

RESEARCH ARTICLE

The Effects of Hypertension Stages on N-Terminal-Pro Brain Natriuretic Peptide (NT-Pro-BNP) Level and Left Ventricular Ejection Fraction

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ABSTRACT

Introduction: Hypertension is the most common risk factor for heart failure causing an increase in N-Terminal-Pro Brain Natriuretic Peptide (NT-proBNP) level and a decrease in left ventricular ejection fraction (LVEF). **Objective:** To investigate the effect of hypertension on NT-proBNP level and LVEF in patients with chronic heart failure.

Methods: This cross sectional study takes 29 people with hypertension stage-1 (HTD-1) and 27 people with hypertension stage-2 (HTD-2) as sample. The left ventricular ejection fraction and NT-proBNP level obtained from medical records are analyzed using independent t test and Mann Withney test, followed with Spearman correlation between NT-proBNP level and LVEF.

Results: Mann-Whitney test indicates that the mean value of NT-proBNP level of HTD-2 is significantly higher compared to that of HTD-1, $p = 0,000$. On the contrary, the independent t test shows that LVEF in HTD-2 is lower than that of HTD-1, $p = 0,001$. The Spearman correlation analysis conducted on the NT-proBNP level and the LVEF results in value of $-0,651$, $p = 0,000$. The cut-off-point value of NT-proBNP level is 1511pg/ml (sensitivity 0.82% and specificity 0.80%) and the value of area under the ROC curve $> 0,7$. The left ventricular ejection fraction has an area under the ROC curve $> 0,7$ with a cut-off-point value of 39% (sensitivity 0.67% and specificity 0.69%).

Conclusion: The NT-proBNP level and the LVEF of HTD-2 are significant higher and lower respectively compared to those of HTD-1. The NT-proBNP level and LVEF also show a strong negative correlation. The cut-off-point value of NT-proBNP level and LVEF can be utilized to compare the stages of hypertension in patients with chronic heart failure.

Keywords: Hypertension stage, NT-proBNP, left ventricular ejection fraction, chronic heart failure.

ABSTRAK

Pendahuluan: Hipertensi merupakan faktor resiko tersering pada gagal jantung yang menyebabkan peningkatan kadar N-Terminal-Pro Brain Natriuretic Peptide (NT-proBNP) dan penurunan fraksi ejeksi ventrikel kiri (FEVK). **Tujuan:** Untuk mengetahui pengaruh derajat hipertensi terhadap kadar NT-proBNP dan FEVK pada pasien gagal jantung kronik.

Metode: Penelitian observasional ini menggunakan rancangan *cross sectional study*. Sampel penelitian terdiri dari 29 orang dengan hipertensi derajat 1 (HTD-1) dan 27 orang dengan hipertensi derajat 2 (HTD-2) yang telah memenuhi kriteria inklusi. Data FEVK dan kadar NT-proBNP diperoleh dari rekam medis, masing-masing dianalisis dengan independent t test dan Mann Withney test. Korelasi antara kadar NT-proBNP dengan FEVK dianalisis dengan korelasi Spearman.

Hasil: Hasil uji Mann-Whitney menunjukkan bahwa rerata kadar NT-proBNP HTD-2 lebih tinggi bermakna disbanding HTD-1, $p < 0,01$. Hasil independent t test menunjukkan bahwa FEVK pada HTD-2 lebih rendah dibanding HTD-1, $p < 0,05$. Hasil uji korelasi Spearman antara kadar NT-proBNP dengan FEVK sebesar $-0,651$, $p = 0,000$. Nilai *cut-off-point* kadar NT-proBNP didapatkan sebesar 1511pg/ml (sensitivitas 0,82% dan spesifitas 0,80%) dan nilai luas area dibawah kurva ROC $> 0,7$. Fraksi ejeksi ventrikel kiri memiliki luas area bawah kurva ROC $> 0,7$ dengan nilai *cut-off-point* sebesar 39% (sensitivitas 0,67% dan spesifitas 0,69%).

Kesimpulan: Kadar NT-proBNP pada HTD-2 dengan gagal jantung kronik lebih tinggi, sedangkan FEVK lebih rendah dibanding HTD-1. Terdapat korelasi negatif yang kuat antara kadar NT-proBNP dengan FEVK. Nilai *cut-off-point* kadar NT-proBNP dan FEVK dapat digunakan untuk membandingkan derajat hipertensi pada pasien gagal jantung kronik.

Kata kunci: Derajat hipertensi, NT-proBNP, fraksi ejeksi ventrikel kiri, gagal jantung kronik.

INTRODUCTION

Heart failure is a complex clinical syndrome with a sign of heart's decreasing capability of pumping blood (Tan et al., 2010). Physiologically, heart failure is defined as inadequate cardiac output to fulfill body's metabolic needs. Epidemiologically, heart failure becomes pandemic, considering that 26 million people

throughout the world have this disease (Savarese and Lund, 2017). In Indonesia, according to the data of RISKESDAS in 2013, the prevalence of heart failure is expected to be 0.13% (229,696 people) with the estimated highest number is of West Java Province of 96,487 people (PERKI, 2015). Hypertension is the most risk factor to cause heart failure as marked with

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an increase in N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) (Weber et al., 2006). According to The Seventh Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII), hypertension is divided into normal, pre-hypertension, hypertension stage 1, and hypertension stage 2 which may potentially cause heart failure and reduce left ventricular ejection fraction. In line with ejection fraction, natriuretic peptide level, heart structural change, and diastolic dysfunction, heart failure is divided into three: heart failure with a decrease of ejection fraction, heart failure with maintained ejection fraction, and heart failure with ejection fraction between both (Ponikowski et al., 2016).

Various evidences show that NT-proBNP is peptide produced by cardiac myocytes as a response to mechanical stretch, oxidative stress, myocardial hypoxia, and toxicity (Drewniak et al., 2015; McKie and Burnett, 2016; Vanderheyden et al., 2004). Therefore, NT-proBNP level will increase in case of pressure and damage to cardiac myocytes, which may be taken as an important sign of heart failure because of various causes, including hypertension (McKie and Burnett, 2016; Nadir et al., 2012). The study reported by Drewniak W, et al. shows that NT-proBNP level with heart failure is significantly higher than that without heart failure (Drewniak et al., 2015). Moreover, an increase in NT-proBNP because of hypertension or any other causes is also followed with a decrease of left ventricular ejection fraction (Volpe et al., 2016b). However, the value of NT-proBNP and left ventricular ejection fraction (FEVK) to be taken to distinguish hypertension stages in chronic heart failure is unknown.

The NT-proBNP level and left ventricular ejection fraction in asymptomatic hypertension, hypertension with breathlessness during exercise, and hypertension with heart failure patients are different. The higher the NT-proBNP level, the lower the ejection fraction in hypertension patient with various clinical manifestations is (Bielecka-dabrowa et al., 2015b). An increase in NT-proBNP level because of hypertension is caused by increasing pressure and volume of left ventricular wall, causing left ventricular wall stress. This left ventricular wall stress will stimulate synthesis and secretion of Brain Natriuretic Peptide (BNP; active) and NT-proBNP (inactive) in cardiomyocytes cells. Hypertension also causes a release of Renin-Angiotensin-Aldosterone System (RAAS), sympathetic nervous system (SNS), endothelin, Reactive Oxygen Species (ROS), inflammation factor (TNF- α and IL-6) and myocardial hypoxia, which will increase quick release of NT-proBNP. An increase in RAAS, SNS,

endothelin, ROS, TNF- α and IL-6, and NT-proBNP will cause heart structural and functional changes like cardiac remodeling, left ventricular hypertrophy, and left ventricular diastolic dysfunction and systolic dysfunction. This will increase the progression of heart failure (Volpe et al., 2016a, 2016b).

The purpose of this research is to examine the effect of hypertension stage on NT-proBNP level and FEVK in chronic heart failure, expected to be utilized as the cornerstone to detect the progress of chronic heart failure and to prevent prognosis from worsening in chronic heart failure because of hypertension stage.

METHODS

In the cross sectional design, 56 patients' medical records from January 2016 to August 2018 are taken from Heart Clinic, Cirebon as samples. The samples are classified into chronic heart failure with hypertension stage 1 (HTD-1) and chronic heart failure with hypertension stage 2 (HTD-2). The samples meet the inclusion criteria: chronic heart failure patients with hypertension and complete medical record data. The chronic heart failure patients with hypertension and other risk factors such as diabetes mellitus, hypercholesterolemia, hypertriglyceridemia and decreased kidney function are excluded. The blood pressure, age, sex, one-time blood sugar, total cholesterol, triglyceride, urea, creatinine, NT-proBNP, and left ventricular ejection fraction data collected from patients' medical record data. This research is conducted in Heart Clinic, Cirebon upon approval of the ethics commission of the Faculty of Medicine, Unissula Semarang under No. 325/IX/2018/Komisi Bioetik.

Research Variables Measurement

All of the data are collected from medical records consisting of blood pressure, NT-proBNP, and left ventricular ejection fraction. Blood pressure is measured using mercury manometer, while NT-proBNP level is diagnosed using ELECSYS 2010 analyzer (Roche Diagnostic) on venous blood and left ventricular ejection fraction is diagnosed using echocardiogram and interpreted by a cardiovascular specialist.

Statistical Analysis

The data collected are tested for their normality using Shapiro-Wilk test, and homogeneity using Levene's test. The difference in NT-proBNP level is tested using Mann Withney, while in left ventricular ejection fraction is tested using independent t-test statistical analysis. The correlation between NT-proBNP level and left

Table 1. Baseline Data of Research Samples

Characteristic	HTD-1 n = 29, (x±SD)	HTD-2 n = 27, (x±SD)	p value
Men/Women	14/15	18/9	0.19 (a)
Age (years)	57.38 ± 13.67	62.70 ± 11.29	0.12(b)
One-Time Blood Sugar (mg/dl)	138.21 ± 30.330	133.11 ± 31.58	0.54(b)
Total Cholesterol (mg/dl)	157.55 ± 28.61	145.15 ± 34.35	0.15(b)
Triglyceride (mg/dl)	118.59 ± 32.95	111.89 ± 29.87	0.43(b)
Urea (mg/dl)	31.41 ± 8.02	34.33 ± 7.75	0.21(c)
Creatinine (mg/dl)	0.87 ± 0.29	1 ± 0.28	0.08(c)

Note: Age, one-time blood sugar, total cholesterol, triglyceride, urea, and creatinine are given in mean. Sex and blood pressure are given in proportion. Tests used: (a) Fisher Exact test, (b) independent t test, and (c) Mann-Whitney Test. The data above is based on patients' medical records.

Table 2. Mean of NT-proBNP Level and Left Ventricular Ejection Fraction

Variables	HTD-1 n = 29, (x±SD)	HTD-2 n = 27, (x±SD)	P value
NT-proBNP (pg/ml)	1603.79 ± 2114.40	7894.15 ± 9173.62	0.001*; 0.000**
FEVK (%)	46.79 ± 13.42	33.19 ± 14.48	0.302*; 0.631**

Note: * Levene test; ** Shapiro Wilk

ventricular ejection fraction is tested using Spearman test. The cut-off-point of NT-proBNP level and left ventricular ejection fraction of each hypertension stage is assessed using Receiver Operating Curve (ROC) analysis. The statistical calculation employs Statistical Package for Social Science (SPSS) Software. The analysis results will be considered significant if the value $p < 0.05$.

RESULTS

The 56 samples meet the inclusion and exclusion criteria, consisting of 29 patients of chronic heart failure with hypertension stage 1 (HTD-1) group and 27 patients of chronic heart failure with hypertension stage 2 (HTD-2) group, with patients' basic characteristics of both groups are presented in Table 1.

The sex, mean age, one-time blood sugar level, total cholesterol, triglyceride, urea, and creatinine variables are insignificantly different between the HTD-1 and HTD-2 groups of heart failure patients. Therefore, the research samples of both groups are comparable. The results of examination of NT-proBNP level and FEVK of sample medical records are as listed in table 2.

The examination results show that the NT-proBNP level of HTD-2 group is higher than that of HTD-1 group. On the contrary, the FEVK of HTD-2 group is lower than that of HTD-1 group. A statistical test needs to be conducted to find out

whether the difference is significant. Considering that the normality and homogeneity tests conducted to the NT-proBNP level show abnormally distributed and non-homogenous data, a Mann-Whitney test is conducted for the difference in the NT-proBNP levels of both groups. The Mann-Whitney test results show that the NT-proBNP level of HTD-2 group is higher than that of HTD-1 group, $p < 0.05$ (figure 1). On the contrary, for the difference in FEVK, an independent T test is conducted considering the normally distributed and homogenous data. The independent T test results show that the FEVK of HTD-2 group is significantly lower than that of HTD-1 group, $p < 0.05$ (figure 2).

The examination results of NT-proBNP level and FEVK in HTD-2 group show high NT-proBNP, followed with low FEVK. On the contrary, low NT-proBNP level is followed with high FEVK. A Spearman correlation test needs to be conducted to find out whether NT-proBNP level is negatively correlated with left ventricular ejection fraction level. The statistical test results show strong negative correlation of 0.651, $p < 0.001$ (Figure 2).

Moreover, the Cut-off-point of NT-proBNP level has area under ROC curve > 0.7 of 0.844 (95% CI=0.743 to 0.944) and p value = 0.000, showing that this NT-proBNP level may be taken to distinguish hypertension stages in chronic heart failure. The Cut-off-point of NT-proBNP level based on the ROC curve analysis is 1511 pg/ml with sensitivity of 0.82% and specificity of 0.80%

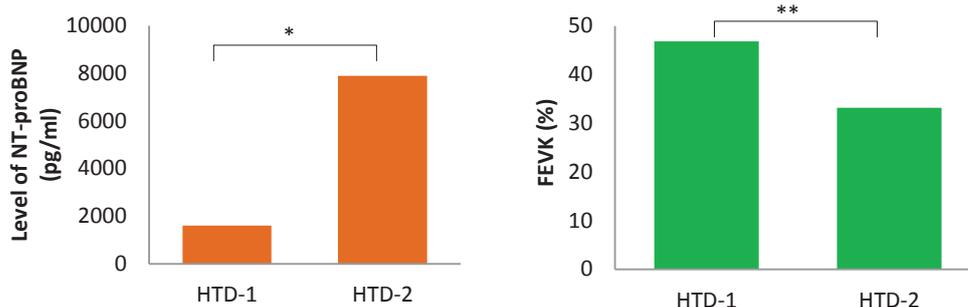


Figure 1. Comparison of NT-proBNP and FEVK in HTD-1 and HTD-2 based on Mann Withney and Independent t tests. * $p < 0.05$: Mann Withney test; ** $p < 0.05$: Independent t test

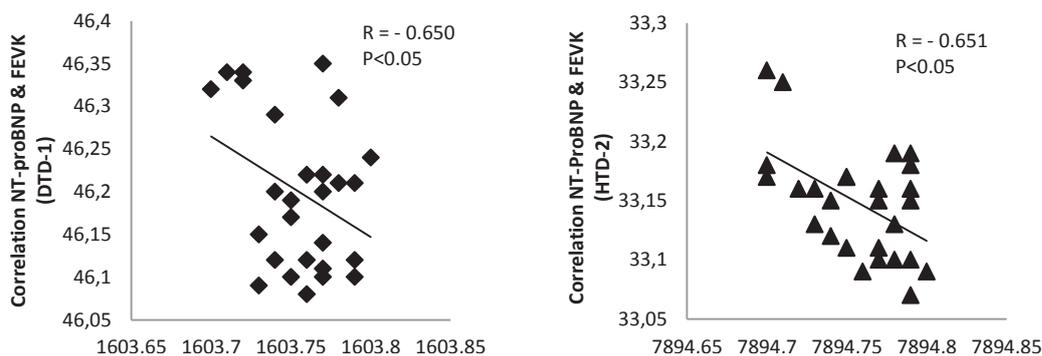


Figure 2. Spearman Correlation between NT-proBNP and LVEF in HTD-1 and HTD-2

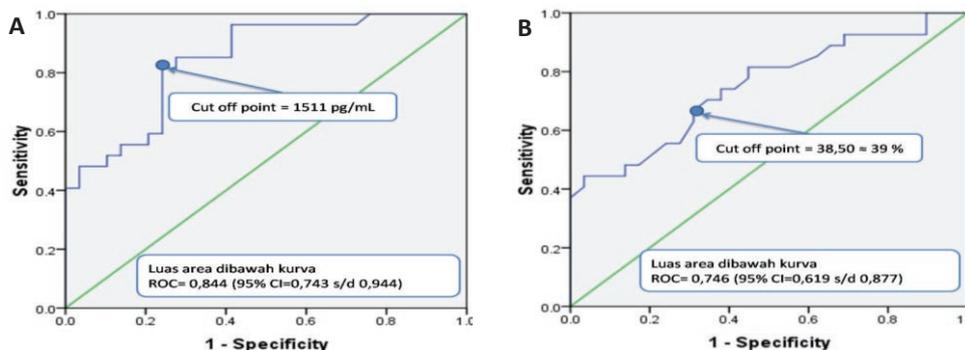


Figure 3. ROC NT-ProBNP in Chronic Heart failure with hypertension stage 1 and stage 2. A. ROC of NT-proBNP; B. ROC of FEVK

(Figure 3A). The Cut-off-point of left ventricular ejection fraction obtained is left ventricular ejection fraction of chronic heart failure patient with hypertension with area under ROC curve > 0.7 and 0.746 (95% CI= 0.619 to 0.877) and p value = 0.001 , showing that this left ventricular ejection fraction may be taken to distinguish hypertension stages in chronic heart failure. The Cut-off-point of left ventricular ejection fraction taken to distinguish hypertension stages in chronic heart failure is 39% with sensitivity of 0.67% and specificity of 0.69 (Figure 3B).

DISCUSSION

The results of this research show that the mean value of NT-proBNP of hypertension stage 2 group is higher than that of hypertension stage 1 group. This

confirms that NT-proBNP is peptide generated by cardiac myocytes after pressure from hypertension. The higher the hypertension, the higher the NT-proBNP level is (Drewniak et al., 2015; McKie and Burnett, 2016; Vanderheyden et al., 2004). The results of this research conform to the research conducted by Macheret et al. which reports difference in the mean of NT-proBNP level in hypertension stage and that the higher the hypertension stage, the higher the NT-proBNP level is (Macheret et al., 2012). Similarly, the research conducted by Ojji et al. also reports that NT-proBNP level of hypertension patients with heart failure is significantly higher than that of hypertension patient without heart failure, with or without left ventricular hypertrophy, $p < 0.0001$ (Ojji DB et al., 2014). However, the NT-proBNP increasing mechanism in hypertension

is not completely known, but this increase describes heart structural and functional changes. These changes include cardiac remodeling, left ventricle hypertrophy, left ventricular diastolic dysfunction and systolic dysfunction, and high intracardiac pressures and thus may be taken to detect early heart failure and to assess progression and prognosis of chronic heart failure with hypertension.

Hypertension causes an increase of NT-proBNP through increasing left ventricular wall pressure during systole (increase of left ventricular filling pressure) and left ventricular wall pressure during systole with left atrial stretch and increased left ventricular mass. This leads to left ventricular wall stress, which will stimulate NT-proBNP secretion, leading to higher blood pressure, higher filling pressure, higher left ventricular mass, and thus more NT-proBNP is released. Stimulation of hormones like endothelin and angiotensin II, free radicals, inflammation factors like TNF- α and IL-6 as well as myocardial hypoxia resulted from hypertension will also lead to heart ventricular wall stress, which will increase NT-proBNP release (McKie and Burnett, 2016; Zipes et al., 2018).

Brain Natriuretic Peptide (BNP) and NT-proBNP are neurohormones secreted by cardiac myocytes in response to heart wall stress caused by increased pressure and volume. Excessively increased pressure and volume in ventricle will stimulate BNP gene (Natriuretic Peptide Precursor B gene, NPPB gene) located at chromosome 1 and encode prehormon-proBNP (pre-proBNP-134 amino acid peptide). Pre-proBNP degrades to pro-BNP (108 amino acids) stored in secretory granules of ventricular myocytes. Pro-BNP is then split by protease to BNP active form (77-108 amino acids) and NT-proBNP (1-76 amino acids) which is BNP inactive form. Brain Natriuretic peptide (BNP) and NT-proBNP are then released to circulation as hormonal counterregulation and the sympathetic nervous system (Fu et al., 2018; Volpe et al., 2016a).

The results of this research also show that the mean of left ventricular ejection fraction is lower in heart failure with hypertension stage 2 than that with hypertension stage 1. This conforms to the research conducted by Bielecka-dabrowa which reports that left ventricular ejection fraction in heart failure patient with hypertension is lower than that in hypertension patient without heart failure, $p < 0.0001$ (Bielecka-dabrowa et al., 2015b). The research conducted by Kattel et al. also reports that hypertension causes concentric hypertrophy to hypertension group with left ventricle hypertrophy and concentric remodeling in hypertension patient

without left ventricular hypertrophy (Kattel et al., 2016). Increased pressure caused by hypertension will lead to diastolic dysfunction with concentric left ventricular hypertrophy, which will cause heart failure with normal or increased ejection fraction, while excessive volume because of hypertension will cause systolic dysfunction with eccentric hypertrophy, which will cause heart failure with decreased ejection fraction. Excessively increased pressure and volume will increase heart failure progression because of hypertension. Other researches also report that a combination of cardiac remodeling and increased cardiac biomarkers (NT-proBNP) because of hypertension may be taken to detect the progression of symptomatic heart failure patient, particularly in heart failure with decreased ejection fraction (Kattel et al., 2016; Messerli et al., 2017).

The results of this research also show that NT-proBNP level is strongly, negatively correlated with left ventricular ejection fraction in hypertension patient with chronic heart failure. This research result is supported by the research conducted by (Kang SH et al., 2015), which shows that heart failure patient with ejection fraction is kept with low NT-proBNP level compared to heart failure patient with decreased ejection fraction (Kang SH et al., 2015). This shows that increased NT-proBNP level will decrease left ventricular ejection fraction. The research conducted by Ojji B, et al. also reports that NT-proBNP level is significantly, negatively correlated with left ventricular ejection fraction of 0.21 with p value of 0.01 (Ojji DB et al., 2014).

The cut-off-point value of NT-proBNP level may be significantly taken to distinguish hypertension stages in chronic heart failure since it has area under ROC curve > 0.7 . The cut-off-point value of NT-proBNP level obtained is 1511 pg/ml with sensitivity of 0.82% and specificity of 0.80%. N-terminal proBNP (NT-proBNP) may be taken to determine hypertension stage and prognosis of chronic heart failure, particularly in in-patient and to predict the mortality of chronic heart failure. NT-proBNP level based on receiver operator characteristic (ROC) curve of 1078 pg/ml may be taken to determine prognosis of chronic heart failure (Gaggin and Januzzi, 2013). The cut-off-point value of NT-proBNP level based on ROC curve > 332.5 pg/ml with sensitivity 0.76% and specificity of 0.95% may be taken to predict heart failure in hypertension patient (Bielecka-dabrowa et al., 2015a).

The cut-off-point value of left ventricular ejection fraction may be taken to distinguish hypertension stages in chronic heart failure since it has area under ROC curve > 0.7 . The cut-off-point value of left ventricular

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ejection fraction obtained is 39% with sensitivity of 0.67% and specificity of 0.69%. This research result is supported by the research conducted by Volpe, et al. which reports that hypertension causes heart failure with decreased ejection fraction (<40%) because of excessively increased stimulation of RAAS, SNS and natriuretic peptide (including NT-proBNP) and thus leads to left ventricular systolic dysfunction (Volpe et al., 2016b).

This research is limited to using secondary data from patients' medical records, thus the researcher does not have information of the history of hypertension duration and routine treatment for the hypertension. In addition, there is no information of the stages, duration of sickness and treatment for chronic heart failure, risk factors other than patients' diabetes mellitus, hypercholesterolemia, hypertriglyceridemia, and decreased kidney function. Therefore, further research is needed to examine the effects of other than the abovementioned factors for better outcome.

CONCLUSION

The results of this research show that NT-proBNP level in hypertension stage 2 is higher than that in hypertension stage 1, while left ventricular ejection fraction in hypertension stage 2 is lower than that in hypertension stage 1 in chronic heart failure patient. The increase in NT-proBNP level will significantly decrease ventricular ejection fraction. The cut-off-point value of NT-proBNP level and left ventricular ejection fraction may be taken to distinguish hypertension stages in chronic heart failure.

CONFLICT OF INTEREST

There is no conflict of interest in this research

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