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Association between Grade of Normoalbuminuria and Left Ventricular Diastolic Dysfunction (LVDD) in Hypertensive Population of Gunungsari Village, Pamijahan-Bogor, Indonesia

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Abstract

Background: Albuminuria has been considered an important diagnostic marker of decreasing renal function, but lately albuminuria has also been linked to cardiovascular and peripheral vascular disease. Many studies have analyzed the association between micro- or macroalbuminuria and the increased risk of cardiovascular disease, but only few examined the association between normoalbuminuria and cardiovascular disease. To analyze the association between the degree of normoalbuminuria and the occurrence of left ventricular diastolic dysfunction in hypertensive patients.

Method: This is cross-sectional analysis in hypertensive patients. Normoalbuminuric subjects are divided into three tertiles based on the cutoff of Urine-Albumin-Creatinine Ratio (UACR). To evaluate left ventricular function, all subjects undergo echocardiography examination. Left ventricular diastolic dysfunction is positive if more than fifty percent of positive findings are present from the fourth parameters stated in the 2016 American Society of Echocardiography criterias.

Results: No significant difference in the occurrence of LVDD was found between the two groups according to age, sex, smoking, dyslipidemia, physical activity, BMI, hypertension therapy and HbA1c, but a significant difference was seen in the UACR tertile of the two group. This study showed that upper-limit normoalbuminuria (third tertile) was associated with the occurrence of LVDD (OR 15.57, 95% CI: 2.88-84.25).

Conclusion: This study showed that normoalbuminuria in hypertensive population is associated with left ventricular diastolic dysfunction.

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Keywords: *hypertension, normoalbuminuria, left ventricular diastolic dysfunction*

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Introduction

Prevalence of hypertension accounts for 30% - 40% of the general population, and it increases with age.[1] Data which is taken from *"Riset Kesehatan Dasar"* (Riskesdas) Indonesia on 2013, the prevalence of hypertension was 25.8%. Provinces that have the highest prevalence in Indonesia are Bangka Belitung (30,9%), South Borneo (30,8%), East Borneo

(29,6%) and West Java (29,4%). Hypertension is a risk factor of Left Ventricular Distolic Dysfunction (LVDD) and being the most common cause of heart failure.[3] This concept has a similarity with study from Perkiomaki, *et al*, which states that increase of blood pressure both systolic and pulse pressure has a relation with diastolic dysfunction. The Renin Angiotensin Aldosterone System (RAAS) has the main role of the occurrence of LVDD and its progression to become heart failure with normal systolic function. Nowadays LVDD is predicted as the bridging pathophysiology between hypertension and heart failure. [3]

Hyperfiltration of glomerulus and endothelial dysfunction has been known as the beginning of essential hypertension before the raise in blood pressure.[4] These conditions will cause albuminuria. Albuminuria is an increase of the serum albumin (protein) excretion to urine. Typically, albuminuria had been an important diagnostic finding and representing kidney function, but nowadays albuminuria is considered as a diagnostic finding for cardiovascular and peripheral vascular disease that links the process between cardiovascular and kidney. A lot of research has been studying the association between microalbuminuria (30-300 mg/g) or macroalbuminuria (≥300 mg/g) and increasing risk of cardiovascular disease, but there were only few researches about the association between normoalbuminuria with cardiovascular disease. Micro or macroalbuminuria is more likely caused by glomerular permeability dysfunction while normoalbuminuria (<30 mg/g) is caused by retrieval pathway dysfunction, where there is only small amount of filtered albumin that does not pass through the retrieval pathway and go through the process of lysosomal degradation and excreted in urine as a small peptide fragment. This degradation pathway is sensitive to metabolic factor that responsible for hypertrophy and fibrosis process, especially angiotensin II (AII) *and transforming growth factor* - β (TGF-β), which production is stimulated by hyperglycemia and hypertension.[5]. It is important to note that increase of RAAS and TGF are involved in dysfunction of the heart and also being a manifestation of hypertrophic and fibrotic process in the heart which causes structural changes such as LVDD and associated with increase of significant cardiovascular risk. Therefore, by understanding mechanism of albuminuria might give us knowledge about the underlying molecular process of the disease.[5]

Table 1 Subject Characteristic (N= 62)

Variables	Value
Age	52,68 ± 12,74
Gender	
Male	22 (35,5%)
Female	40 (64,5%)
Smoking	
No	47 (75,8%)
Yes	15 (24,2%)
Dyslipidemia	
No	51 (82,3%)
Yes	11 (17,7%)
Physical Activity	
No	38 (61,3 %)
Yes	24 (38,7%)
Antihypertensive Therapy	
No	38 (61.3 %)
Yes	24 (38,7%)
Not knowing the name of the drug	19 (79.16%)
Captopril	4 (16.66%)
Amlodipin	1 (4.16%)
LVDD	
Negative	22 (35,5%)
Positive	40 (64,5%)
Physical Examination	
Body weight (kg)	59,85 ± 11,81
Body height (cm)	151,13 ± 10,07
Body Mass Index	26,26 ± 2,98
Blood Pressure (mmHg)	
Systolic pressure in first examination	162,05 ± 17,150
Systolic pressure in second examination (after 2 weeks)	159,15 ± 18,45
Diastolic pressure in first examination	97,29± 7,56
Diastolic pressure in second examination (after 2 weeks)	96,50 (90 – 131)
Laboratory Findings	
Urine Albumin Creatinin Ratio /UACR (mg/gram)	10.66 + 7.84
HbA1C	5,38 ± 0,39
Tertile UACR	
Tertile 1	11 (17,7%)
Tertile 2	17 (27,4%)
Tertile 3	34 (54,8%)

*normal numerical data dispersion expressed in mean ± standard deviation, if the dispersion is not normal it is expressed in median (minimum-maximum)

Most of the researchers agreed that albuminuria is associated with morbidity and mortality risk of cardiovascular events in general population6, and becoming a high risk in patients with diabetes mellitus and hypertension[7,8]. The role of microalbuminuria as a marker of glomerular hyperfiltration, endothelial and cardiovascular dysfunction and LVDD is explained

in someone with hypertension[9], but the role of normoalbuminuria as a biomarker of preclinical hypertensive disease and LVDD has not been researched prospectively.4

There were only few researches that evaluated the association between normoalbuminuria (equal or less than 30 mg/g, that the range is below microalbuminuria) and left ventricular diastolic function. In a research which samples is normotensive people with normoalbuminuria, upper border of albumin concentration in urine can predict the progress of some cardiovascular disease such as hypertension and metabolic syndrome [10,11]. The same finding can be found in a high-risk population (hypertensive people) which has a high level of UACR (urine albumin creatinine ratio) but still lower than the upper border of microalbuminuria significantly associated with the increase of LVDD prevalence in CAD patients that undergone percutaneous coronary intervention. Prevalence of LVDD with normoalbuminuria in CAD patients' population was 29.2%.[12] It is shown that normoalbuminuria in a high risk population can make a stratification of cardiovascular risk.

Methods

The research is cross-sectional study. Research subject is hypertensive patients without heart failure symptoms who was examined based on first screening which had done by public health service in Bogor during January to February 2017.

Inclusion Criteria was patient with uncontrolled hypertension according to *The Eighth Joint National Committee Guideline*. Age ≥ 18 years and normoalbuminuria. We rule out subject with micro/ macroalbuminuria, symptoms of heart failure, moderate to severe valvular heart disease, arrythmia (atrial fibrilation), history of PCI/ CABG, left ejection fraction function < 40%, diabetes, obesity, LVH and subject with hypertension therapy. Urine analysis and echocardiography was done by the staff from Non-Invasive Diagnostic Division of National Cardiovascular of Harapan Kita, Indonesia.

Classification of normoalbuminuria in this study is taken from previous study which classification was already tested on coronary disease population21. UACR <3.4 mg/g, 3.4 mg/ gram ≤ UACR < 7.4 mg/g and 7.4 mg/ gram ≤ UACR < 30 mg/g.

LVDD is a condition that is related to thickening and narrowing of ventricular chamber, in which made a decrease in one or both ventricular filling, with normal systolic function. This definition is based on echocardiography, especially mitral inflow velocity and TDI, to define either normal diastolic function or LVDD. LVDD is considered positive when there is more than 50% positive findings from four parameters according to the criteria from American Society of Echocardiography (ASE) 2016: mean comparison E/e' > 14, septal velocity < 7 cm/second or lateral < 10 cm/second, tricuspid regurgitation velocity > 2.8 m/second, left atrial volume index > 34 mL/m^2 [23]

Results

The number of samples or subjects is one hundred twenty six (126) taken from January 2017 to February 2017. Sixty four (64) samples were excluded due to exclusion criteria and eventually left sixty two (62) samples to be going on this research as research subjects (Figure 5.1).

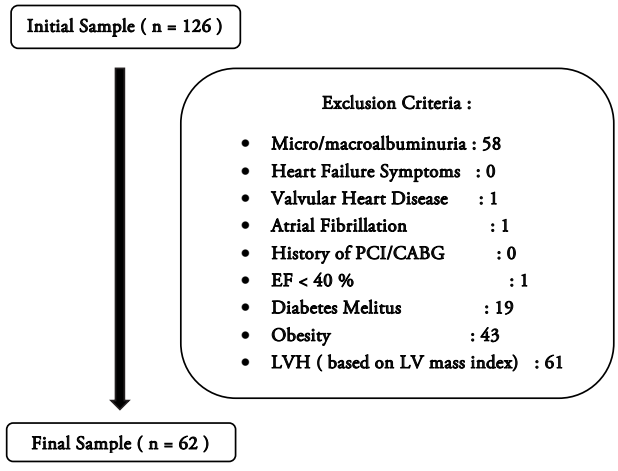

Figure 1 Sampling Methods

Gender of the subjects is dominantly female (64.2%), mean age is 52 years old, with no habit of smoking (75.8%), no history of dyslipidemia (82.3%), no physical activity (61.3%) and mean albuminuria is 10.66 + 7.84 mg/gram. Among sixty two patients, forty two patients have left ventricular diastolic dysfunction (64.5%). Characteristic data is shown on Table 1

Table 2 Subject Characteristic (N= 62)

Variables	Value
Age	52,68 ± 12,74
Gender	
Male	22 (35,5%)
Female	40 (64,5%)
Smoking	
No	47 (75,8%)
Yes	15 (24,2%)
Dyslipidemia	
No	51 (82,3%)
Yes	11 (17,7%)
Physical Activity	
No	38 (61,3 %)
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Urine Albumin Creatinin Ratio /UACR (mg/gram)	10.66 + 7.84
HbA1C	5,38 ± 0,39
Tertile UACR	
Tertile 1	11 (17,7%)
Tertile 2	17 (27,4%)
Tertile 3	34 (54,8%)
Echocardiography	
LVEF (%)	70.38 + 3.03
Right ventricular systolic function / TAPSE (cm)	2.12 (2 - 2.5)
LV Mass index male (g/m²)	90,79 ± 14,77
LV Mass index female (g/m²)	86,18 ± 10,64
LVEDD (mm)	44,35 ± 4,77
LVESD (mm)	25,64 ± 4,59
IVSD (mm)	10,64 ± 1,72
IVSS (mm)	15,32 ± 2,07
LVPWD (mm)	10,00 (8 – 18)
LVPWS (mm)	15,00 (13 – 20)
Left Atrial Volume Index / LAVI (ml/m²)	39,64 + 11,33
Medial e wave velocity (cm/second)	7 (3 – 12)
Lateral e wave velocity (cm/second)	7.5 (4 – 16)
Mean E/e' wave	16 (6 – 28)

*normal numerical data dispersion expressed in mean ± standard deviation, if the dispersion is not normal it is expressed in median (minimum-maximum)

Table 3 Relationship between demographic characteristic with LVDD

Variable	LVDD		P value
	Yes (N = 40)	No (N =22)	
Age	53,30 ± 12,13	51,55 ± 14,00	0,608**
Gender			
Male	14 (63,6%)	8 (36,4%)	0.914*
Female	26 (65,0%)	14 (35,0%)	
Smoking			
No	31 (66,0%)	16 (34,0%)	0.675*
Yes	9 (60,0%)	6 (40,0%)	
Dyslipidemia			
No	33 (64,7%)	18 (35,3%)	0,946*
Yes	7 (63,6%)	4 (36,4%)	
Physical Activity			
No	24 (63,2%)	14 (36,8%)	0,779*
Yes	16 (66,7%)	8 (33,3%)	
Antihypertensive Therapy			
No	25 (64.1%)	14 (35,.%)	0,929*
Yes	15 (65.2%)	8 (34.7%)	
Body Weight	59,45 ± 12,22	60,59 ± 11,29	0,719**
Body Height	151,43 ± 9,28	150,59 ± 11,61	0,758**
LV Mass index	83,97±16,45	79,79±17,47	0.352**
BMI	23,89 ± 4,82	24,22 ± 5,32	0,444**
Laboratory Finding			
HbA1C	5,42 ± 0,37	5,31 ± 0,44	0,281**
UACR (mg/gram)	12.74±7.64	6.88 ± 6.81	0,004**
Tertile UACR			
Tertile 1 (<3,39)	3 (27,3%)	8 (72,7%)	
Tertile 2 (3,4 - 7,39)	9 (52,9%)	8 (47,1%)	0,002*
Tertile 3 (7,4 - 30)	28 (82,4%)	6 (17,6%)	

* Chi-Square Tests,**one way anova

Table 4 LVDD risk factor multivariate analysis

Variable	Coefficient B	P value	PR	CI 95%
UACR Tertile				
Tertile 1	(Reference)			
Tertile 2	1,042	0.219	2,836	0.54 - 14.96
Tertile 3	2,745	0.001	15.57	2.88 - 84.25
Age	0.014	0.567	1,015	0.96 - 1.06
Gender	-0.568	0.448	0.567	0.44 - 7.24
Antihypertensive Therapy	-0.040	0.953	0.961	0.25-3.621

Relationship between demographic characteristic, laboratory finding with LVDD is shown in Table 2 and 3. There is no significant difference between age, gender, smoking status, dyslipidemia, physical activity, antihypertensive therapy, body mass index, and HbA1C between two groups, but there is significant difference between UACR tertile in both groups. Prevalence of LVDD in tertile 3 is higher than tertile 2 and 1 (82.4%, 52.9% and 27.3%) with P = 0.002.

Multivariate Analysis

Final results of multivariate logistic analysis that searched relationship between LVDD and UACR tertile, age, gender and antihypertensive therapy is shown in table 4. This research shows upper border of normoalbuminuria (tertile 3) is associated with left ventricular diastolic dysfunction (odd ratio: 15.57; CI 95% 2.88 – 84.25). Age, gender and antihypertensive

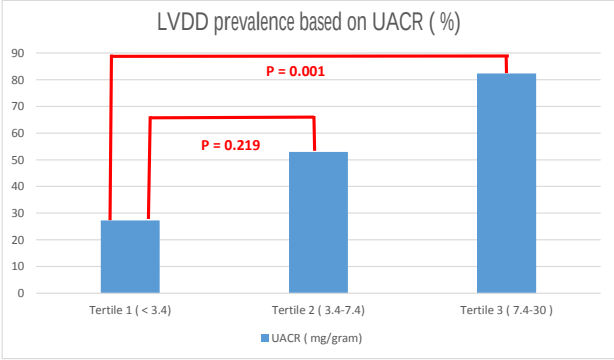

Figure 5.2. Prevalence of LVDD based on Urine Albumine Creatinine Ratio (UACR)

therapy are not statistically significant, but in conceptual and empirical context, both are confounding factor of left ventricular diastolic dysfunction thus it is included in multivariate analysis.

Discussion

We found that subject with hypertension with normoalbuminuria and urine albumin creatinine ratio (UACR) range from 7.4 – 30 mg/gram is associated with left ventricular diastolic dysfunction. UACR classification was adapted from previous study that had been tested on coronary disease.[21] Most of confounding variable can be excluded by-design (by using exclusion criteria) and excluded "by-criteria" (by using multivariate analysis). This research hypothesis is based on theory that Renin Angiotensin Aldosterone System affects both kidney and heart. This research is not intended to search cut off point of normoalbuminuria for LVDD, but to search pathophysiology and association between normoalbuminuria with LVDD through RAAS in heart and kidney.

Data in this research shows that upper border of normoalbuminuria in high risk population can make a higher cardiac risk stratification. It is supported by recent studies that focused on association between lower albuminuria and cardiovascular risk. Johan, et al, on The Framingham Heart Study was using non-hypertensive and non-diabetic population for the study found that low albuminuria could predict cardiovascular disease progress[24]. Hong, et al, also found that low albuminuria was associated with 10 years metabolic syndrome prevalence and risk for coronary disease measured by Framingham Risk Score > 20% (high risk) was 22,5 ± 0,7% and 14,5 ± 0,7%, respectively[114]. Moreover, HOPE (Heart Outcomes Prevention Evaluation) found that there was no clear threshold for UACR and UACR increase that affect cardiovascular risk continuously[25]. It was found that increase of 3.01 mg/gr UACR increased major cardiovascular events by 5.9%. It was concluded that normal range UACR significantly associated with increase myocard dysfunction prevalence. Low albuminuria independently associated with left ventricular diastolic dysfunction and the cutoff point used in this analysis was almost identical with the one that was defined in a large cohort study which used for cardiovascular death risk [25].

It is not clearly known about pathophysiology of albuminuria in heart failure patients with normal ejection fraction, there are several possible mechanisms. One of them is albuminuria associated with many inflammatory markers. Systemic inflammation can affect coronary microvascular endothel, reduce bioavailability of myocardial nitric oxide (NO), which results in lower protein kinase G (PKG). Decrease of PKG activity will enhance hypertrophy/prohypertrophy process, myocyte stiffness, left ventricular diastolic dysfunction and ventricular stiffness[26]. The second possible explanation is albuminuria might become an early sign of renal damage. Even though renal function is clinically stable, decrease of number of nephrons and hyperfiltration, and increase of renal proximal tubule saturation can result in albuminuria[27]. There are several compensatory mechanisms such as Renin Angiotensin Aldosterone System and increase of symphatetic activity, in which will affect cardiovascular system. It is supported by previous study that has shown an association between pulmonary capillary hypertension with renal damage[23]. Thus, low albuminuria represents early renal damage and pulmonary capillary hypertension.

The biggest issue regarding to left ventricular diastolic dysfunction algorithm recommendation from American Society of Echocardiography and European Association of Cardiovascular Imaging (ASE/EACVI) 2016 is about indeterminate category. In this recommendation, indeterminate category is defined when there is 50% of positive findings in 4 parameters of LVDD. This category is considered in a grey area because there is a possibility for someone fall into LVDD

without fulfilling more than 50% LVDD positive findings. On ASE/EACVI 2016 editorial stated that 60 – 80% indeterminate subjects had been classified for LVDD based on previous guideline, ASE/EACVI 2009. Thus, ASE/EACVI 2016 recommendation has a lower left ventricular diastolic dysfunction prevalence, but its specificity and sensitivity are higher than previous guideline. In this research we found 23 subjects fall into indeterminate category. Therefore, based on ASE/EACVI 2009, our LVDD patients might be more than 62 subjects.

According on literature, left ventricular mass affects parameter for diastolic function and left ventricular filling pressure. The larger left ventricular mass will result in higher risk for LVDD.[28] Compared to Framingham Criteria that is not including body surface area (BSA) to calculate left ventricular mass, [29] on ASE 2016 criteria included BSA on the formula to calculate left ventricular mass, therefore this criteria can be used in many populations and considered to be more accurate. In our research, there is no statistically significant association between left ventricular mass with LVDD events. Our subjects fall into normal left ventricular mass based on ASE 2016 category.

Gender, age and percentage of antihypertensive therapy was analyzed in multivariate analysis. Even it is not statistically significant, but in conceptual and empirical context these aspects are confounding factor of LVDD events and it is supported by many scientific data. Woman is considered to have a higher end-systolic blood pressure than man (139,7 ± 21,1 vs 123,6 ± 12,6 mmHg, P = 0,001) and smaller left ventricular chamber volume (end-diastolic volume: 96,4 ± 30,6 vs 139 ± 30,7 ml, P = 0,001). Left ventricular end-systolic elastance (2,65 ± 0,10 vs 1,96 ± 0,09 mmHg ml-1, P <0,002) and left ventricular diastolic compliance (6.12 ± 0.37 vs. 10.0 ± 0.50 ml mmHg-1, P <0.001) is found to be higher in woman than in man. Therefore it is concluded that woman has a higher systolic chamber function and lower left ventricular diastolic compliance30. In our study, we found no statistic significance between gender (dominated by female) and LVDD. One possible explanation is body height index that is used for calculation of left ventricular mass will decrease the effect of gender to LVDD events. Every 100 cm of body height approximately increase left ventricular mass by 51 grams. In our study population, even though dominated by women, their body height is shorter than men.

There is association between aging process and cardiovascular diseases, that risk of cardiovascular diseases increases with age. Cardiovascular disease is the leading cause of death for people at age 65 years old and above (40%) and 80% of cardiovascular death occurred in this group.[31] For normal population and asymptomatic patients, declining diastolic function represents with comparison E/e' > 15, seldom is found on people below 65 years old. In people ≥ 65 years old, it is 14% at group age 65 – 74 years old and 24% at group age > 74 years old.[32] A cross-sectional study done by Zanchetti, et al, (APROS diadys study) found that from 2425 elderly patients (≥ 65 years old), the prevalence of LVDD was 25.8% (649 patients). This diastolic dysfunction prevalence is increasing along with increasing age, with minimal value of 22.7% (65 – 70 years old) and maximal value of 41.2% (> 80 years old) [33]. Our population study has average age of 52 years old.

Sabine, et al[34], found that long term weight loss on obesity people is associated with left ventricular diastolic improvement. Our study found that body mass index and physical activity were not significantly related to LVDD event. This might be explained by absence of previous BMI history recorded, and we could not conclude that the normal BMI at our sampling time was due to physical activity and/or exercise with a higher BMI previously. We also found no significant association between smoking and dyslipidemia with LVDD. This might be due to our samples were dominantly not smoking and not having dyslipidemia.

Antihypertensive therapy that altering RAAS such as angiotensin converting enzyme inhibitor (ACE inhibitor) can affect to LVDD event.[35] Reduced preload that induced by ACE inhibitor will affect both ventricular dimension, left ventricular geometry and both ventricular filling. Reduced right ventricular dimension is associated with left ventricular geometry adaptation and reduced left ventricular diastolic pressure, which facilitates left ventricular filling and pulmonary vein drainage.[35] Most of our samples had no antihypertensive therapy (61.3%). From twenty four subjects (38.7%) with antihypertensive therapy, four subjects had ACE inhibitor, one subject had calcium channel blocker and nineteen subjects had not known the name of antihypertensive drug. Small number of

subjects with antihypertensive therapy made association between antihypertensive therapy and LVDD events in our study was not statistically significant.

Limitation of the Study

First of all, this study was not intended to prove a causal relationship because independent and dependent variable sampling was done in one time thus we had no clear temporal relationship between these variables and could not conclude which one which was the cause and the effect. Second, this research was not representing progression of the disease, its incidence and prognosis. Third, there might be prevalence or incidence bias due to possibility of misinterpretation of risk factor effects over a time period as an effect of the disease. Fourth, even though electrocardiography (ECG) was used in our study, but it was not enough to exclude chronic or stable coronary disease. We could not use Framingham score to estimate cardiovascular risk in our population because we did not include one of Framingham 2008 variable score. Moreover, regional wall motion abnormality (RMWA) of myocard with echocardiography also can't be used for exclusion because our population had intermediate pretest probability. Therefore, echocardiography stress test would be more sensitive to diagnose stable coronary disease.[36]

Our population was dominated by woman, age 52 years old (average), not smoking, no obesity, no diabetes mellitus and no left ventricular hypertrophy, which fall into moderate risk for cardiovascular disease according to Framingham 1991. Fifth, confounding factor such as anemia could not be excluded. Nagueh, et al[23] stated echocardiography that affected by blood volume is Doppler mitral inflow method, while our study diagnosed LVDD by using Tissue Doppler Imaging (TDI) due to normal ejection fraction according to recent ASE guideline for LVDD criteria. Therefore, it might not be affected with low hemoglobin concentration (loading condition). Other confounding factor such as systemic inflammation (e.g. sarcoidosis, urinary tract infection) could not be excluded. These disease proportion in general population were very small: 0.1%[37] and 0.7%[38] respectively, thus it might me assumed its effect on our study would be very low. On urinary tract infection (UTI) patients, proteinuria might not be found, but if there is existed, it will be a macroalbuminuria. Even though UTI often associated with proteinuria, its relationship is not clearly known.

Ethical Clearance

This study was approved by the ethic committee of Universitas Indonesia.

Conflict Of Interest

None

Publication Agreement

The authors of this article give permission to Indonesian Journal of Cardiology to publish this article if this article is accepted

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List of Abbreviations

AII: Angiotensin II
ACE: Angiotensin Converting Enzyme
BMI: Body Mass Index
LVDD: Left Ventricular Distolic Dysfunction
RAAS: Renin Angiotensin Aldosterone System
TDI: Tissue Doppler Imaging
TGF-β: transforming growth factor - β
UACR: Urine-Albumin-Creatinine Ratio

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