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Association between serum endothelin-1 level and major adverse cardiovascular events following percutaneous coronary intervention in stable coronary artery disease

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ABSTRACT

Coronary artery disease (CAD) affects greatly the global population, exhibits high mortality and morbidity rates. Major adverse cardiovascular events (MACE), such as stroke, myocardial infarction, heart failure, and death, are the focus of research due to their significant contribution to morbidity and mortality in patients with CAD. Endothelin-1 is identified as a CAD prognostic indicator, especially for heart failure outcome. This study aimed to investigate the association between serum endothelin-1 level and MACE within 1 yr observation in patients with CAD underwent percutaneous coronary intervention (PCI). It was a retrospective cohort study where conducted at Dr. Sardjito General Hospital, Yogyakarta, Indonesia. Subjects were patients with stable CAD who underwent elective PCI. Baseline serum endothelin-1 level was measured by ELISA at the time of elective PCI procedure. The outcome was MACE, which consisted of heart failure, acute coronary syndrome, stroke, and cardiac death, occurred within 1 yr after elective PCI. The ROC curve was designed to determine serum endothelin-1 cut-off value to predict MACE. Sixty-three subjects were enrolled and the endothelin-1 level in serum samples was analyzed. Out of these, 11 (17.5%) experienced MACE within 1 yr post elective PCI. Serum endothelin-1 cut-off value was 1.932 pg/mL, which determined based on ROC curve. There was no significant association between serum endothelin-1 and MACE. There was a trend of higher incidence of MACE, in subjects with above-cut-off endothelin-1 level (≥1.932 pg/mL) (MACE incidence: 23.1% vs. 8.3%; p=0.181). Above-cut-off endothelin-1 level significantly associated with incidence of heart failure (100% vs. 0%; p=0.039) for 1 yr follow-up after elective PCI. Higher serum endothelin-1 level had a trend of higher incidence of 1-yr MACE in patients with stable CAD undergone elective PCI. Among 1-yr MACE, higher serum endothelin-1 associated with increased incidence of heart failure.

ABSTRAK

Penyakit jantung koroner (PJK) berdampak besar bagi populasi global, yang menunjukkan tingginya angka kematian dan kesakitan. Kejadian kardiovaskular buruk (KKB), seperti stroke, infark miokard, gagal jantung, dan kematian, menjadi fokus penelitian karena perannya yang signifikan terhadap angka kematian dan kesakitan pada pasien dengan PJK. Endotelin-1 telah diidentifikasi sebagai indikator prognostik pada PJK, terutama pada kejadian gagal jantung. Penelitian ini bertujuan untuk mengkaji hubungan antara kadar endothelin-1 serum dengan KKB dalam kurun 1 tahun observasi pada pasien dengan PJK yang menjalani intervensi koroner perkutan (IKP). Disain penelitian ini adalah studi kohort retrospektif. Penelitian ini dilakukan di Rumah Sakit Umum Pusat Dr. Sardjito, Yogyakarta, Indonesia. Subjek adalah pasien dengan PJK stabil yang menjalani IKP elektif. Kadar endothelin-1 serum awal diukur dengan metode ELISA pada saat prosedur IKP elektif. Luaran yang dinilai adalah KKB, terdiri dari gagal jantung, sindrom koroner akut, stroke, dan kematian jantung, yang terjadi dalam waktu 1 tahun setelah IKP elektif. Kurva ROC didisain untuk menentukan nilai ambang batas endothelin-1 serum untuk prediksi KKB. Enam puluh tiga subjek diikutsertakan dalam penelitian dan kadar endothelin-1 pada sampel serumnya dianalisis. Sebelas dari 63 subjek (17,5%) mengalami KKB dalam waktu 1 tahun pasca IKP elektif. Nilai ambang batas endothelin-1 serum adalah 1,932 pg/mL, yang ditentukan berdasarkan kurva ROC. Hasil analisis tidak menunjukkan hubungan yang signifikan antara endothelin-1 serum dan

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KKB. Ditemukan adanya kecenderungan insiden KKB yang lebih tinggi pada subjek dengan kadar endothelin-1 di atas ambang batas (≥1,932 pg/mL) (insiden KKB: 23,1% vs. 8,3%; p=0,181). Kadar endothelin-1 di atas ambang batas secara signifikan terkait dengan insiden gagal jantung (100% vs. 0%; p=0,039) yang teramati dalam kurun 1 tahun setelah IKP elektif. Kadar endothelin-1 serum yang lebih tinggi mempunyai kecenderungan peningkatan insidensi KKB dalam 1 tahun pada pasien PJK yang dilakukan IKP elektif. Di antara KKB dalam satu tahun, kadar endothelin-1 yang lebih tinggi berhubungan dengan kenaikan insidensi gagal jantung.

INTRODUCTION

Coronary artery disease (CAD) contributes to patients' morbidity and negatively impacts health-related quality of life. Many CAD patients eventually require hospitalization for acute coronary syndrome (ACS) and heart failure (HF).[1] Major adverse cardiovascular events (MACE), an endpoint often used in cardiovascular research, are also a major cause of morbidity and mortality in patients living with CAD.[2] It includes non-fatal strokes, non-fatal myocardial infarction or ACS and/or deaths resulting from cardiovascular events and is sometimes extended to include de novo HF.[3,4]

Currently, contemporary data that estimates the incidence of MACE in patients with CAD remain limited. Patients with CAD treated regularly and concurrently had a high risk for MACE in the first and fourth years during the treatment period.[5] Percutaneous coronary intervention (PCI) has been known for four decades, aimed at overcoming angina in stable CAD. Currently, more than 500,000 PCI procedures are performed annually worldwide for this indication.[6] Meanwhile, in ACS, PCI aims to reduce mortality and infarction of the myocardium. However, in stable CAD, its role remains clearly controversies among studies. Current data show that PCI provides benefits beyond symptom relief, namely reduction in mortality, myocardial infarction, left ventricular dysfunction and other sequelae due to ischemia, including HF.[6]

Several biomarkers have recently been introduced as prognostic indicators in ACS and stable CAD. Among them, endothelin-1 has been proposed as a prognostic indicator of ACS. Meanwhile, its role in predicting MACE patients with stable CAD remains unclear. Endothelin-1, which originates mostly from endothelial cells, is related to endothelial dysfunction and has potent vasoconstriction property. Endothelial dysfunction and persistence vasoconstriction were studied as atherosclerotic risk factors and correlate with future MACE. Our previous study showed that endothelin-1 level were elevated in patients with CAD and it is associated with the disease severity.[7,8] Furthermore, the PCI procedure disrupts endothelial cell integrity inducing endothelin-1 release, which may have future post-procedural consequences. The study aimed to investigate the association between higher serum endothelin-1 level and MACE within 1 yr follow up in patients with CAD who underwent elective PCI.

MATERIAL AND METHODS

Design and subject

It was a comparative analytic study with a retrospective cohort design where conducted in Dr. Sardjito General Hospital, Yogyakarta, Indonesia, from

May 2018 until August 2019. The baseline data, including serum endothelin-1 levels, were retrieved from the electronic database of previously published study.[7] The study measured biomarkers, including endothelin-1, in patients with stable CAD who underwent coronary angiography (CAG) examination in Dr. Sardjito General Hospital, Yogyakarta.[7] In this current study, we selected patients who had elective PCI procedure and conducted a follow-up observation within period of 1 yr after the baseline when elective PCI was performed, by collecting medical record data and/or contacting patients directly by phone.

Protocol

The subjects of the study were patients with stable CAD who underwent elective PCI at Dr. Sardjito General Hospital, Yogyakarta and met the inclusion and exclusion criteria. The inclusion criteria were (1) male or female patients with age ≥ 30 yo; (2) patients diagnosed with stable IHD by CAG; (3) patients electively treated for PCI; (4) patients were able to be followed up related outcome (MACE), observed for 1 yr after the PCI through medical records or direct phone contact. The exclusion criteria were (1) patients who did not have sufficient data regarding outcome within 1 yr follow up, (2) patients with malignant disease, chronic kidney failure, acute infection, and (3) patients with a history of peripheral artery disease. Minimal sample size calculation was performed by inserting the alpha value 5% and beta value 80% and derived from previously published result of big-endothelin-1 and MACE among CAD subjects.[8] The minimal sample requirement was 38 subjects in each endothelin-1 level group.

The baseline data of the subjects included demographic data, clinical data, cardiovascular risk factors, and comorbidities. Blood samples were collected for routine laboratory tests and endothelin-1 measurement were carried out during hospital stay, specifically before the subjects underwent the elective PCI. The venous blood samples were collected on BD Vacutainer tubes (Becton Dickinson, USA) and serum was collected by centrifugation at 200 g for 20 min, and the supernatant was kept in a freezer (−80° C). The frozen supernatant was processed for endothelin-1 measurement using immunoassay Quantikine ELISA system (R&D Systems, Minneapolis, MN, USA) as described previously.[7]

The outcome of this study was MACE during 1 yr after the elective PCI procedure. The MACE was collected from the patient's history by tracking subjects' medical record data and/or contacting the subjects directly by phones. The MACE outcomes assessed included HF, recurrent ACS, new and recurrent stroke, and deaths presumed to be of cardiac origin.

Protocol of the study was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta/Dr. Sardjito General Hospital, Yogyakarta, Indonesia. The ethical clearance number issued is No.: KE/FK/1971/EC/2023.

Data analysis

Statistical analysis was performed using SPSS software version 25 (I.B.M., U.S.A). The distribution of numerical data was analyzed using the Kolmogorov Smirnov normality test. Numerical variables were analyzed by independent T test or Mann-Whitney test, when applicable. Categorical variables were analyzed with chi square test. To determine endothelin-1 cut-off value for predicting 1-yr MACE, the receiver operating characteristic (ROC) curve was designed and analyzed. The ROC curve was designed because currently no consensus regarding cut-off value

of endothelin-1 for prognostication. A p value <0.05 was considered to be statistical significance.

RESULTS

During the data collection from baseline, 84 subjects met the study's inclusion criteria. During 1-yr follow up for MACE assessment, 21 patients were excluded due to unavailable or incomplete outcome data and/or inability to be contacted by phones. Therefore, a total of 63 subjects were enrolled for the study.

TABLE 1 shows a description of the subjects' baseline variables and their comparison based on the incidence of MACE. Baseline variables included demographic data, clinical characteristics, cardiovascular risk factors, previous history of coronary heart disease, profile of coronary arteries affected by significant stenosis and PCI procedure.

There were no significant differences of baseline variables between subjects who experienced MACE [MACE (+)] and those who did not [MACE (-)] during the 1-yr following elective PCI. The amount of significant coronary stenosis involvements did not different between the MACE (+) and MACE (-) groups. Similarly, the type of PCI procedure-whether stenting or balloon angioplasty-did not differ significantly between these groups.

The incidence of MACE in this study, which was observed for 1-yr after the elective PCI, was 17.5% (11 subjects). Three subjects (4.8%) experienced HF, 3 subjects (4.8%) experienced acute ACS recurrence, 4 subjects (6.3%) experiencing both HF and ACS, and 1 subject (1.6%) dead (FIGUR 1).

TABLE 1. Baseline variables in all subjects and the comparison between MACE incidence

Baseline variables	Subjects (n=63)	MACE (+) (n=11)	MACE (-) (n=52)	p
Males [n (%)]	54 (85.7)	10 (90.9)	44 (84.6)	0.505
Age [yr (median, min-max)]	58 (5–64)	54 (46.5–61.6)	58.8 (56.2–61.5)	0.185
Obesity [n (%)]	24 (38.1)	7 (63.6)	17 (32.7)	0.276
Hypertension [n (%)]	42 (66.7)	7 (63.6)	17 (32.7)	0.536
Dyslipidemia [n (%)]	37 (96.8)	7 (63.6)	30 (57.7)	0.495
Diabetes mellitus [n (%)]	15 (23.8)	2 (18.2)	13 (25.0)	0.482
History coronary heart disease, n (%)	61 (96.8)	10 (90.9)	51 (98.1)	0.321
Vessel involvements				
CAD1 VD	9 (14.3)	1 (9.1)	8 (15.4)	
CAD2 VD	20 (31.7)	3 (27.3)	17 (32.7)	0.458
CAD3 VD	34 (54.0)	7 (63.6)	27 (51.9)	
PCI procedures				
Stenting	59 (93.7)	9 (81.8)	50 (96.2)	0.137
Blood angioplasty	4 (6.3)	2 (18.2)	2 (3.8)	

Note: MACE: major adverse cardiovascular events; CAD: coronary artery disease; VD: vessel disease; PCI: percutaneous coronary intervention

The ROC calculation was carried out at the level of endothelin-1 in predicting MACE. The result showed a very weak category area under the ROC curve (AUC) of 0.505 with p = 0.503. This indicates that endothelin-1 level was not a significant predictor of 1-yr MACE. The cut-off value determined using the Youden Index method was 1.932 pg/mL, with a sensitivity of 81.8% and a specificity of 42.3% (FIGURE 2).

The relationship of MACE with endothelin-1 level is illustrated in TABLE 2. Bivariate analysis showed no significant association, although there was a trend toward a higher incidence of MACE in patients with endothelin-1 level above the cut-off value (≥1.932 pg/mL) compared to those below-cut-off (< 1.932 pg/mL) (MACE incidence: 23.1% vs. 8.3%; p=0.181). An endothelin-1 level above the cut-off was significantly associated with the incidence of HF (100% vs. 0%; p=0.039), but not with ACS (p=0.156) or dead (p=0.434) during the 1-yr following elective PCI.

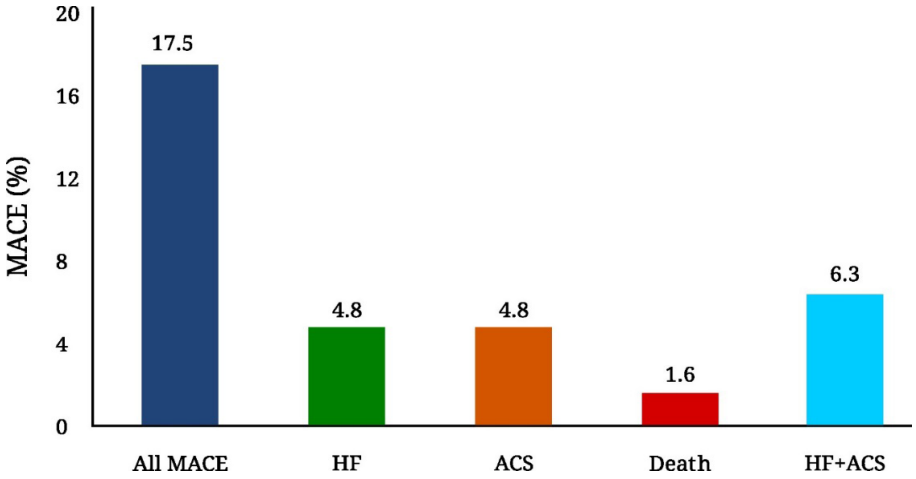

FIGURE 1. The incidence of MACE in patients with stable CAD underwent elective PCI (HF: heart failure; ACS: acute coronary syndrome).

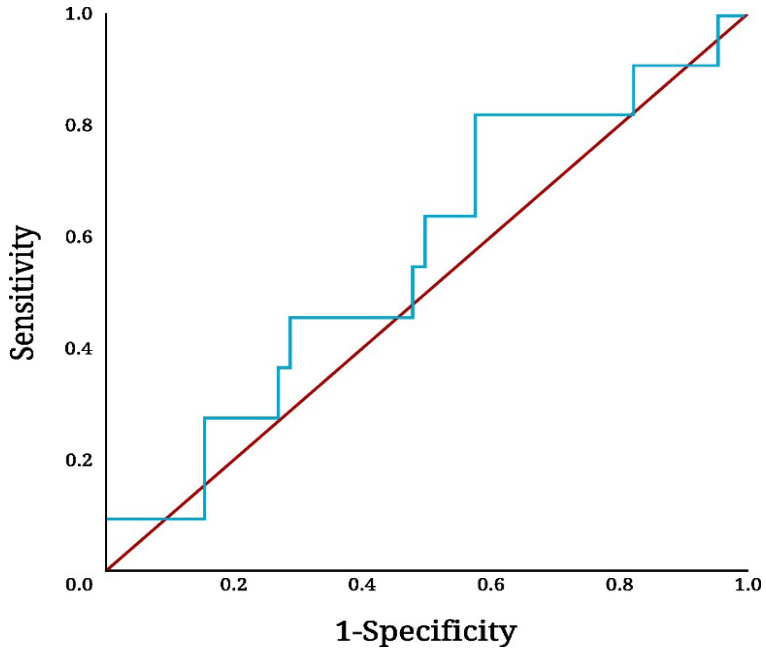

FIGURE 2. The ROC curve to determine the cut-off value of endothelin-1 for 1 yr MACE

TABLE 2. Association between cut-off endothelin-1 level and incidence of MACE within 1-yr after elective PCI

Endothelin-1 level (pg/mL)	MACE (-) (n=52)	MACE (+) (n=11)	Death (+) (n=1)	HF (+) (n=7)	ACS (+) (n=7)
< 1.932 (n=24)	22 (91.7)	2 (8.3)	1 (100)	0 (0)	1 (14.3)
≥ 1.932 (n=39)	30 (76.9)	9 (23.1)	0 (0)	7 (100)	6 (85.7)
p	References	0.181	0.434	0.039	0.156

Note: Value in n (%); MACE: major adverse cardiovascular events; HF: heart failure; ACS: acute coronary syndrome

DISCUSSION

The overall incidence of MACE within 1-yr after elective PCI was 17.5%. Higher endothelin-1 level, defined by values above cut-off (≥1.932 pg/mL) tended to be associated with a greater incidence of 1-yr MACE. This endothelin-1 threshold was significantly associated with a higher incidence of heart failure within 1-yr post-elective PCI among CAD patients. This finding further support the deleterious role of elevated endothelin-1 level in cardiovascular disease, particularly in the development of cardiac dysfunction and subsequent heart failure.

Endothelin-1 plays a role in the development of atherosclerosis.[9] Increased endothelin-1 level are associated with an increased risk of all-cause mortality (both cardiovascular and non-cardiovascular) in patients with coronary heart disease.[10] Endothelin-1 and its peptides have been shown to predict cardiovascular events in patients with stable IHD.[11] Our study provides additional data supporting this concept. However, the AUC was 0.050, indicating a very weak predictive value. The endothelin-1 cut-off value generated from the curve showed a non-significant trends, suggesting poor predictive value of endothelin-1 for 1-yr MACE among CAD patients who underwent PCI.

Endothelin-1 is a potent vasoconstrictor peptide initially isolated from endothelial cells. Its production is stimulated by various cells types under the influence of cardiovascular risk factors and during the progression of cardiovascular diseases. Based on these observations and its biological effects, namely profound vasoconstriction, pro-inflammatory activity, mitogenic and proliferative effects, stimulation of free radical formation, and platelet activation, endothelin-1 has been implicated in the development of the cardiovascular disease.[12]

Several studies have examined the association between level of endothelin-1, big endothelin-1, or C-terminal proendothelin-1 and all-causes mortality or MACE in patients with CHD. Previous studies including 30,181 comparing the highest and lowest endothelin-1 levels reported a combined risk ratio (RR) for all-cause mortality of 3.77 (95% CI: 1.59–8.94) for endothelin-1 and 1.65 (95% CI: 1.25-2.18) for big endothelin-1. The combined RR for MACE was 2.24 (95% CI 1.85–2.72) for endothelin-1, 1.49 (95% CI 1.10–2.03) for big endothelin-1, and 3.55 (95% CI 2.12–5.96) for CT-pro endothelin-1, respectively. Subgroup analysis showed that increased endothelin-1 levels associated with a 2.66-fold and 2.09-fold increased risk of short- and long-term MACE, respectively.[13] ARTEMIS prospective cohort study, which included

1,946 patients with angiographically documented CAD, showed that higher circulating endothelin-1 level were significantly associated with higher risk of all-cause mortality (HR: 2.06; 95% CI 1.5-2.83).[10] In this present study, endothelin-1 level above the cut-off value showed a trend toward increased MACE incidence and a significantly increase in the HF incidence. However, the multivariable analysis adjusting for covariates was not performed due to limited sample size which restricts the study's findings.

Chronic HF is considered to be the final common pathway of all heart diseases.[14] Endothelin-1 has been suggested as a predictor and prognostic marker in patients with both acute and chronic HF.[15] The endothelin-1 related peptide, C-terminal pro endothelin-1, also holds significant prognostic value in HF.[16] Elevated level of C-terminal pro endothelin-1, together with high NT-proBNP level, enable identification of patients with chronic HF who are at risk of poor outcomes.[17] In this study, increased endothelin-1 was significantly associated with a higher incidence of HF within 1-yr of follow-up after elective PCI in patients with CAD.

Increased peripheral vascular resistance is a major feature of HF, implicating endothelin-1 in its pathophysiology. In addition to activating neurohormonal systems, endothelin-1 contributes significantly to vasoconstriction. Studies have shown markedly increased endothelin-1 expression in the heart and lung of mice with HF . Consequently, plasma endothelin-1 level rise, along with increased density of myocardial endothelin receptors. In HF, pulmonary blood vessels appear to be the primary source of circulating endothelin-1. Given the correlation between plasma endothelin-1 level, heart filling pressure, and the severity of pulmonary hypertension, vascular distension may stimulate its increased production and release.[18]

Although there is a tendency suggesting a significant role of increased endothelin-1 level in1 year MACE -particularly the incidence of HF- after elective PCI, this study has several limitations. One major limitation was small sample size, which did not meet the minimum requirement of one of the groups. Additionally, the exclusion of 25% of subjects based on inclusion criteria may have introduced bias in this study. The relatively short follow-up period for observing MACE may also have affected the results. The retrospective cohort design carries inherent limitations, including potential selection bias and recall bias related to outcome reporting. Furthermore, reliance on medical record and phone interviews may introduce reporting bias. Despite these limitations, the potential use of endothelin-1 as a prognostic biomarker in CAD patients warrants further investigation. We recommend conducting a prospective cohort study with a larger sample size to address these issues.

CONCLUSION

In conclusion, higher serum endothelin-1 level shows a trend toward a higher incidence of 1-yr MACE in patients with stable CAD who underwent elective PCI. Among the components of 1-yr MACE, higher serum endothelin-1 level are significantly associated with increased incidence of HF.

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