narra j

Short Communication

Association between NT-proBNP level and the number of stents with major advanced cardiovascular events (MACE) in patients with multivessel coronary artery disease treated with percutaneous coronary intervention: A prospective cohort study

Muhammad Subkhan[1], Teuku Heriansyah[1,2*], Haris Munirwan[1,2], Adi Purnawarman[1,2] and Herlina Dimiati[3,4]

[1]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia; [2]Department of Cardiology and Vascular Medicine, Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia; [3]Department of Pediatric, Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia; [4]Department of Pediatric, Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia

*Corresponding author: teuku_hery@usk.ac.id

Abstract

Complex revascularization strategies, particularly complete revascularization, are controversial in coronary artery disease (CAD), and data supporting routine revascularization in stable CAD is lacking. The importance of percutaneous coronary intervention (PCI) in CAD and N-terminal pro-brain natriuretic peptide (NT-proBNP), which has been studied as a predictor of major advanced cardiovascular events (MACE) in CAD patients, still requires further research. The aim of this study was to determine the association between NT-proBNP levels and the number of stents with MACE incidence in CAD cases. A prospective cohort study was conducted in both types of CAD (acute coronary syndrome (ACS) and chronic coronary syndrome (CCS)). The NT-proBNP levels were measured pre- and post-PCI using fluorescence immunoassay, while MACE was assessed three months post-PCI. The Student t-test was used to compare the levels of NT-proBNP between pre- and post-PCI and between those who had MACE and did not; both in patients treated with single or multiple stenting groups. A total of 32 CAD patients were recruited, consisting of 20 ACS cases and 12 CCS cases. NT-proBNP levels post-PCI increased significantly in both ACS and CCS patients compared to pre-PCI either among those treated with single and multiple stentings. MACE occurred in 4 (12.5%) out of a total of 32 patients, all of which occurred in ACS patients treated with multiple stentings. Those who had MACE had higher post-PCI NT-proBNP levels compared to those who did not have MACE (23,703.50 vs 11,600.17 pg/mL, p=0.013). This study highlights the association between elevated NT-proBNP levels and multiple stenting with the presence of MACE in CAD patients, particularly in ACS cases.

Keywords: Acute coronary syndrome, chronic coronary syndrome, PCI, NT-proBNP, MACE

Introduction

Coronary artery disease (CAD) is characterized by compromised heart function due to insufficient oxygen supply to the heart muscle resulting from the narrowing of coronary blood

https://narraj.org/

Received: February 8, 2024 - Accepted: April 11, 2024 - Published online: April 16, 2024

vessels [1]. CAD stands as the leading cause of global mortality in 2022 with an annual mortality rate of nine million individuals out of 126 million affected by CAD worldwide [2]. In Indonesia, heart disease is a major health issue, affecting 0.5% in 2013 and increasing to 1.5% in 2018, with prevalence rates in over 15 provinces surpassing the national average [3].

In efforts to reduce CAD mortality rates, percutaneous coronary intervention (PCI) was introduced, a minimally invasive procedure that has proven effective in decreasing mortality, myocardial infarctions, and strokes [4]. Over 50% of CAD patients have multivessel disease, straining healthcare finances [3]. Although PCI relieves symptoms, the risk of post-procedural events emphasizes the delicate balance between patient quality of life and major advanced cardiovascular events (MACE) [5-7]. Outcomes are intricately influenced by factors such as age, gender, hypertension, chronic heart failure, smoking, stent count, multivessel CAD, and glomerular filtration rate [8]. Studies have highlighted a correlation between the number of stents implanted during PCI procedures and higher mortality rates, underscoring the multifaceted nature of ischemic-reperfusion injury and endothelial dysfunction in shaping the outcomes of PCI [9,10].

In the complex strategies of managing CAD, the use of N-terminal pro-brain natriuretic peptide (NT-proBNP), one of the cardiac enzymes, stands out as a potential marker for predicting MACE in CAD patients who undergo PCI. Early studies suggested that considering NT-proBNP alongside factors like age and ejection fraction holds promise for early detection and risk assessment in CAD patients undergoing PCI [11]. However, more extensive studies are necessary to understand the detailed relationship between NT-proBNP levels and other factors, such as the number of stents used and MACE, particularly in cases of both stable and unstable multivessel CAD [11]. The aim of this study was to assess the correlation of NT-proBNP levels and the number of stents with MACE in patients with multivessel coronary artery disease undergoing PCI.

Methods

Study design and patients

A prospective cohort study including following up was undertaken in Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia, from May 2023 until September 2023. This study included patients aged 18–75 years, with CAD diagnosed by a cardiologist and undergoing PCI with stent placement, and experiencing multivessel disease (≥2 vessels with a minimum 70% stenosis based on coronary angiography) [13]. Patients diagnosed with heart failure, post-coronary artery bypass graft (CABG) phase, and experiencing cardiogenic shock were excluded from the study. Patients with chronic kidney failure, chronic obstructive pulmonary disease (COPD), and other chronic lung diseases were considered eligible [14]. The study also considered individuals with cancer, history of stroke, and valve heart disease, whether congenital or acquired.

To determine the sample size, the Slovin formula was used and a minimum sample size of 31 was required. The number of samples was rounded up to 32, consisting of 16 CAD patients with single stent and 16 CAD patients with multiple stents. A quota sampling method was used to recruit the samples in the study.

Percutaneous coronary intervention (PCI) procedure

Patients with multiple vessel diseases, defined as having at least two stenoses out of a total of three coronary arteries of the heart (those with only one stenosis then the patient were excluded) underwent the PCI procedure in the Cardiac Catheterization Lab at Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia. To identify patients with multiple vessel disease, coronary angiography (a non-invasive diagnostic measure) was performed to ensure a patient was eligible for the study. During PCI, patients may receive either a single stent or multiple stents.

Data collection

Data collection was performed on CAD patients diagnosed with both acute coronary syndrome (ACS) and chronic coronary syndrome (CCS). Patients categorized as ACS presented with unstable angina pectoris, non-ST elevation myocardial infarction, and ST elevation myocardial infarction, while CCS patients were characterized by stable angina pectoris. All CAD patients who

met the criteria signed informed consent and provided contact details. Subsequently, blood samples were collected from the brachial vein within one day before PCI for NT-proBNP examination. The blood samples were then placed in a pre-cooled tube containing ethylenediaminetetraacetic acid (EDTA) for NT-proBNP level measure using a fluorescence immunoassay (FIA) method with the Ichrom NT-proBNP kit (Boditech Med Inc., Gang-won-do, Korea), following the manufacturer's instructions. A second blood collection from the brachial vein was performed 12–24 hours after PCI, and NT-proBNP levels were re-measured. Normal NT-proBNP levels were considered less than 300 pg/mL.

Follow-up assessments were performed three months post-PCI to evaluate MACE, which included all-cause mortality, cardiac-related mortality, heart failure, fatal myocardial disorders, severe arrhythmias, and recurrent cardiac interventions.

Study variables

In this study, the independent included the number of stents (single or multiple stents (2 stents)) and the level of NT-proBNP, while the dependent variable was the incidence of MACE (present or absent).

Statistical analysis

The Student t-test and Chi-squared test were used to compare the clinical variables and NT-proBNP levels between ACS and CCS. The paired Student t-test was employed to compare the levels of NT-proBNP between pre- and post-PCI. To compare the levels of NT-proBNP between patients with and without MACE, the Student t-test was also used. All statistical analyses were performed using the statistical software SPSS version 25 (IBM SPSS., Chicago, USA). Statistical significance was considered at $p<0.05$.

Results

Characteristics of patients

A total of 32 patients with CAD were included in the study, and the characteristics are presented in **Table 1**. Most of the patients were male (87.5%) with the mean age of 58 years old. The mean systolic blood pressure was 133.15 mmHg in ACS patients and 124.25 mmHg in CCS patients. Four MACE incidences were reported in the ACS patients (12.5%).

Our data indicated that systolic and diastolic blood pressure and mean arterial pressure were significantly higher in ACS in contrast to CCS. In addition, the levels of the NT-proBNP were significantly higher in ACS compared to CCS both during pre-PCI (6,054.65 pg/mL vs 1,326.33 pg/mL, $p<0.001$) and post-PCI (12,607.95 pg/mL vs 2,775.00 pg/mL, $p<0.001$) (**Table 1**).

Table 1. Characteristics, NT-proBNP levels and incidence of MACE between two types of multivessel coronary artery disease (CAD) (n=32)

Characteristics	Total (n=32) Mean±SD	CAD type (mean±SD)		*p*-value
		Acute coronary syndrome (n=20)	Chronic coronary syndrome (n=12)	
Age (years)	58.19±9.62	58.20±10.98	58.17±7.23	0.992[a]
Gender, n (%)				0.534[b]
Male	28 (87.5)	18 (90.0)	10 (83.3)	
Female	4 (12.5)	2 (10.0)	2 (16.6)	
Weight (kg)	80.2±12.08	80.40±11.49	79.92±13.52	0.919[a]
Height (cm)	168.47±8.55	167.85±9.13	169.50±7.76	0.591[a]
Body mass index (kg/m²)	28.10±2.49	28.38±2.13	27.62±3.05	0.459[a]
Systolic blood pressure (mmHg)	129.81±10.44	133.15±9.65	124.25±9.59	0.018[a*]
Diastolic blood pressure (mmHg)	84.44±7.72	87.00±7.39	80.17±6.45	0.011[a*]
Mean arterial pressure (mmHg)	99.56±8.41	102.38±7.95	94.86±7.17	0.011[a*]
Heart rate (beats/minute)	83±10.98	84±13.0	80±8.0	0.269[a]
Number of stents	1.50±0.51	1.50±0.51	1.50±0.52	0.260[a]
Number of stents, n (%)				0.759[b]
Single	16 (50.0)	10 (50.0)	6 (50.0)	

Characteristics	Total (n=32) Mean±SD	CAD type (mean±SD)		*p*-value
		Acute coronary syndrome (n=20)	Chronic coronary syndrome (n=12)	
Multiple	16 (50.0)	10 (50.0)	6 (50.0)	
NT-proBNP (pg/mL)				
Pre-PCI	4,281.5±4478.3	6,054.6±4,802.4	1,326.33±1,200.0	<0.001[a] **
Post-PCI	8,920.5±9618.0	12,607.9±10,396.2	2,775.00±2,844.6	<0.001[a] **
MACE, n (%)				0.400[b]
Yes	4 (12.5)	4 (20.0)	0 (0.0)	
No	28 (87.5)	16 (80.0)	12 (100.0)	

[a] Analyzed using Student t-test
[b] Analyzed using Chi-squared test
* Statistically significant at p=0.05
** Statistically significant at p=0.001

Comparison of NT-proBNP levels based on stenting number in CAD patients

Our data indicated that the levels of NT-proBNP were significantly higher in post-PCI compared to pre-PCI in ACS patients, observed in both single stenting (p=0.006), multiple stentings (p=0.004) and combined single and multiple stent groups (p<0.001). However, NT-proBNP levels were only significantly higher in post-PCI compared to pre-PCI in CCS patients who had single stenting (p=0.004) (**Table 2**).

Table 2. Comparison of NT-proBNP level based on number of stents in patients with multivessel coronary artery disease (CAD) (n=32)

CAD type	Category	NT-proBNP	Level of NT-proBNP (mean±SD)	*p*-value [a]
ACS	Single stenting	Pre-PCI	5,311.00±4,808.35	0.006*
		Post-PCI	8,774.40±7,580.05	
	Multiple stenting	Pre-PCI	6,798.30±4,933.51	0.004*
		Post-PCI	16,441.50±11,749.78	
CCS	Single stenting	Pre-PCI	956.83±836.56	0.004*
		Post-PCI	1,320.00±1,008.91	
	Multiple stenting	Pre-PCI	1,695.83±1,463.09	0.052
		Post-PCI	4,230.00±3,420.98	

ACS: acute coronary syndromes; CAD: coronary artery disease; CCS: chronic coronary syndromes
[a] Analyzed using Student t-test
* Statistically significant at p=0.05

Association between post-PCI NT-proBNP level and MACE in CAD patients

As reported, MACE occurred among ACS patients, comprising four patients (12.5%). No MACE incidents were observed among ACS patients treated with single stenting, whereas among ACS patients with multiple stenting (n=10), MACE occurred in 40% (4/10) of patients. Our data indicated that NT-proBNP levels post-PCI were significantly higher among those who had MACE compared to those who did not (23,703.50 vs 11,600.17 pg/mL, p=0.013) (**Table 3**).

Table 3. Association between the level of NT-proBNP post-percutaneous coronary intervention (PCI) and the incidence of major advanced cardiovascular events (MACE) in patients with acute coronary syndrome (ACS) (n=12)

Groups	MACE	Post-PCI NT-proBNP level	*p*-value
Single stenting (n=10)			NA
	Yes (n=0)	NA	
	No (n=10)	8,774.40±7580.05	
Multiple stenting (n=10)			0.013
	Yes (n=4)	23,703.50±14514.48	
	No (n=6)	11,600.17±7196.20	

NA: not available
[a] Analyzed using Student t-test
* Statistically significant at p=0.05

Discussion

Our study found that NT-proBNP levels increased in ACS patients. In ACS patients with ST-segment elevation myocardial infarction (STEMI), the increase in NT-proBNP levels is attributable to acute myocardial infarction, which induces the release of NT-proBNP from the

ventricles due to elevated stress on the left ventricular wall [15-18]. NT-proBNP levels can also be used to assess silent myocardial ischemia [19,20]. NT-proBNP is also associated with the regulation of various physiological functions that control energy metabolism, myocardial ischemia, and the development of organ damage, including left ventricular hypertrophy and peripheral artery disease. Additionally, an increase in NT-proBNP levels can also reflect subclinical left ventricular dysfunction or diastolic dysfunction, vascular dysfunction, and renin-angiotensin-aldosterone system (RAAS) activation [21,22].

In ACS, atherosclerosis progresses over time and is exacerbated by plaque rupture, leading to acute events. This process is associated with an increase in levels of IL-6, leptin, blood homocysteine, cystatin-c (CYS-C), and c-reactive protein, indicating the presence of chronic inflammation related to MACE [23]. The elevation of left ventricular end-diastolic pressure (LVEDP) is closely correlated with the overall ventricular function and directly proportional to the left ventricular remodeling process [24]. LVEDP reflects ventricular compliance, thereby being linked to MACE. During post-PCI, LVEDP may increase in patients experiencing MACE [25]. Our study reported four incidents of MACE in ACS patients. Even in cases where there is no immediate decline in left ventricular ejection fraction (LVEF) and signs of heart failure, LVEDP tends to rise in the acute phase following PCI, which can provoke MACE. Therefore, the assessment of the LVEF/LVEDP ratio is more indicative of heart failure events post-PCI. Impaired epicardial blood flow, particularly in the infarct-related artery, triggers an increase in LVEDP. This is also correlated with the extent of myocardial infarction, serving as an independent predictor in post-PCI patients [26].

Our study found that the multiple stenting groups had increased levels of NT-proBNP in both ACS and CCS groups. This suggests that patients undergoing multiple stenting would have a significant increase in NT-proBNP levels post-PCI, thereby elevating the risk of MACE. These findings contrast with the outcomes of the complete revascularization with multivessel PCI for myocardial infarction (COMPLETE) [26] and complete versus lesion-only primary PCI Trial (CvLPRIT) studies [27], which revealed that complete revascularization STEMI can reduce mortality. While both of these significant studies demonstrated that directly performed complete revascularization versus the staged approach showed no significant difference, findings also revealed a lower rate of MACE in directly performed complete revascularization compared to the staged approach. We also found no MACE reported in the single stenting group. This could be because of the limited post-PCI observation, given that the large studies like COMPLETE and CvLPRIT assessed MACE outcomes after at least one year [26]. Meanwhile, other studies reported that MACE was observed in subjects who received multiple stents and exhibited a more than a threefold increase in NT-proBNP levels [28-30].

Conclusion

Our data suggested that the levels of NT-proBNP were significantly higher in ACS compared to CCS patients either pre- and post-PCI. NT-proBNP levels significantly increased after PCI in both types of multivessel CAD patients (ACS and CCS) treated either with single or multiple stenting. Our data also indicated that multiple stentings were associated with an increased risk of MACE incidence in patients with ACS.

Ethics approval

The study was approved by the Health Research Ethics Committee of Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia (ref no. 023/ETIK-RSUDZA/2024).

Acknowledgments

We thank all the volunteers who participated in this study and the staff at Cardiac Catheterization Laboratory and staff at Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia. We also appreciate Pertamedika Umi Rosnati Laboratory staff for the assistance.

Competing interests

All the authors declare that there are no conflicts of interest.

Funding

The cost for the exercise program was funded by Dr. Zainoel Abidin Hospital collaborated with the Research and Community Service Institute of Universitas Syiah Kuala. The funding source was not involved in the design or conduct of the study or during the preparation of the manuscript, and the analyses and opinions expressed are those of the authors alone.

Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

How to cite

Subkhan M, Heriansyah T, Munirwan H, *et al*. Association between NT-proBNP level and the number of stents with major advanced cardiovascular events (MACE) in patients with multivessel coronary artery disease treated with percutaneous coronary intervention: A prospective cohort study. Narra J 2024; 4 (1): e710 - http://doi.org/10.52225/narra.v4i1.710.

References

1. Coerkamp CF, Hoogewerf M, van Putte BP, *et al*. Revascularization strategies for patients with established chronic coronary syndrome. Eur J Clin Invest 2022;52(8):e13787.
2. Nowbar AN, Rajkumar C, Al-Lamee RK, Francis DP. Controversies in revascularisation for stable coronary artery disease. Clin Med 2021;21(2):114-118.
3. Repositori Badan Kebijakan Pembangunan Kesehatan. Laporan nasional riskesdas 2018. Available from: https://repository.badankebijakan.kemkes.go.id/id/eprint/3514/. Accessed: 23 May 2023.
4. Chan MY, Sun JL, Newby LK, *et al*. Long-term mortality of patients undergoing cardiac catheterization for ST-elevation and non-ST-elevation myocardial infarction. Circulation 2009;119(24):3110-3117.
5. Bradley SM, Spertus JA, Kennedy KF, *et al*. Patient selection for diagnostic coronary angiography and hospital-level percutaneous coronary intervention appropriateness: Insights from the national cardiovascular data registry. JAMA Intern Med 2014;174(10):1630.
6. Boden WE, O'Rourke RA, Teo KK, *et al*. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356(15):1503–1516.
7. Kumboyono K, Indah NC, Nadya NS, et al. Nicotine is associated with smoking dependence and vascular inflammation through cotinine: A mediation analysis. Tob Induc Dis 2024;22: 10.18332/tid/171356.
8. De Bruyne B, Pijls NH, Kalesan B, *et al*. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367(11):991-1001.
9. Yusuf S, Hawken S, Ounpuu S, *et al*. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case–control study. Lancet 2004;364(9438):937-952.
10. Chhatriwalla AK, Nicholls SJ, Wang TH, *et al*. Low levels of low-density lipoprotein cholesterol and blood pressure and progression of coronary atherosclerosis. J Am Coll Cardiol 2009;53(13):1110-1115.
11. Rudolf H, Mügge A, Trampisch HJ, *et al*. NT-proBNP for risk prediction of cardiovascular events and all-cause mortality: The getABI-study. Int J Cardiol Heart Vasc 2020;29:100553.
12. Serruys PW, Hara H, Garg S, Kawashima H. Coronary computed tomographic angiography for complete assessment of coronary artery disease. J Am Coll Cardiol 2021;78(7):713-736.
13. Ray P, Delerme S, Jourdain P, *et al*. Differential diagnosis of acute dyspnea: The value of B natriuretic peptides in the emergency department. QJM 2008;101(11):831-843.
14. Maisel AS, Krishnaswamy P, Nowak RM, *et al*. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347(3):161-167.
15. Kara K, Mahabadi AA, Geisel MH, *et al*. B-type natriuretic peptide: Distribution in the general population and the association with major cardiovascular and coronary events-the Heinz Nixdorf Recall Study. Clin Res Cardiol 2014;103(2):125-132.
16. Nadir MA, Rekhraj S, Wei L, *et al*. Improving the primary prevention of cardiovascular events by using biomarkers to identify individuals with silent heart disease. J Am Coll Cardiol 2012;60(11):960-968.
17. Niccoli G, Conte M, Marchitti S, *et al*. NT-proANP and NT-proBNP circulating levels as predictors of cardiovascular outcome following coronary stent implantation. Cardiovasc Revasc Med 2016;17(3):162-168.

18. Wang L, Cong HL, Zhang JX, *et al*. Prognostic significance of preprocedural N-terminal Pro-B-type natriuretic peptide assessment in diabetic patients with multivessel coronary disease undergoing revascularization. Front Cardiovasc Med 2021;8:721260.
19. Diao Y, Yin M, Zhang B, Sun B. Predictive value of N-terminal pro-B-type natriuretic peptide (NT-pro BNP) combined with D-dimer for no-reflow phenomenon in patients with acute coronary syndrome after emergency of percutaneous coronary intervention. Bioengineered 2021;12(1):8614-8621.
20. Hong SN, Ahn Y, Hwang SH, *et al*. Usefulness of preprocedural N-terminal pro-brain natriuretic peptide in predicting angiographic no-reflow phenomenon during stent implantation in patients with ST-segment elevation acute myocardial infarction. Am J Cardiol 2007;100(4):631-634.
21. Sivachandran G, Senthilvelan M, Baburaj K, *et al*. Study of NT-Pro BNP in acute coronary syndromes. J Med Sci Clin Res 2018;6(10):988-995.
22. Zdravkovic V, Mladenovic V, Colic M, *et al*. NT-proBNP for prognostic and diagnostic evaluation in patients with acute coronary syndromes. Kardiol Pol 2013;71(5):472-479.
23. Khan IA, Fink J, Nass C, *et al*. N-terminal pro BNP and BNP for identifying coronary artery disease and LVH in ambulatory chronic kidney disease patients. Am J Cardiol 2006;97(10):1530-1534.
24. Zhang LJ, Li N, Li Y, *et al*. Cardiac biomarkers predicting MACE in patients undergoing noncardiac surgery: A meta-analysis. Front Physiol 2019;9:1923.
25. Liu HH, Cao YX, Jin JL, *et al*. Prognostic value of NT-proBNP in patients with chronic coronary syndrome and normal left ventricular systolic function according to glucose status: A prospective cohort study. Cardiovasc Diabetol 2021;20(1):84.
26. Jakimov T, Mrdović I, Filipović B, *et al*. Comparison of RISK-PCI, GRACE, TIMI risk scores for prediction of major adverse cardiac events in patients with acute coronary syndrome. Croat Med J 2017;58(6):406-415.
27. Azzalini L, Seth M, Sukul D, *et al*. Impact of left ventricular end-diastolic pressure on the outcomes of patients undergoing percutaneous coronary intervention. Am J Cardiol 2022;185:107-114.
28. Ndrepepa G, Cassese S, Emmer M, *et al*. Relation of ratio of left ventricular ejection fraction to left ventricular end-diastolic pressure to long- term prognosis after ST-segment elevation acute myocardial infarction. Am J Cardiol 2019;123(2):199-205.
29. Kumar R, Shah JA, Solangi BA, *et al*. The burden of short-term major adverse cardiac events and its determinants after emergency percutaneous coronary revascularization: A prospective follow-up study. J Saudi Heart Assoc 2022;34(2):100-109.
30. Gong X, Zhang T, Feng S, *et al*. Association between N-terminal pro-BNP and 12 months major adverse cardiac events among patients admitted with NSTEMI. Ann Palliat Med 2021;10(5):5231-5243.