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THE DIFFERENCE BETWEEN ST2 AND NT-PRO BNP CONCENTRATIONS BEFORE AND AFTER-TREATMENT OF ACE-INHIBITORS IN NYHA III-IV HEART FAILURE PATIENTS

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ABSTRACT

The American Heart Association (2016) stated that at the age of forty the risk of developing heart failure is one in five. Medication is based on clinical signs and symptoms that are often late. Early cardiac markers are required to guide therapy. This study compared the difference between ST2 and NT-ProBNP concentrations before and after ACE inhibitors (ACE-I) in NYHA III-IV heart failure patients. This was a randomized prospective observational study without controls. The respondents were males or females, 21-75 y.o in NYHA III-IV heart failure patients. Twenty-five respondents were appropriate to inclusion criteria. The ST2 was measured by Quantikine®ST2/IL-33R quantitative sandwich ELISA immunoassay while NT-proBNP was measured by Immulite Turbo® 1000. Majority of respondents were males (60%) and had comorbidities (60.7%), consisting of NYHA Class III (36%), and IV (64%). Coronary artery disease and valvular heart disease (40%.36% respectively). Length of stay was 6.4±3.4 days. The concentration difference of ST2 and NT-proBNP before and after ACE-I were both significant, however, NT-proBNP was more significant (p=0.001 vs. p=0.023). NYHA at admission influenced ST2 difference but not NT-proBNP. NT-proBNP concentration correlated to length of stay while ST2 was not. ST2 had a negative correlation with age, no correlation to GFR and weight. NT-proBNP was correlated to weight, negatively correlated to GFR, not correlated to age. ACE-I subtypes difference did not affect the study result. NT-proBNP was a better heart failure cardiac marker than ST2 due to its ability in diagnosis, prognosis and showing more significant difference after ACE-I administration.

Key words: NT-proBNP, ST2, ACE-I therapy, NYHA, heart failure

INTRODUCTION

Heart failure occurs when the heart fails to pump blood into the body to fulfill the metabolism requirement.[1] The American Heart Association in 2016 stated that at the age of forty the risk of developing heart failure is one fifth.[2] The estimated heart failure treatment will cost approximately USD 68.7 in 2030. Indonesian heart failure patients are younger than in Europe and America with a higher severity. Therefore, it will decrease productivity and increase hospitalization burdens, both cost, and resources.[3] The average hospital length stay for Asian Pacific heart failure patients is approximately 6-9 days.[4]

Medication titration dose for heart failure (e.g. angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers, Beta Blockers (BB)) is based on clinical signs and symptoms that frequently appears late. Heart remodeling as the main objective of heart failure treatment is unable to be recognized until worsening or improving clinical signs and symptoms appear.[1] Early cardiac markers are required to guide therapy and reduce heart failure rehospitalization and mortality.[5,6]

N-terminal pro-Brain Natriuretic Peptides (NT-proBNP) is the most recommended laboratory parameter for supporting heart failure diagnosis at present (Class I recommendation, level of evidence is A).[1] However, several studies reported its inconsistent result during application in heart failure treatment guidance or monitoring.[6-8] The ST2 is expected to be more objective in guiding heart failure therapy compared to NT-proBNP due to its that is not affected by age, renal function, sex, and weight.[5,9,10] However, some researches have shown that ST2 was influenced by many other conditions such as inflammation, systolic blood pressure, body mass index, and diabetes.[9,11]

This study aimed to compare the concentration difference between ST2 and NT-Pro BNP in heart failure patients New York Heart Association (NYHA) Class III-IV, before and after treatment of ACE-I. Angiotensin-Converting Enzyme Inhibitor (ACE-I) is

the heart failure first-line therapy. This study was expected to reveal a cardiac marker with more significant difference after ACE-I and related factors affected.

METHODS

This was a prospective observational study. Samples were taken consecutively random without a control group. The concentration of ST2 and NT-ProBNP before ACE-I was compared to the concentration of ST2 and NT-ProBNP after ACE-I. There were twenty-five respondents who met inclusion criteria as follows: age of 21-75 years old, classified as NYHA class III-IV heart failure, receiving treatment of ACE-I and willing to participate in the study by signing the informed consent. Patients with following comorbidities such as asthma, infection, an autoimmune condition, and cancer. Ethics clearance was obtained from the Ethical Department of the Dr. Soetomo Hospital Surabaya with the number of 712/Panke.KKE/X1/2017. All respondents were inpatients in the Cardiology Department of the Dr. Soetomo Hospital Surabaya.

The concentration of ST2 was measured from a serum sample of SST (Serum-separating tubes), while NT pro-BNP was measured from the heparin plasma sample. Researchers compared the concentration of ST2 and NT-ProBNP before ACE-I and after ACE-I reached a steady state. Blood was taken approximately 2.5-3 mL and then centrifuged at 3,000 rpm for 15 minutes. Serum and plasma were separated and refrigerated in -80C.[12,13] This was a comparative study with a standard deviation of 24.44 and requirement of 25 samples.[14] The concentration of ST2 was measured with Quantikine® Human ST2/IL-33R quantitative ELISA sandwich and NT-proBNP concentration was measured with Immulite Turbo® 1000 two-sites chemiluminescent immunometric assay.

RESULTS AND DISCUSSION

The majority of patients were males (60%, 15 patients) and having comorbidities (60.7%, 14 patients). The Table 1 described the patient characteristics. Coronary artery disease was the major etiology of heart failure in this study followed by valvular heart disease and hypertension (40%, 36%, 16%, respectively). Mean length of stay was 6.4±3.4 days, similar to the mean length of stay in Asia Pacific.[4] Concentrations of ST2 and NT-proBNP before therapy were not correlated to the patient length of stay with p-value of 0.451 and 0.889, respectively). Difference of NT-proBNP concentration was moderately correlated to patient length of stay (r -0.431; p=0.031) while ST2 was not (r -0.17; p= 0.416).

From Table 2 and 3, there was a significant difference between ST2 and NT-proBNP concentration before and after therapy. However, the difference of NT-proBNP concentration was more

Table 1. Patient characteristics

Sample Size	25	**Comorbidity**	
Sex		No comorbidity	11(39.3%)
Male	60%	Cerebrovascular disease	2(7.1%)
Female	40%	Diabetic kidney disease	1 (3.6%)
Heart Failure Etiology:		Diabetes mellitus	2(7.1%)
Coronary artery disease	40%	DM, dyslipidemia	1 (3.6%)
Valvular heart disease	36%	DM, hypertension	3 (7.1%)
Hypertension	16%	Hypertension	2 (7.1%)
Cardiomyopathy	4%	Hypertension, arrhythmia	

Table 2. Difference test of ST2 concentration before and after ACE-I therapy

ST2	**N**	**Mean ± SD (ng/mL)**	**Mean ± SD of Difference(ng/mL)**	**P-value**
Before	25	267.81±317.42	-120.76	0.023
After	25	147.05±158.52	±248.23	

Table 3. Difference test of NT-proBNP concentration before and after ACE-I

NT-pro BNP	**N**	**Mean ±SD (pg/mL)**	**Mean±SD Difference (pg/mL)**	**P-value**
Before	25	37,776.24±57,711.87	-11,039.48	0.001
After	25	26,736.76±45,486.19	±14,281.34	

significant (p=0.001) than that of ST2 (p=0.023). The data were normally distributed based on the Kolmogorov-Smirnov test. Immulite within-run SD was 41.4 with CV 3.75 while ST2 measurement using Quantikine showed SD 15.1 with CV 5.6.

Patients consisted of NYHA III (36%, 9 patients) and NYHA IV (64%, 16 patients). Correlation analysis showed that the concentration of ST2 and NT-proBNP before therapy was not affected by NYHA Class. However, the difference of ST2 concentration before and after ACE-I was affected by NYHA (p=0.014) (Figure 1), while the difference of NT-proBNP concentration was not (p=0.848).

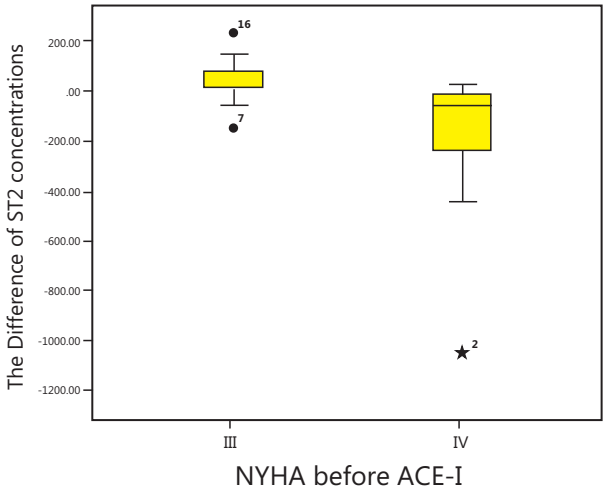

Figure 1. Correlation between NYHA class before ACE-I and the difference of ST2 concentrations

This study demonstrated an inverse correlation between ST2 concentration and age (r=-0.464; p=0.02). No correlation was found between ST2 with either glomerular filtration rate (GFR) (r=-0.416, p=0.038) or weight (r=-0.445, p=0.026) as seen in Table 4. These results were similar to the results from Breathing Not Properly (BNP Study) and PRoBNP Investigation on Dyspnea in the Emergency Department (PRIDE).[15,16] This correlation showed a tendency of higher NT pro-BNP concentration following the lower GFR concentration.

The concentration of ST2 was higher in males while the concentration of NT pro-BNP was higher in females, although these differences were not statistically significant. Compared to the Framingham study, this study did not demonstrate a significant influence of systolic blood pressure on the difference of ST2 concentration and NT pro-BNP concentration (p=0.756 and p=0.565, respectively).[11] Brown-Forsythe analysis showed that the difference in ACE-I types did not affect the changes between ST2 and NT pro-BNP concentrations (Table 5). The influence of diabetes mellitus on the difference between ST2 and NT pro-BNP concentrations were not determined due to the low proportion number of patients.

Heart failure is a clinical syndrome characterized by a decrease of cardiac output and/or the increase of intracardiac pressure, both during resting and stress.[17] The sympathetic system will compensate for

Table 4. Correlation of ST2 and NT-proBNP Concentration with age, weight, and GFR

Correlation	n	Correlation Coefficient	P-value
ST2 with GFR	25	0.122	0.560
ST2 with age	25	-0.464	0.020
ST2 with weight	25	-0.106	0.615
NT-proBNP with GFR	25	-0.416	0.038
NT-proBNP with age	25	0.072	0.734
NT-proBNP with weight	25	-0.445	0.026

Table 5. Correlation of ACE-I types with the difference of ST2 and NT-proBNP concentration

ACE-I	N	Mean ±SD ST2 (ng/mL)	P	Mean ±SD NT-proBNP (pg/mL)	p
Captopril	8	378.66±502.52	0.496	16,802.50±14,588.702	0.378
Ramipril	8	250.37±228.41		25,390.50±20,448.455	
Lisinopril	8	181.06±131.72		49,170.25±74,503.297	
Lisinopril - Captopril	1	214.55		21,3500	
Total	25			30,454.42±45,573.820	

Table 6. Heart failure classification based on NYHA class[3]

NYHA	Definition
Class I	Unlimited physical activities. The daily activity does not cause any exhaustion, palpitation and/or shortness of breath
Class II	Limitation to mild activity. No complaint at rest. However, daily activity may cause exhaustion, palpitation and/or shortness of breath
Class III	Significant daily activity limitation. No complaint at rest, however, mild physical activity causes exhaustion, palpitations or shortness of breath
Class IV	No physical activity without complaint. Sign and symptoms are observed at rest. Increased complaint during activity.

the decrease of cardiac output by increasing the myocardial strain. The neurohormonal system will decrease the intracardiac pressure with myocardial hypertrophy, regeneration changes, and myocyte apoptosis.[18,19] Angiotensin II and aldosterone activations will increase preload, facilitate myocardial hypertrophy in cellular concentration and induce cellular apoptosis. These mechanisms will remodel the cardiomyocytes, increase the stimulation of the renin-angiotensin-aldosterone system and worsen the decrease of cardiac function.[17-19]

The NT-proBNP is an inactive form of Brain Natriuretic Peptide (BNP). Both are endogen peptides that are produced by the atrium and ventricle of the heart as responses to strain, pressure and or heart volume increase. Both are secreted equivalently in number. Experts frequently choose NT-proBNP due to its longer half-life (120 minutes) than BNP (22 minutes) higher plasma concentration: NT-proBNP was found 35 times higher than BNP in plasma. At room temperature, BNP in the sample only lasts for less than 4 hours, while NT-proBNP 72 hours. Both are vasodilators and natriuretics with the capability to decrease ventricular filling pressures, preload, and afterload.[20-22]

Suppression of Tumorigenicity 2 (ST2) is a receptor from the interleukin family (IL-1R). The ligand of this receptor is Interleukin-33 (IL-33). Two common forms of ST2 are a transmembrane form (ST2L) and soluble form in circulation (sST2). The sST2 particularly is expressed in cardiomyocytes and cardiac fibroblast cells, and macrovascular endothelial (e.g. aorta, mast cell surface, macrophage and activated T helper (Th2) cell.[9,13] Cardiomyocyte trauma will increase the production of IL33, ST2L, and sST2.[23] The binding of IL33 to ST2L results in cardioprotective effects such as myocardial fibrosis, decrease of cardiomyocyte hypertrophy, and decrease of apoptosis. The sST2 tends to bind IL-33 stronger than the ST2L, causing the cardioprotective effect unable to occur and this formation will lead to cardiomyocyte death and fibrosis.[9,23]

The difference of NT-proBNP concentrations before and after ACE-I therapy was more significant ($p=0.001$) than the difference of ST2 ($p=0.023$). This was in accordance with the result of several types of research that demonstrated BNP/NT-proBNP concentration in heart failure correlate higher to heart structure condition and functional class than ST2.[24] This study used the New York Heart Association (NYHA) to assess heart functional class and structure (Table 6).[3] Treatment and clinical improvement were also based on this NYHA functional class.

Lu *et al*. stated that the concentration of NT-proBNP correlated with NYHA ($r= 0.87$; $p=0.00$).[24] However, Nair *et al*. in 2016 showed that ST2 was also correlated with NYHA ($r= 0.62$; $p< 0.0001$).[25] Kim-Gaggin *et al*. with 151 patients showed that NT-pro BNP guidance in therapy decreased cardiovascular events. Nevertheless, the following study revealed that ST2 showed a larger difference (40%) than NT-proBNP (25%).[26] Grande *et al*. in 2017 demonstrated that NT-proBNP had a better correlation ($r= 0.399$; $p< 0.001$) to NYHA than ST2 ($r= 0.223$; $p < 0.001$).[27]

Many types of research attempted to guide therapy with NT-proBNP. Most agreed that therapy with NT-proBNP or BNP guidance led to a better clinical result and decreased rehospitalization, however, these researches reported various results in mortality.[7,28,29] This was probably affected by the respondent's NYHA variations, non-uniformity of therapy, and patient types diversity (outpatient, inpatient, acute heart failure, chronic heart failure, etc.). For example, Xin and Hartoto stated that there was a significant difference between NT-proBNP concentration before and after ACE-I.[30,31]

Nevertheless, Khand *et al*. revealed that the decrease of BNP was related to ACE-I treatment but uncorrelated to carvedilol, a beta blocker.[32]

Other large-scale studies had analyzed the potential of ST2 for predicting prognosis.[5,10,27,33] Nowadays, ST2 is recognized as a marker to support risk stratification and prognosis of heart failure patients.[1,34] Imanuel *et al*. in Jakarta also showed that there was a significant difference between ST2 concentration before and after therapy.[22] Laqqan *et al*. and van Vark demonstrated that serial ST2 measurement gave an additional value to NT-proBNP in predicting prognosis. However, these studies did not use ST2 as therapy guidance or monitoring. It was also stated that ST2 added additional value to NT-proBNP in predicting mortality although it did not exceed NT-proBNP in predicting hospital admission. In addition, it was showed that NT-proBNP was preferable to ST2 in predicting acute heart failure events.[35,36] There was a tendency of increased concentration of ST2 in asthma, acute lung inflammation, lung fibrosis, sepsis, and systemic infection.[37] There was still a controversy whether ST2 concentrations always increased in inflammation conditions.

This study showed that NT-proBNP concentration was affected by GFR and body weight, consistent with multicenter research such as BNP and PRIDE.[15,16] It was due to renal clearance pathway of NT-proBNP. The negative correlation between NT-proBNP and body weight was also consistent with previous studies. A developing theory stated that BNP, through the NPR-A receptor, increased lipolysis of adipose tissue. However, hyperinsulinemia played a role in lowering natriuretic peptide concentration in obesity.

There was a tendency of higher concentration of ST2 in males than females. This was according to the results of Immanuel *et al*. and Coglianese *et al*. Similar to many reviews, NT-proBNP concentration was similarly reported higher in females. The European Society of Cardiology (ESC) adjusted the concentration of NT-proBNP based on gender for supporting the heart failure diagnosis.[1,11]

Heart failure patients in this study mostly were males with an average age of approximately 55.89±11.66 years old. It was similar to the gender profile of heart failure patients in the Asia Pacific. The similarity in age average was also observed. The mean age of heart failure patients in the Asia Pacific was 64 to 69 years old.[4] Two types of research such as PRIDE and BNP stated that NT-proBNP concentration was influenced by age of the patient. Therefore, they divided the NT-proBNP cut-off into three groups (<50, 50-7,>75 years old).[15,16] This study revealed that age was not influenced by the concentration of NT-proBNP (p=0.996). The ESC guideline also did not adjust NT-proBNP concentration to age.

The heart failure etiology was dominated by coronary artery disease, valvular heart disease, hypertension, and cardiomyopathy. It was again similar to the Asia Pacific heart failure etiology profile: ischemic heart disease, valvular heart disease, hypertension and cardiomyopathy.[1,4,8]

The ACE-I should be administered to all heart failure patients with left ventricular ejection fraction ≤ 40% both symptomatic and asymptomatic patients unless being contraindicated (Class recommendation I, level of evidence A). This drug inhibits the activation of Angiotensin II thus prevents the production of aldosterone, delivers vasodilatation, decreases artery resistance, increases vein capacity, prevents natriuresis and water retention in order to improve congestion symptoms. This drug also increases circulating bradykinin which is important for vasodilatation and decrease of ventricular remodeling. Different subtypes of ACE-I in this study were not statistically significant in affecting the difference of ST2 and NT-proBNP concentrations in patients with p-value of 0.496 and 0.378, respectively (Table 5).[1,3]

CONCLUSION AND SUGGESTION

The NT-proBNP seemed to be a better cardiac marker than ST2 particularly for ACE-I treatment monitoring and guidance because it showed more significant differences before and after ACE-I therapy. Functional NYHA Class before ACE-I affected the difference of ST2 concentration but not that of NT-proBNP. Further studies were required to determine whether the use of NT-proBNP for therapy monitoring and guidance requires adjustment to renal function, gender, and weight. Moreover, NT-proBNP has been highly recommended in supporting heart failure diagnosis and prognosis. These facts should optimize clinician demand on NT-proBNP.

The limitation of this study was the relatively small number of samples. The advantage of this study was the administration of the same drug type, the consideration of drug steady-state time, the limited NYHA Class and direct comparison of NT-proBNP and ST2 concentrations. A research with larger samples was needed to determine what factors that

influence changes of ST2 and NT-proBNP concentrations particularly during ACE-I, considering the larger coefficient of variation of the difference of ST2 and NT-proBNP concentrations compared to previous studies. Further research was likewise needed to determine whether the use of NT-proBNP in monitoring therapy requires adjustments to kidney function, gender, and weight.

REFERENCES

1. The task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal, 2016; 37: 2129–2200.
2. Savarese G, Lund LH. Global public health burden of heart failure. Cardiac Failure Review, 2017; 3(1): 7-11.
3. Perhimpunan Dokter Spesialis Kardiovaskular Indonesia. Pedoman tatalaksana gagal jantung. Jakarta, PERKI, 2015; 1-46.
4. Rajadurai J, Tse HF, Wang CH, Yang NI, Zhou J, Sim D. Understanding the epidemiology of heart failure to improve management practices: An Asia-Pacific perspective. J Card Fail, 2017; 23(4): 327-339.
5. Januzzi JL, Pascual-Figal D, Daniels LB. ST2 testing for chronic heart failure therapy monitoring: The international ST2 consensus panel. Am J Cardiol 2015; 115[suppl]: 70Be75B.
6. Savarese G, Trimarco B, Dellegrottaglie S, Prastaro M, Gambardella F, *et al*. Natriuretic peptide-guided therapy in chronic heart failure: a meta-analysis of 2,686 patients in 12 randomized trials. PLoS One, 2013; 8: e58287.
7. Xin W, Lin Z, Mi S. Does B-type natriuretic peptide-guided therapy improve outcomes in patients with chronic heart failure? A systematic review and meta-analysis of randomized controlled trials. Heart Fail Rev, 2015; 20: 69-80.
8. Yancy C, Jessup M, Bozkurt B., Butler J, Casey D, *et al*. 2017 ACCF/AHA Guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the heart failure society of America. Circulation, 2017; 136(6): e137-e161.
9. Villacorta H, Maisel AS. Soluble ST2 Testing: A promising biomarker in the management of heart failure. Arq Bras Cardiol, 2016; 106(2): 145–152.
10. Dupuy AM, Curinier C, Kuster N, Huet F, Leclercq F, *et al*. Multi-marker strategy in heart failure: Combination of ST2 and CRP predicts poor outcome. PLoS ONE, 2016; 11(6): e0157159.
11. Ciccone MM, Cortese F, Gesualdo M, Riccardi R, Nunzio DD, Moncelli M, *et al*. A Novel cardiac bio-marker: ST2: A Review. Molecules, 2013; 18: 15314-15328.
12. Siemens. IMMULITE/IMMULITE 1000 Turbo NT-ProBNP. 2017.
13. R&D Systems. Quantikine ELISA: Human ST2/IL-33R Immunoassay 2016; 1-10.
14. Gaggin HK, Szymonifka J, Bhardwaj A, Belcher A, De Berardinis B, *et al*. Head-to-head comparison of serial soluble ST2, growth differentiation factor-15, and highly-sensitive troponin T measurements in patients with chronic heart failure. JACC Heart Fail, 2014; 2(1): 65-72.
15. Madamanchi C, Alhosaini H, Sumida A, Runge MS. Obesity and natriuretic peptides, BNP and NT-proBNP: Mechanisms and diagnostic implications for heart failure. –Int J Cardiol, 2014; 176(3): 611617.
16. Kim MS, Jeong TD, Han SB, Min WK, Kim JJ. Role of soluble ST2 as a prognostic marker in patients with acute heart failure and renal insufficiency. J Korean Med Sci, 2015; 30(5): 569–575.
17. Dumitru I, Ooi HH. Heart failure. Updated: Feb 04th, 2016 available in http://emedicine.medscape.com/article/2500037overview-showall (accessed June 1st, 2017)
18. Mann L, Chakinala M. Heart failure: Pathophysiology and diagnosis. In J. Fauci, D. Kasper, S. Hauser, D. Longo, J. Jameson, & Loscalzo, Harrison's principles of Internal Medicine. 16th Ed., New York, Mc Graw Hill. 2015; 1500-1506.
19. Mentz RJ, O'Connor CM. Pathophysiology and clinical evaluation of acute heart failure. Nature reviews: Cardiology, 2016; 13(33): 28-35.
20. Schreiber D, Schraga ED. Natriuretic peptides in congestive heart. Updated Sep show all 2/16 (accessed June 15th, 2017).
21. McKie PM, Burnett JC. NT-proBNP: The gold standard biomarker in heart failure. Journal of The American College of Cardiology, 2016; 68: 22.
22. Immanuel S, Mandey NMAG, Makmun LH. ST2 concentrations before and after treatment of NYHA III and IV heart failure. Acta Medica Indonesiana, 2015; 47(4): 304-310.
23. Breidthardt T, Balmelli C, Twerenbold R, Mosimann T, Espinola J, *et al*. Heart failure therapy-induced early ST2 changes may offer long-term therapy guidance. J Card Fail, 2013; 19: 821-8.
24. Lu Z, Wang B, Wang Y, Qian X, Zheng W, WeI M. Relationship between CCR and NT-proBNP in Chinese HF patients, and their correlations with severity of HF. BioMed Research International, 2014; 1: 1-7.
25. Nair N, Gongora E. Association of sST2 with GDF-15 and matrix metalloproteinases in idiopathic dilated cardiomyopathy. The Journal of Heart and Lung Transplantation, 2016; 35: 1-4
26. Gaggin HK, Mohammed AA, Bhardwaj A, Rehman SU, Gregory SA, *et al*. Heart failure outcomes and benefits of NT-proBNP guided management in the elderly: Results from the prospective, randomized ProBNP outpatient tailored chronic heart failure therapy (PROTECT) study. J Card Fail, 2012; 18: 626-34.
27. Grande D, Leone M, Rizzo C, Terlizzese P, Parisi G, *et al*. A Multiparametric approach based on NT-proBNP, ST2, and galectin 3 for stratifying one year prognosis of chronic heart failure outpatients. J Cardiovasc. Dev.

Dis. 2017; 3: 1-11
28. Troughton RW, Frampton CM, Brunner-La Rocca HP, Pfisterer M, Eurlings LW, *et al*. Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis. Eur. Heart J, 2014; 35: 1559-67.
29. Stienen S, Salah K, Moons AH, Adrianus B, van Pol PE, *et al.* Rationale and design of PRIMA II: A multicenter, randomized clinical trial to study the impact of in-hospital guidance for acute decompensated heart failure treatment by a predefined NT-PRoBNP target on the reduction of readmission and mortality rates. Am Heart J, 2014; 168: 30-6.
30. Xin W, Lin Z, Mi S. Does B-type natriuretic peptide-guided therapy improve outcomes in patients with chronic heart failure? A systematic review and meta-analysis of randomized controlled trials. Heart Fail Rev, 2015; 20: 69-80.
31. Hartoto HH, Zulkarnain BS, Aminuddin M. Analysis of changes in the serum concentration NT-proBNP after ACE inhibitor Therapy in Patients with Heart Failure. Folia Medica Indonesiana, 2016; 52(3): 193-197.
32. Khand AU, Chew PG, Douglas H, Jones J, Jan A, *et al.* The Effect of carvedilol on B-type natriuretic peptide and cardiac function in patients with heart failure and persistent atrial fibrillation. Cardiology, 2015; 130: 153–158.
33. Dieplinger B, Mueller T. Soluble ST2 in heart failure. Clinica Chimica Acta, 2014; 443:57-70.
34. Wettersten N, Maisel AS. Biomarkers for Heart Failure: An update for practitioners of internal medicine. Am J Med, 2016; 129(6): 560-7.
35. van Vark LC, Lesman-Leegte I, Baart SJ, Postmus D, Pinto YM, *et al.* TRIUMPH investigators. Prognostic value of serial ST2 measurements in patients with acute heart failure. J Am Coll Cardiol, 2017; 70(19): 2378-2388.
36. Laqqan M, Schwaighofer C, Graeber S, Raedle-Hurst T. Predictive value of soluble ST2 in adolescent and adult patients with complex congenital heart disease. PLOS ONE, 2018; 13(8): e0202406.
37. Xu H, Turnquist HR, Hoffman R, Billiar TR, Horwich TB, Fonarow GC. Role of the IL-33-ST2 axis in sepsis. Mil Med Res–, 2017; 8(1): 3041.