, at 3 years. Secondary outcomes included the individual components of MACE and a composite of cardiac death or admission for heart failure at 3 years. Fol-

low-up echocardiographic data were assessed among 1,054 patients with a left ventricular ejection fraction (LVEF)  $> 50\%$  at the index echocardiography and for whom both index and follow-up echocardiography data were available. Recurrent MI was defined as the recurrence of symptoms or the presence of electrocardiographic changes associated with a rise in cardiac biomarker concentrations above the upper limit of normal. Periprocedural MI was not included as a clinical outcome. Clinically driven revascularization that occurred after discharge from the index hospitalization was coded as an unplanned repeat revascularization event according to the Academic Research Consortium definitions.<sup>23</sup> Clinical events that occurred within the 3-year follow-up period were analyzed in the present study. The median follow-up duration of the study was 1,062 days (interquartile range: 1,086.0–1,155.0 days).

### Statistical Analysis

All discrete and categorical variables are presented as numbers and relative frequencies (percentages). Categorical data were compared using the Chi-squared test. Continuous variables are reported as the mean  $\pm$  SD and were compared using Student's *t*-test. The cumulative incidence of clinical events was estimated by the Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazards model was used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for MACE. The assumption of proportionality was assessed by the Schoenfeld residuals and graphically by the log-log plot. A multivariable Cox model was fitted using all variables with  $P < 0.1$  from the univariable analyses and variables that could be clinically relevant. The final model included the following variables: age, sex, high Killip class (Class 3 or 4), hypertension, diabetes, end-stage renal disease, previous CHF, LVEF  $< 50\%$ , left ventricular (LV) end-diastolic diameter, atrial fibrillation, 3-vessel disease, and failure to achieve complete revascularization. A restricted cubic spline curve with 3 knots was used to evaluate the prognostic implications of NT-proBNP on MACE at 3 years as a continuous value.

For sensitivity analysis, propensity score matching and inverse probability treatment-weighting (IPTW) analyses were performed using the propensity score from a multivariable logistic regression model. The covariables of age, sex, body mass index (BMI), high Killip class (Class 3 or 4), hypertension, diabetes, dyslipidemia, end-stage renal disease, previous CHF, previous MI, previous cerebrovascular accident (CVA), LVEF, multivessel disease, Type B2 or C lesion according to the American College of Cardiology (ACC)/American Heart Association (AHA) classification,<sup>24</sup> and failure to achieve complete revascularization were included in the model. The balance between the 2 groups after propensity score matching or IPTW adjustment was assessed by calculating percentage standardized mean differences, which were within 10% across all matched covariables, suggesting successful balance was achieved between the comparative groups by propensity score matching and IPTW adjustment (Supplementary Table 1). A subgroup analysis of the primary outcome was performed according to clinical and procedural factors of interest between the low and high NT-proBNP groups.

All probability values were 2-sided, and  $P < 0.05$  was considered statistically significant. Statistical analyses were performed using SPSS 27.0 for Windows (SPSS-PC, Chicago, IL, USA) and R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

<b>Table 1. Baseline Clinical Characteristics</b>				
	Total population (n=3,083)	NT-proBNP		P value
		Low (n=1,813)	High (n=1,270)	
Age (years)	64.5±12.0	60.8±11.3	69.8±11.0	<0.001
Male sex	2,203 (71.5)	1,509 (83.2)	694 (54.6)	<0.001
BMI (kg/m <sup>2</sup> )	24.1±3.3	24.5±3.1	23.4±3.5	<0.001
<b>Killip class</b>				<0.001
Class 1	2,492 (80.8)	1,640 (90.5)	852 (67.1)	
Class 2	283 (9.2)	116 (6.4)	167 (13.1)	
Class 3	265 (8.6)	43 (2.4)	222 (17.5)	
Class 4	43 (1.4)	14 (0.8)	29 (2.3)	
<b>Hemodynamic data</b>				
SBP (mmHg)	135.8±26.6	138.1±25.7	132.6±27.6	<0.001
DBP (mmHg)	81.3±15.7	82.8±15.2	79.1±16.3	<0.001
Heart rate (beats/min)	79.2±17.7	75.6±15.5	84.3±19.4	<0.001
<b>Cardiovascular risk factors</b>				
Hypertension	1,650 (53.5)	854 (47.1)	796 (62.7)	<0.001
Diabetes	943 (30.6)	444 (24.5)	499 (39.3)	<0.001
Current smoking	1,141 (37.0)	832 (45.9)	309 (24.3)	<0.001
Dyslipidemia	351 (11.4)	246 (13.6)	105 (8.3)	<0.001
End-stage renal disease	63 (2.0)	1 (0.1)	62 (4.9)	<0.001
Previous MI	256 (8.3)	133 (7.3)	123 (9.7)	0.024
Previous angina	351 (11.4)	171 (9.4)	180 (14.2)	<0.001
Previous CVA	207 (6.7)	82 (4.5)	125 (9.8)	<0.001
Previous CHF	47 (1.5)	11 (0.6)	36 (2.8)	<0.001
Family history of IHD	19 (0.6)	16 (0.9)	3 (0.2)	0.043
<b>Cardiac enzyme level</b>				
Peak CK-MB (ng/mL)	56.8±85.9	62.7±90.9	48.3±77.4	<0.001
Peak troponin-I (ng/mL)	21.0±42.2	20.8±42.6	21.2±41.6	0.824
<b>Laboratory data</b>				
Hemoglobin (g/dL)	13.6±2.1	14.3±1.6	12.6±2.2	<0.001
Creatinine (mg/dL)	1.1±1.0	0.9±0.3	1.4±1.5	<0.001
Total cholesterol (mg/dL)	178.0±45.7	184.3±44.6	169.0±45.7	<0.001
HDL-C (mg/dL)	42.9±11.5	43.0±10.8	42.7±12.6	0.584
LDL-C (mg/dL)	111.9±38.1	116.5±36.6	105.2±39.1	<0.001
HbA1c (%)	6.5±1.5	6.4±1.4	6.7±1.6	0.001
<b>Medications at discharge</b>				
Aspirin	3,077 (99.8)	1,810 (99.8)	1,267 (99.8)	0.981
Clopidogrel	2,439 (79.1)	1,375 (75.8)	1,064 (83.8)	<0.001
Prasugrel	354 (11.5)	255 (14.1)	99 (7.8)	<0.001
Ticagrelor	709 (23.0)	441 (24.3)	268 (21.1)	0.040
RAAS blocker	2,555 (82.9)	1,504 (83.0)	1,051 (82.8)	0.923
β-blocker	2,657 (86.2)	1,577 (87.0)	1,080 (85.0)	0.137
Statin	2,931 (95.1)	1,746 (96.3)	1,185 (93.3)	<0.001
Oral anticoagulant	88 (2.9)	14 (0.8)	74 (5.8)	<0.001
<b>Echocardiographic data</b>				
LVEF (%)	53.6±10.8	57.1±8.3	48.6±11.9	<0.001
LVEDd (mm)	49.5±6.4	49.0±5.5	50.3±7.4	<0.001
Atrial fibrillation	136 (4.4)	39 (2.2)	97 (7.6)	<0.001

Unless indicated otherwise, data are presented as the mean±SD or n (%). BMI, body mass index; CHF, congestive heart failure; CK-MB, creatine kinase-myocardial band; CVA, cerebrovascular accident; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; IHD, ischemic heart disease; LDL-C, low density lipoprotein cholesterol; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure.

Table 2. Baseline Procedural Profiles	Total population (n=3,083)	NT-proBNP		P value
		Low (n=1,813)	High (n=1,270)	
<b>Angiographic disease extent</b>				
Single vessel disease	1,399 (45.4)	898 (49.5)	501 (39.4)	<0.001
Three-vessel disease	583 (18.9)	286 (15.8)	297 (23.4)	<0.001
Left main artery disease	157 (5.1)	71 (3.9)	86 (6.8)	0.001
Culprit-only PCI at index procedure	2,287 (74.2)	1,386 (76.4)	901 (70.9)	0.001
Complete revascularization during index hospitalization	2,133 (69.2)	1,309 (72.2)	824 (64.9)	<0.001
<b>Culprit lesion location</b>				
Unprotected left main artery	75 (2.4)	31 (1.7)	44 (3.5)	<0.001
LAD	1,304 (42.3)	710 (39.2)	594 (46.8)	
LCX	799 (25.9)	521 (28.7)	278 (21.9)	
RCA	905 (29.4)	551 (30.4)	354 (27.9)	
ACC/AHA Type B2/C lesion <sup>A</sup>	2,602 (84.4)	1,492 (82.3)	1,110 (87.4)	<0.001
Transradial approach	1,597 (51.8)	997 (55.0)	600 (47.2)	<0.001
Glycoprotein IIb/IIIa inhibitor	242 (7.8)	152 (8.4)	90 (7.1)	0.211
Thrombus aspiration	425 (13.8)	281 (15.5)	144 (11.3)	0.001
<b>Treatment modalities</b>				
Drug-eluting stent	2,189 (71.0)	1,284 (70.8)	905 (71.3)	0.813
Plain balloon angioplasty	252 (8.2)	153 (8.4)	99 (7.8)	
Others	642 (20.8)	376 (20.7)	266 (20.9)	
Stent diameter (mm)	3.10±0.43	3.12±0.44	3.06±0.41	<0.001
Total stent length (mm)	30.01±15.60	28.95±14.54	31.51±16.87	<0.001
Total no. stents implanted	1.11±0.55	1.08±0.53	1.13±0.57	0.016
<b>Pre-PCI TIMI flow</b>				
Grade 0	877 (28.4)	509 (28.1)	368 (29.0)	0.356
Grade 1	373 (12.1)	232 (12.8)	141 (11.1)	
Grade 2 or 3	1,833 (59.5)	1,072 (59.1)	761 (59.9)	
<b>Post-PCI TIMI flow</b>				
Grade 0	7 (0.2)	3 (0.2)	4 (0.3)	0.641
Grade 1	6 (0.2)	4 (0.2)	2 (0.2)	
Grade 2 or 3	3,070 (99.6)	1,806 (99.6)	1,264 (99.5)	
<b>Intravascular imaging</b>				
IVUS	650 (21.1)	422 (23.3)	228 (18.0)	<0.001
OCT	573 (18.6)	364 (20.1)	209 (16.5)	0.013
<b>Mechanical hemodynamic support</b>				
IABP	26 (0.8)	8 (0.4)	18 (1.4)	0.007
ECMO	24 (0.8)	8 (0.4)	16 (1.3)	0.019
	3 (0.1)	0 (0.0)	3 (0.2)	0.138

Unless indicated otherwise, data are presented as the mean ± SD or n (%). <sup>A</sup>Type B2 or C lesions according to American College of Cardiology (ACC)/American Heart Association (AHA) classification.<sup>24</sup> ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IVUS, intravascular ultrasound; LAD, left anterior descending artery; LCX, left circumflex artery; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, Thrombolysis in Myocardial Infarction.

## Results

### Baseline Clinical Characteristics

Baseline clinical characteristics are summarized in **Table 1**. Among the total population, 1,813 (58.8%) patients were categorized in the low (<700 pg/mL) NT-proBNP group and 1,270 (41.2%) patients were classified in the high (≥700 pg/mL) NT-proBNP group. The mean age of the entire cohort was 64.5±12.0 years and 71.5% were male. Patients in the high NT-proBNP group were older, presented with higher Killip class (Class 3 or 4), and lower systolic and diastolic blood pressures than those in the low NT-proBNP group. In addition, patients in the high NT-proBNP group had a higher prevalence of major cardiovascular comorbidities, including hypertension, diabetes,

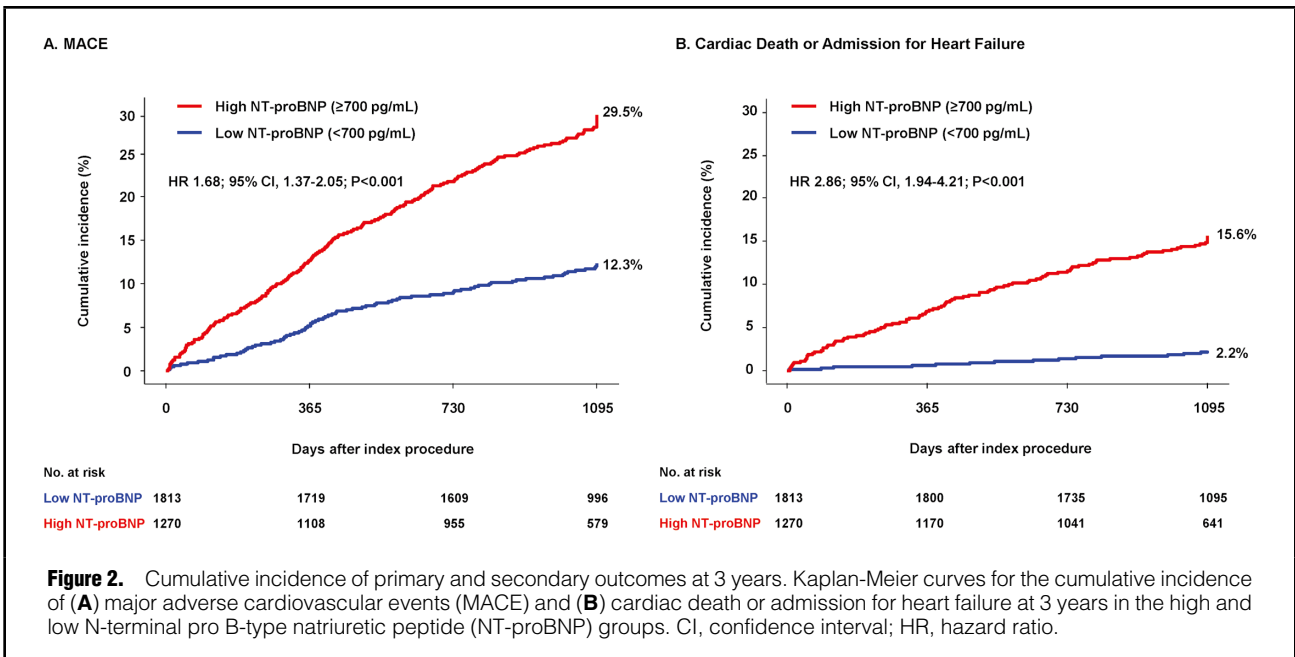
end-stage renal disease, previous MI, angina, CVA, CHF, and atrial fibrillation, than those in the low NT-proBNP group. The high NT-proBNP group had lower LVEF (48.6±11.9% vs. 57.1±8.3%; P<0.001) and higher LV end-diastolic diameter (50.3±7.4 mm vs. 49.0±5.5 mm; P<0.001) than the low NT-proBNP group. Conversely, there was no significant difference in peak cardiac troponin-I concentrations between the 2 groups (**Table 1**).

### Procedural Characteristics

**Table 2** presents the procedural characteristics in the study population. The high NT-proBNP group had a higher prevalence of left main artery disease and 3-vessel disease than the low NT-proBNP group. More extensive coronary artery disease in the high NT-proBNP group resulted in

	NT-proBNP		Univariable analysis			Multivariable analysis <sup>A</sup>		
	Low (n=1,813)	High (n=1,270)	HR	95% CI	P value	HR	95% CI	P value
	MACE <sup>B</sup>	216 (12.3)	359 (29.5)	2.63	2.23–3.12	<0.001	1.68	1.37–2.05
All-cause death	44 (2.5)	153 (12.8)	5.30	3.79–7.42	<0.001	2.12	1.44–3.10	<0.001
Cardiac death	24 (1.4)	87 (7.5)	5.54	3.53–8.70	<0.001	1.88	1.13–3.16	0.016
Recurrent MI	31 (2.2)	58 (6.3)	2.91	1.88–4.50	<0.001	1.88	1.12–3.16	0.017
Unplanned repeat revascularization	159 (9.0)	143 (12.3)	1.34	1.08–1.70	0.008	1.27	0.96–1.67	0.089
Admission for HF	14 (0.8)	115 (9.6)	12.63	7.25–21.99	<0.001	4.74	2.60–8.66	<0.001
Cardiac death or admission for HF	38 (2.2)	186 (15.6)	7.71	5.44–10.92	<0.001	2.86	1.94–4.21	<0.001

Unless indicated otherwise, data are shown as n (%). The cumulative incidence of clinical outcomes is presented as Kaplan-Meier estimates over a median follow-up of 1,062 days. <sup>A</sup>The adjusted variables included in the multivariable analysis were age, sex, high Killip class (Class 3 or 4), hypertension, diabetes, end-stage renal disease, previous CHF, LVEF <50%, LVEDd, atrial fibrillation, 3-vessel disease, and failure to achieve complete revascularization. <sup>B</sup>Major adverse cardiovascular events (MACE) were defined as a composite of all-cause death, recurrent MI, unplanned repeat revascularization, or admission for heart failure (HF). CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.



**Figure 2.** Cumulative incidence of primary and secondary outcomes at 3 years. Kaplan-Meier curves for the cumulative incidence of (A) major adverse cardiovascular events (MACE) and (B) cardiac death or admission for heart failure at 3 years in the high and low N-terminal pro B-type natriuretic peptide (NT-proBNP) groups. CI, confidence interval; HR, hazard ratio.

lower achievement of complete revascularization during the index hospitalization than in the low NT-proBNP group (64.9% vs. 72.2%;  $P<0.001$ ). Pre- and post-PCI TIMI flow did not differ significantly between the 2 groups. Intravascular imaging was more commonly used in the low NT-proBNP group than high NT-proBNP group (23.3% vs. 18.0%, respectively;  $P<0.001$ ), whereas mechanical hemodynamic support was more frequently used in the high NT-proBNP group than low NT-proBNP group (1.4% vs. 0.4%, respectively;  $P=0.007$ ).

#### Clinical Outcomes According to NT-proBNP Concentration

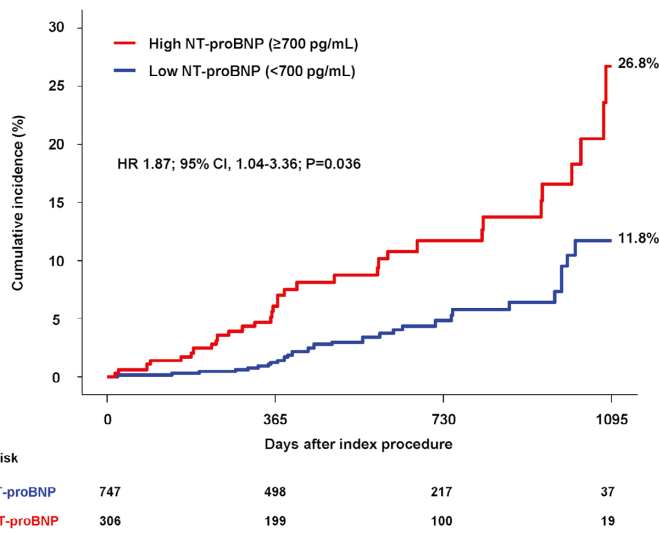
A comparison of clinical outcomes between the 2 groups is presented in Table 3 and Figure 2. The risk of MACE at 3 years was significantly higher in the high than low NT-proBNP group (29.5% vs. 12.3%, respectively; adjusted [a] HR 1.68; 95% CI 1.37–2.05;  $P<0.001$ ). The higher risk of

MACE in the high NT-proBNP group was primarily driven by a higher risk of cardiac death or admission for heart failure in this group (15.6% vs. 2.2%; aHR 2.86; 95% CI 1.94–4.21;  $P<0.001$ ). The high NT-proBNP group had a significantly higher risk of all-cause death, cardiac death, recurrent MI, and admission for heart failure than the low NT-proBNP group. Conversely, there was no significant difference in the risk of unplanned revascularization between the 2 groups (Table 3; Supplementary Figure 2). There was a significant association between the NT-proBNP concentration and risk of MACE at 3 years as a continuous value ( $P<0.001$ ; Supplementary Figure 3).

Sensitivity analysis was performed using propensity score matching and IPTW analyses to adjust for differences in baseline characteristics. Both propensity score matching and IPTW analyses constantly showed a significantly higher risk of 3-year MACE in the high NT-proBNP

	Low NT-proBNP (N=1,813)	High NT-proBNP (N=1,270)		HR (95% CI)	P value	P <sub>interaction</sub>
<b>Overall</b>	216/1813 (12.3%)	359/1270 (29.5%)		2.63 (2.23-3.12)	<0.001	
<b>Age</b>						
> 75 years	34/201 (17.6%)	148/421 (36.8%)		2.30 (1.59-3.35)	<0.001	0.845
≤ 75 years	182/1612 (11.7%)	211/849 (26.0%)		2.40 (1.97-2.93)	<0.001	
<b>Sex</b>						
Male	176/1509 (12.0%)	196/694 (29.5%)		2.68 (2.18-3.28)	<0.001	0.573
Female	40/304 (13.8%)	163/576 (29.6%)		2.38 (1.69-3.37)	<0.001	
<b>Killip class at the initial presentation</b>						
High Killip class (Class 3 or 4)	7/57 (12.5%)	105/251 (43.9%)		4.09 (1.90-8.79)	<0.001	0.134
Low Killip class (Class 1 or 2)	209/1756 (12.3%)	254/1019 (26.0%)		2.27 (1.89-2.73)	<0.001	
<b>Hypertension</b>						
Yes	113/854 (13.7%)	262/796 (34.3%)		2.84 (2.28-3.54)	<0.001	0.059
No	103/959 (11.1%)	97/474 (21.5%)		2.02 (1.53-2.66)	<0.001	
<b>Diabetes</b>						
Yes	68/444 (15.9%)	174/499 (36.5%)		2.62 (1.98-3.47)	<0.001	0.668
No	148/1369 (11.2%)	185/771 (25.0%)		2.40 (1.94-2.98)	<0.001	
<b>Left ventricular ejection fraction</b>						
< 50%	37/296 (13.0%)	211/619 (35.7%)		3.15 (2.22-4.47)	<0.001	0.063
≥ 50%	167/1455 (11.9%)	142/621 (23.8%)		2.14 (1.71-2.67)	<0.001	
<b>Angiographic disease extent</b>						
Multivessel disease	115/844 (14.1%)	209/683 (31.9%)		2.53 (2.01-3.17)	<0.001	0.781
Single vessel disease	101/969 (10.8%)	150/587 (26.8%)		2.67 (2.08-3.44)	<0.001	
<b>Complete revascularization</b>						
Yes	132/1309 (10.5%)	192/824 (24.5%)		2.50 (2.00-3.12)	<0.001	0.752
No	84/504 (17.0%)	167/446 (38.9%)		2.59 (1.99-3.37)	<0.001	

**Figure 3.** Subgroup analyses of major adverse cardiovascular events (MACE) in the high and low N-terminal pro B-type natriuretic peptide (NT-proBNP) groups. The cumulative incidence and hazard ratios (HRs) with 95% confidence intervals (CIs) of MACE at 3 years are presented for the high and low NT-proBNP groups across various subgroups. The interaction P value indicates the likelihood of an interaction between the variable and the relative prognostic value.



**Figure 4.** Cumulative incidence of left ventricular ejection fraction (LVEF) decline to <50% at follow-up echocardiography. Kaplan-Meier curves for the 3-year cumulative incidence of LVEF decline to <50% at follow-up echocardiography in the high and low N-terminal pro B-type natriuretic peptide (NT-proBNP) groups. Adjusted variables were age, sex, high Killip class (Class 3 or 4), hypertension, diabetes, dyslipidemia, previous congestive heart failure, and 3-vessel disease. CI, confidence interval; HR, hazard ratio.

group than in the low NT-proBNP group (Supplementary Table 2). Patients with elevated initial NT-proBNP showed a consistently higher risk of MACE across various subgroups without significant interaction (Figure 3). In addition, the higher risk of MACE in the high NT-proBNP group was consistently observed, regardless of target vessels (Supplementary Figure 4).

When evaluating follow-up echocardiographic data among 1,053 patients with an LVEF >50% at index echocardiography and for whom both index and follow-up echocardiograms were available, the cumulative incidence of LVEF decline to <50% at 3 years was significantly higher in the high than low NT-proBNP group (26.8% vs. 11.8%; aHR 1.87; 95% CI 1.040–3.365; P=0.036; Figure 4).

## Discussion

The present study compared clinical outcomes at 3 years according to the initial NT-proBNP concentration in patients with NSTEMI who underwent PCI. The main findings are as follows. First, approximately 40% of NSTEMI patients had high NT-proBNP concentrations (>700 pg/mL) and this group had a higher prevalence of major cardiovascular risk factors and more extensive coronary artery disease. Second, the high NT-proBNP group had an increased risk of MACE at 3 years compared with the low NT-proBNP group, driven primarily by an increased risk of cardiac death or admission for heart failure. The prognostic implications of NT-proBNP were consistent after propensity score matching and IPTW analysis. In the subgroup analysis, high NT-proBNP was associated with worse clinical outcomes across various subgroups. Third, patients in the high NT-proBNP group had a significantly higher cumulative incidence of LVEF decline to <50% compared with those in the low NT-proBNP group during the 3 years of follow-up.

Recently, with advancements in biomarkers used for the working diagnosis of ACS, such as high-sensitivity cardiac troponin,<sup>25</sup> the incidence of NSTEMI has steadily increased, establishing its predominance among all ACS patients.<sup>3,4</sup> Although the overall prognosis of NSTEMI patients has improved, there remains a residual risk of mortality even after successful revascularization. Indeed, NSTEMI reports a 1-year mortality rate of approximately 6% and is known to leave sustained sequelae, such as ischemic cardiomyopathy and CHF.<sup>3,6</sup> Consequently, there is a growing need for reliable prognostic biomarkers for risk stratification and long-term management in patients with NSTEMI. Several studies have investigated biomarkers associated with the prognosis of NSTEMI patients. Hjort et al conducted a study on various cardiovascular biomarkers using blood samples extracted from patients during the acute phase of STEMI and NSTEMI.<sup>9</sup> However, the pathophysiologic pattern of biomarkers in the NSTEMI patient group was heterogeneous, and failed to demonstrate the prognostic value of NT-proBNP for mortality and MACE.<sup>9</sup> Zelniker et al reported that C-terminal telopeptide was associated with the prognosis of cardiac death and heart failure in NSTEMI patients; however, C-terminal telopeptide, known as a biomarker of collagen turnover, showed limited cardiac specificity.<sup>8</sup> Furthermore, previous studies showed limited prognostic value of CK-MB or galectin-3 in NSTEMI patients.<sup>6,10</sup>

NT-proBNP has been established as a reliable biomarker for predicting prognosis in various heart diseases, especially CHF.<sup>11,12</sup> However, only a few studies have investigated the prognostic value of NT-proBNP in patients with NSTEMI. Schellings et al showed that elevated NT-proBNP was a prognostic factor predicting 30-day mortality among 1,324 NSTEMI patients.<sup>18</sup> Similarly, Takahashi et al evaluated 218 NSTEMI patients without elevation of creatine kinase and reported that a higher BNP concentration (>100 pg/mL) was associated with an increased risk of adverse clinical events at 3 years.<sup>17</sup> However, the results of these previous studies should be interpreted with caution. Although coronary revascularization by PCI or bypass surgery is the dominant treatment in contemporary practice, revascularization was performed in less than two-thirds of the study populations: 54.1% in the study of Takahashi et al<sup>17</sup> and 67.0% in the study of Schellings et al.<sup>18</sup> As a result, there is limited evidence regarding the

long-term prognostic implications of NT-proBNP in patients with NSTEMI who have undergone PCI in large study populations with long-term follow-up. In this regard, the present study assessed the prognostic implications of NT-proBNP among 3,083 NSTEMI patients treated by PCI during index hospitalization and evaluated clinical outcomes during a median follow-up of 2.9 years using data from the large-scale nationwide KAMIR-NIH registry.

In the present study, the risk of MACE at 3 years was significantly higher in the high compared with low NT-proBNP group, driven primarily by an increased risk of cardiac death or admission for heart failure. It should be noted that the high NT-proBNP group had a higher prevalence of cardiovascular comorbidities and more extensive and complex coronary artery disease than the low NT-proBNP group. Regarding procedural results, the total length and number of implanted stents were higher, and the rate of complete revascularization was lower in the high compared with low NT-proBNP group. However, even after adjusting for various clinical factors that showed significant differences between the 2 groups through sensitivity analyses, the risk of MACE at 3 years remained significantly higher in the high NT-proBNP group. Furthermore, the risk of MACE at 3 years increased proportionally with the NT-proBNP concentration, showing the prognostic value of NT-proBNP concentrations for patients with NSTEMI who underwent PCI.

In addition, the high NT-proBNP group had a higher cumulative incidence of LVEF decline to <50% than the low NT-proBNP group. These results suggest that patients with elevated NT-proBNP concentrations would have a higher risk of developing LV systolic dysfunction and the onset of heart failure, even if the LVEF at index hospitalization is within the normal range. Another plausible explanation of the prognostic association between initial NT-proBNP concentrations and long-term clinical outcomes is that some acute MI patients presented with pre-existing elevated LV filling pressure.<sup>26</sup> Elevated LV filling pressure indicates underlying structural and functional abnormalities of cardiac diastolic dysfunction before the acute MI event and is associated with clinical outcomes. Considering the limited evidence regarding reliable prognostic biomarkers in NSTEMI patients, the findings of the present study suggest that NT-proBNP may be a reliable prognostic indicator in NSTEMI patients treated with PCI.

## Study Limitations

Some study limitations should be addressed. First, the study population was derived from prospective observational data. Although we tried to adjust for confounding variables through various statistical methods, there remains the risk of unintentional bias. Second, the optimal cut-off value of NT-proBNP (>700 pg/mL) for predicting MACE for NSTEMI patients was determined based on ROC analysis of the study population. Therefore, external validation of this cut-off value would be needed. Third, a high NT-proBNP concentration was associated with decreased LV systolic function during follow-up. However, diastolic function could not be assessed according to NT-proBNP concentrations because data pertaining to diastolic function were not collected in the KAMIR-NIH registry. Fourth, guideline-directed medical treatment including up-titration of  $\beta$ -blockers may influence NT-proBNP concentrations, but the current registry data did not systematically collect detailed information regarding medical treatment,



especially during the follow-up period.

## Conclusions

In patients with NSTEMI who underwent PCI, an elevated initial NT-proBNP concentration was associated with a higher risk of MACE at 3 years, driven primarily by the higher risk of cardiac death and admission for heart failure. The results of the present study suggest that the NT-proBNP concentration at the time of initial presentation may have a clinically significant prognostic value in NSTEMI patients undergoing PCI.

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## IRB Information

This study was approved by the Institutional Review Board of the Samsung Medical Center (Approval no. 2011-10-080).

## Data Availability

The deidentified participant data will not be shared.

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## Supplementary Files

Please find supplementary file(s):  
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