Relationship between intrarenal renin-angiotensin activity and re-hospitalization in patients with heart failure with reduced ejection fraction

Ozcan Orscolik, Bugra Ozkan, Ayca Arslan, Emre Ertan Sahin, Ozan Sakarya, Orçun Ali Sürmeli, Şenay Balci Fidanç*, Ahmet Çelik, Burak Yavuz Çimen*, Ismail Türkay Özcan

Departments of Cardiology and *Biochemistry, Faculty of Medicine, Mersin University; Mersin-Turkey

Introduction

Heart failure (HF) is a clinical syndrome accompanied by typical signs and symptoms that develop as a result of structural and/or functional defects (1). While the overall prevalence of HF is estimated to be 2%, it increases with age and affects more than 10% of individuals older than 65 years (2). Despite improvements in the survival of patients with HF achieved with current treatments, mortality and morbidity rates are still high. This results in a serious economic and health burden for the society (3, 4). In the natural course of HF patients go through repeated re-hospitalizations, and acute decompensated HF (ADHF) is the leading cause of hospitalizations in the USA (5). Studies have shown that most re-hospitalizations related to HF occur in the early post-discharge period or in the period before death (6).

As a result, new methods are increasingly being investigated to predict both short- and long-term re-hospitalization and death in patients with ADHF (7).

Although previous studies have shown that plasma renin–angiotensin system (RAS) activation increases the severity of HF and the number of hospitalizations due to HF (8, 9), the effect of intrarenal RAS activity is still unknown. Angiotensinogen (AGT), which is synthesized by the liver, released into the systemic circulation, and found in abundance in the plasma, is converted to angiotensin I by renin (10). Because of its high molecular weight, plasma AGT is unable to pass through the glomerular membrane. Thus, it is claimed that urinary AGT (UAGT) is synthesized by the kidneys and is an indicator of direct intrarenal RAS activation (11).

Therefore, different clinical responses to similar treatments and varying rates of re-hospitalization and mortality among pa-
tients with HF may be because of the differences between in intrarenal RAS activation in patients. In the present study, we investigated the relationships between UAGT level and New York Heart Association (NYHA) class and number and duration of hospitalizations within the previous year in patients being followed up for HF with reduced ejection fraction (HFrEF).

**Methods**

This study included 85 patients who were admitted to the cardiology clinic between April and June 2017, had an ejection fraction (EF) of <40% on transthoracic echocardiography, and were receiving optimal medical treatment. Data regarding patients’ demographic characteristics (age and gender), medical history (diabetes mellitus (DM), hypertension (HT), coronary artery disease, and coronary artery bypass graft surgery), medications used (beta-blockers, angiotensin-converting enzyme inhibitors (ACE-i), angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), and ivabradine), device therapy (implantable cardioverter defibrillator and cardiac resynchronization therapy), and cardiac rhythm (sinus rhythm, atrial fibrillation, and pacemaker rhythm) were recorded. The NYHA functional class of each patient was determined. In order to avoid statistical errors that may arise from numerical differences, the patients were divided into two groups, NYHA I-II and NYHA III-IV, and an equal number of patients was recruited for each group. Re-hospitalization was defined as two or more occurrences of hospitalization due to HF in the previous year. The study was approved by the Local Clinical Research Ethics Committee.

Patients who were aged <18 years or >90 years; who had a history of acute coronary syndrome or primary coronary intervention within the past 6 months; and who had hypotension, pulmonary edema, or cardiogenic shock were excluded from the study. In addition, patients with stage 4-5 chronic kidney disease (CKD); those with an active focus of infection, neurological illness severe enough to affect biochemical and hematological results, chronic obstructive pulmonary disease (COPD), malignancy, or liver function impairment/liver failure; and those who did not consent to participate in the study were excluded from the study.

Six of the 85 patients included in the study later withdrew. After the evaluations, 13 patients were excluded from the study because they had non-cardiac diseases. Three of these patients had COPD, eight had stage 4-5 CKD, and two had malignancy. Three patients were excluded from the study because of incomplete data.

Echocardiographic imaging was performed for all participants using a GE Vivid E90 echocardiography device. Based on the guidelines of the American Society of Echocardiography, patients were evaluated in the left lateral decubitus position. Measurements were made using the two-dimensional, M-mode, and color Doppler methods with parasternal long-axis view, short-axis view, and apical four- and five-chamber views. At least three consecutive pulses were recorded by a blinded experienced operator, and the average was calculated. Left ventricular diameters, interventricular septum and posterior wall thicknesses, and ventricular EF were measured by placing an M-mode cursor just below the mitral valve leaflets in the parasternal long-axis view, as described in the guidelines of the American Society of Echocardiography (12).

Blood pressure was measured twice from the right arm with an interval of 2 min in the sitting position after at least 10 min of resting. The average of the two measurements was recorded as the blood pressure value. Body mass index (BMI) was calculated at the first examination using the following formula: height/weight².

Hemogram and biochemical analyses were performed using the Sysmex XN-1000 (Sysmex America, Inc. Lincolnshire, IL, USA) and Roche Cobas C501 (Roche Diagnostics GmbH, Penzberg, Germany) devices, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) analyses were done using an Immulite 2000® immunoassay analyzer (Diagnostic Products Corporation, Los Angeles, CA, USA). Blood samples were obtained from the antecubital fossa veins in the sitting position after a 20-min rest following 12 h of fasting.

Urine samples for UAGT measurement were collected in sterile tubes and centrifuged at 3000 rpm for 20 min. The supernatants were carefully collected and stored at -70°C in a freezer for further analysis. UAGT measurement was done using the sandwich ELISA immunoassay method (YHB20.60901646, YH Bioresearch Laboratory, Shanghai, China). The UAGT concentration was normalized to the urine creatinine value measured from the same urine sample (UAGT/UCR). All laboratory values are those obtained at the time of admission.

Statistical analyses were performed using 64-bit Windows version of SPSS (version 22.0, SPSS, Chicago, IL, USA). Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Variables with normal distribution were assessed using parametric tests. Continuous variables were expressed as mean±SD for parametric variables and median and minimum–maximum values for nonparametric variables. Comparisons of parametric variables between the two groups were performed using independent samples t-test. Comparisons of nonparametric values between the two groups were performed using the Mann–Whitney U test. Categorical variables were compared using the chi-square test. Correlation analysis was performed using the Spearman’s correlation method. Multiple linear regression analysis was used to study the predictive factors for prehospitalization. Analysis results were evaluated within a 95% confidence interval, and p<0.05 was interpreted as a statistically significant difference.

**Results**

Among the patients included in the study, 30 had NYHA functional classes I-II symptoms and 33 had NYHA functional classes...
III-IV symptoms. When the patients were grouped as NYHA functional class I-II and III-IV, there were no differences between the groups in terms of age, gender, or duration of HF (p>0.05). Compared with the other patients, patients with NYHA functional classes III-IV had significantly greater number of hospitalizations and total length of hospital stay (p<0.001). In addition, patients with NYHA functional classes III-IV had significantly higher BMI and higher use of furosemide compared with those with better functional classes (p=0.02, p=0.005, respectively). Data for both groups regarding demographics, medications used, medical history, device therapy received, and cardiac rhythm are given in Table 1.

Comparison of laboratory values of patients with NYHA classes I-II and classes III-IV revealed that the group with poorer functional capacity (NYHA classes III-IV) had significantly higher UAGT, NT-proBNP, and high-sensitivity C-reactive protein (Hs-CRP) levels [82.4 (12.5–338.3) and 226.3 (10.7–1233), p<0.001; 523 (67–5112) and 5270 (850–19971), p<0.001; 2.6 (0.33–25) and 15.5 (0.89–82), p<0.001, respectively].

Table 2 shows a comparison of the patients based on re-hospitalizations. In terms of demographics, patients who were hospitalized more than two times in the previous year had higher NYHA functional classes (p<0.001), and these patients were mostly males (p=0.008). These patients also had significantly lower systolic blood pressures (p=0.007). Biochemical analyses showed that patients who were re-hospitalized had significantly lower serum potassium, total cholesterol, and triglyceride levels (p=0.005, p=0.03, p=0.01, respectively). Compared with patients with fewer hospitalizations, patients who were hospitalized more than two times in the previous year had significantly higher NT-proBNP, UAGT, and Hs-CRP levels [709 (67–19971) and 4254 (81–14598), p<0.001; 99 (13.3–1233) and 193.2 (10.7–804), p=0.007;
Table 2. Basal characteristic and biochemical variables according to re-hospitalization

|                                | Hospitalized <2 times (n=27) | Hospitalized ≥2 times (n=36) | P      |
|--------------------------------|-------------------------------|--------------------------------|--------|
| Age (year)                     | 66.4±13.1                     | 63.4±10.5                      | 0.313  |
| Gender (F/M)                   | 11/16                         | 4/32                           | 0.008  |
| Duration of HF (months)        | 40 (10-200)                   | 33 (10-240)                    | 0.873  |
| NYHA classes III-IV (%)        | 5 (15.2%)                     | 28 (84.8%)                     | <0.001 |
| Hemoglobin (g/L)               | 13.3±1.6                      | 12.4±2                         | 0.066  |
| Platelet count (×1000/mm³)     | 223±84                        | 229±75                         | 0.771  |
| White blood cell count (10³/µL)| 8.6±2.4                       | 8.7±2.8                        | 0.865  |
| BMI (kg/m²)                    | 26.2±2.9                      | 27.2±3.6                       | 0.253  |
| Systolic blood pressure (mm Hg)| 129.2±21.6                    | 114.1±21                       | 0.007  |
| Diastolic blood pressure (mm Hg)|75.5±12.4                      | 70.6±14.3                      | 0.161  |
| Heart rate (beat/min)          | 74.7±12.9                     | 82±15.6                        | 0.051  |
| **Biochemical parameters**     |                               |                                |        |
| Creatinine (mg/dL)             | 1.0±0.27                      | 1.0±0.34                       | 0.573  |
| Serum sodium (mEq/L)           | 139.7±3.6                     | 137.7±4.6                      | 0.088  |
| Serum potassium (mEq/L)        | 4.8±0.5                       | 4.4±0.6                        | 0.005  |
| eGFR (mL/min per 1.73 m²)³     | 68.6 (35-115)                 | 75.4 (30.6-133.9)              | 0.560  |
| Fasting total cholesterol (mg/dL)|181.8±51                      | 152.7±51.4                     | 0.030  |
| Fasting LDL cholesterol (mg/dL)|100.1±39.3                    | 91.6±41.5                      | 0.421  |
| Fasting triglyceride (mg/dL)   | 201.8±149.5                   | 125.9±58                       | 0.012  |
| NT-proBNP (pg/mL)              | 709 (67-19971)                | 4254 (81-14598)                | <0.001 |
| UAGT/UCre (µg/g)               | 99 (13.3-1233)                | 193.2 (10.7-804)               | 0.007  |
| Hs-CRP (mg/dL)                 | 3.2 (0.33-70)                 | 14 (1.32-82)                   | <0.001 |
| **Heart rhythm**               |                               |                                |        |
| Sinus rhythm                   | 24                            | 24                             |        |
| Atrial fibrillation            | 1                             | 10                             |        |
| Pacemaker rhythm               | 2                             | 2                              |        |
| **Disease history**            |                               |                                |        |
| Diabetes mellitus              | 8                             | 16                             | 0.344  |
| Hypertension                   | 21                            | 17                             | 0.028  |
| Coronary artery disease        | 21                            | 23                             | 0.971  |
| Coronary artery bypass grafting| 7                             | 14                             | 0.138  |
| **Device history**             |                               |                                |        |
| Implantable cardioverter defibrillator | 13                        | 13                             | 0.117  |
| Cardiac resynchronization therapy | 0                       | 4                              |        |
| **Drug information**           |                               |                                |        |
| Beta-blocker                   | 24                            | 34                             | 0.645  |
| Ace-i/ARB                      | 26                            | 29                             | 0.121  |
| MRA                            | 24                            | 30                             | 0.729  |
| Furosemide                     | 17                            | 30                             | 0.338  |
| Ivabradine                     | 8                             | 10                             | 0.903  |
| **Echocardiographic parameters** |                               |                                |        |
Patients who were re-hospitalized had significantly greater left ventricular diastolic diameters and left atrial diameters and significantly lower EF compared with the other group (p=0.04, p<0.001, p=0.02, respectively).

Univariate correlations of selected markers for all 63 patients are given in Table 3 and Figure 1. Within the entire study group, UAGT was significantly correlated with NT-proBNP (r=0.514, p<0.001), Hs-CRP (r=0.437, p<0.001), hemoglobin (r=–0.283, p=0.02), number of hospitalizations in the previous year (r=0.432, p=0.041), and systolic blood pressure (r=0.08, p=0.58).

Figure 1. Univariate correlates of selected markers in all 63 study participants.
p<0.001), and hospitalization time (r=0.464, p<0.001). There were also significant correlations between the number of hospitalizations within the previous year and NT-proBNP (r=0.507, p<0.001), Hs-CRP (r=0.511, p<0.001), hemoglobin (r=−0.419, p=0.001), serum sodium (r=−0.26, p=0.04), and systolic blood pressure (r=−0.283, p=0.02).

The independence of multiple correlations was assessed using multiple linear regression analysis (Table 4). In the model, UAGT, NT-proBNP, Hs-CRP, hemoglobin, and serum sodium levels and systolic blood pressure were used as independent variables and ≥2 hospitalizations was used as the dependent variable. According to this analysis, NT-proBNP, Hs-CRP, and hemoglobin levels are independent predictors of re-hospitalization, whereas UAGT, serum sodium, and systolic blood pressure are not.

Discussion

This study was conducted to investigate the potential role of UAGT, an important indicator of intrarenal RAS activity, in patients with HFrEF. Our results showed that NT-proBNP, Hs-CRP, and UAGT levels were significantly higher in patients with a history of re-hospitalizations within the previous year. In addition, patients with higher NYHA functional classes were found to have high UAGT levels. The number of hospitalizations within the previous year was also significantly positively correlated with UAGT, NT-proBNP, and Hs-CRP levels and significantly negatively correlated with hemoglobin and serum sodium levels and systolic blood pressure. Regression analysis revealed that UAGT is not an independent predictor for re-hospitalizations.

HF is a common syndrome worldwide and is the leading cause of hospitalizations in the adult population. Although the overall prevalence is estimated to be 2%, it exponentially increases with age and affects more than 10% of people aged >65 years (2). With poor survival rates and 10-year mortality rates of approximately 100% in the follow-up of patients with newly diagnosed HF, it has been emphasized that this disease is even deadlier than cancer (13). Previous studies have shown that re-hospitalization because of pre-existing HF is a predictor of mortality (6, 14, 15). This has led scientists to look for new markers for predicting hospitalizations and mortality because of HF (7).

RAS plays a key role in the pathogenesis of HF (8, 9, 16). This compensatory system activated in chronic HF has been shown to be associated with cardiac remodeling and poor prognosis (17). Clinical trials have shown that ACE-i, ARB, and MRA, which block RAS, effectively improve the prognosis of HF. As a result, these drugs are recommended in contemporary guidelines for HF management (8). The increase in renin, a rate-limiting enzyme, in the formation of angiotensin I from systemic AGT leads to RAS activation. In contrast, AGT is abundant in the plasma and is not a rate-limiting molecule for RAS activity. However, it has been reported that AGT, which is 103–104 times locally scarcer in the kidney than in the plasma, may activate RAS (10). Systemic AGT is produced by the liver but cannot pass through the glomerular basement membrane because of its high molecular weight. Therefore, UAGT is considered to reflect locally produced AGT released from proximal tubular cells. Kobori et al. (18) showed that UAGT was a specific marker of intrarenal RAS status in hypertensive rats, independent of plasma AGT. In addition, elevated UAGT levels have been demonstrated to be an indicator of intrarenal RAS status in various patient populations such as those with HT, CKD, DM, and amyloidosis (19-22). Schunkert et al. (23) found that renal AGT, renin, and angiotensin II levels were high in rats with HF. However, there are no studies in the literature on intrarenal RAS activity status in humans with HF.

In the present study, we found that among patients receiving optimal HF therapy to the extent that they could tolerate, those with a high NYHA class and a history of repeated hospitalization had higher UAGT levels. In their review, Kobori et al. (18) reported that renal RAS activation increased following HF induction in rats. They noted that as a result of this, water/salt retention and peripheral vascular resistance increased, subsequently initiating a vicious cycle that impaired cardiac performance and led to cardiac remodeling (18). This may explain our finding that high UAGT level (i.e., marker of intrarenal RAS activation) was associated with worse NYHA class and higher frequency of re-hospitalization.

Studies have shown that the use of ACE-i/ARB suppresses both plasma and intrarenal RAS activation (24, 25). However, approximately 5%–20% of patients treated with ACE inhibitors cannot tolerate these drugs because of dry cough, angioedema, hypotension, hyperkalemia, or renal dysfunction. Similarly, some patients have to discontinue their treatment because of the side effects of ARBs such as hypotension, hyperkalemia, renal dysfunction, and angioedema (26). In addition, as the tolerance limits for both drugs are exceeded, the dose may have to be reduced or the desired target dose may not be achieved during follow-up. In our study, drug use rates were generally high, most likely because patients with stage 4-5 CKD were excluded from the study. The frequent hospitalizations of some patients despite high rates of drug use may be because of the fact that the target doses could not be reached or that the target dose required for achieving both systemic and intrarenal RAS inhibition varied for each patient. This may explain the high UAGT ratios in patients with high NYHA class symptoms or a history of repeated hospitalizations.

Consistent with our results, previous studies have shown that serum sodium, Hs-CRP, NT-proBNP, hemoglobin, and blood pressure are important prognostic factors in patients with HF. Amin et al. (7) reported that 30-day HF readmission and mortality due to all causes were higher among patients with low serum sodium levels, and that this parameter was a predictor independent of other factors.

Although BNP value at the time of admission in previous studies was found to be correlated with mortality and prolonged hospitalization time, it could not be correlated with the number of hospitalizations (7, 27, 28). In contrast to those findings, we
observed in the present study that high NT-proBNP level at the time of admission was an independent risk factor for re-hospitalization.

There are contradictory results in the literature concerning hemoglobin and CRP levels in patients with HF. While Jug et al. (29) claimed that CRP is not an independent determinant of mortality and re-hospitalization because of HF, Lourenço et al. (30) have shown that elevated CRP level increases the risk of death due to HF or the number of re-hospitalizations independently of other prognostic predictors, consistent with our results. Anemia is a common comorbidity in patients with chronic HF, and its prevalence is 10%–50%. A study by O’Meara et al. (31) showed that anemia increases the risk of mortality and hospitalization in patients with HF, whereas another report asserted that anemia only increases mortality and has no effect on repeated hospitalizations (32). In the present study, hemoglobin level was found to be an independent risk factor for re-hospitalization.

**Study limitations**
The main limitations of our study were the limited number of patients. Second limitation is the lack of a healthy control group. Another limitation is that the doses of the ACE-i/ARBs used by the patients were not standardized.

**Conclusion**
Although UAGT levels are high in patients with poor NYHA functional class and re-hospitalizations, this marker is not valuable for predicting re-hospitalization in patients with HFrEF.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept – Ö.Ö., B.Ö., A.Ç., B.YÇ., İ.TÖ.; Design – Ö.Ö., B.Ö., A.Ç.; Supervision – Ö.Ö., AA., E.E.$, O.S.; Fundings – Ş.B.F., B.YÇ., İ.TÖ.; Materials – AA., E.E.$, O.S., Ş.B.F.; Data collection &/or processing – AA., E.E.$, O.S., O.A.S.; Analysis &/or interpretation – O.A.S., Ş.B.F.; Literature search – Ö.Ö., O.A.S.; Writing – Ö.Ö., B.Ö.; Critical review – A.Ç., B.YÇ., İ.TÖ.

**References**

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al: Authors/Task Force Members. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129-200.
2. Moster A, Hoes AW. Clinical epidemiology of heart failure. Heart 2007; 93: 1137-46.
3. Levy D, Kchaicha S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002; 347: 1397-402.
4. Basu R, Pogliatsch M, Yogasundaram H, Thomas J, Rowe BH, Oudit GY. Roles of Angiotensin Peptides and Recombinant Human ACE2 in Heart Failure. J Am Coll Cardiol 2017; 69: 805-19.
5. Blecker S, Paul M, Taksler G, Ogedegbe G, Katz S. Heart failure–associated hospitalizations in the United States. J Am Coll Cardiol 2013; 61: 1259-67.
6. Chun S, Tu JV, Wijeyasurya HC, Austin PC, Wang X, Levy D, et al. Lifetime analysis of hospitalizations and survival of patients newly admitted with heart failure. Circ Heart Fail 2012; 5: 414-21.
7. Amin A, Chitsazan M, Shiu Kh Ahad Afad F, Taghavi S, Naderi N. On admission serum sodium and uric acid levels predict 30 day rehospitalization or death in patients with acute decompensated heart failure. ESC Heart Fail 2017; 4: 162-8.
8. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987; 316: 1429-35.
9. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341: 709-17.
10. Wysocki J, Battle D. Urinary Angiotensinogen: A Promising Biomarker of AKI Progression in Acute Decompensated Heart Failure: What Does It Mean? Clin J Am Soc Nephrol 2016; 11: 1515-7.
11. Kocyigit I, Yilmaz MI, Unal A, Ozturk F, Ergolu E, Yazici C, et al. An link between the intrarenal renin angiotensin system and hypertension in autosomal dominant polycystic kidney disease. Am J Nephrol 2013; 38: 218-25.
12. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pelikka PA, et al: Chamber Quantification Writing Group; American Society of Echocardiography’s Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18: 1440-63.
13. Rocha BM, Menezes Falcão L. Acute decompensated heart failure (ADHF): A comprehensive contemporary review on preventing early readmissions and postdischarge death. Int J Cardiol 2016; 223: 1035-44.
14. Khazanie P, Heizer GM, Hasselblad V, Armstrong PW, Califf RM, Ezekowitz J, et al. Predictors of clinical outcomes in acute decompensated heart failure: Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure outcome models. Am Heart J 2015; 170: 290-7.
15. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, et al: Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 2002; 106: 2194-9.
16. Borghi C, Rossi F. SIIA Task Force, SIF Task Force. Role of the Renin-Angiotensin-Aldosterone System and Its Pharmacological Inhibitors in Cardiovascular Diseases: Complex and Critical Issues. High Blood Press Cardiovasc Prev 2015; 22: 429-44.
17. Mann DL, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. Circulation 2005; 111: 2387-49.
18. Kobori H, Nangaku M, Navar LG, Nishiyama A. The intrarenal renin-
angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. Pharmacol Rev 2007; 59: 251-87.

19. Kobori H, Alper AB Jr., Shenava R, Katsurada A, Saito T, Ohashi N, et al. Urinary angiotensinogen as a novel biomarker of the intrarenal renin-angiotensin system status in hypertensive patients. Hypertension 2009; 53: 344-50.

20. Sawaguchi M, Araki SI, Kobori H, Urushihara M, Haneda M, Koya D, et al. Association between urinary angiotensinogen levels and renal and cardiovascular prognoses in patients with type 2 diabetes mellitus. J Diabetes Investig 2012; 3: 318-24.

21. Kobori H, Navar LG. Urinary Angiotensinogen as a Novel Biomarker of Intrarenal Renin-Angiotensin System in Chronic Kidney Disease. Int Rev Thromb 2011; 6: 108-16.

22. Kutlugün AA, Altun B, Aktan U, Turkmen E, Altindal M, Yildirim T, et al. The relation between urinary angiotensinogen and proteinuria in renal AA amyloidosis patients. Amyloid 2012; 19: 28-32.

23. Schunkert H, Tang SS, Litwin SE, Diamant D, Riegger G, Dzau VJ, et al. Regulation of intrarenal and circulating renin-angiotensin systems in severe heart failure in the rat. Cardiovasc Res 1993; 27: 731-5.

24. Komine N, Khang S, Wead LM, Blantz RC, Gabbari FB. Effect of combining an ACE inhibitor and an angiotensin II receptor blocker on plasma and kidney tissue angiotensin II levels. Am J Kidney Dis 2002; 39: 159-64.

25. Uzu T, Araki SI, Kashiwagi A, Haneda M, Koya D, Yoykoma H, et al. Comparative Effects of Direct Renin Inhibitor and Angiotensin Receptor Blocker on Albuminuria in Hypertensive Patients with Type 2 Diabetes. A Randomized Controlled Trial. PLoS One 2016; 11: e0164936.

26. Caldeira D, David C, Sampao C. Tolerability of angiotensin-receptor blockers in patients with intolerance to angiotensin-converting enzyme inhibitors: a systematic review and meta-analysis. Am J Cardiovasc Drugs 2012; 12: 263-77.

27. Omar HR, Guglin M. Extremely elevated BNP in acute heart failure: Patient characteristics and outcomes. Int J Cardiol 2016; 218: 120-5.

28. O’Connor CM, Hasselblad V, Mehta RH, Tasissa G, Califf RM, Fuzzat M, et al. Triage after hospitalization with advanced heart failure: the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) risk model and discharge score. J Am Coll Cardiol 2010; 55: 872-8.

29. Jug B, Salobir BG, Vene N, Sebestjen M, Sabovic M, Keber I. Interleukin-6 is a stronger prognostic predictor than high-sensitive C-reactive protein in patients with chronic stable heart failure. Heart Vessels 2009; 24: 271-6.

30. Lourenço P, Paulo Araújo J, Paulo C, Mascarenhas J, Frioès F, Azevedo A, et al. Higher C-reactive protein predicts worse prognosis in acute heart failure only in noninfected patients. Clin Cardiol 2010; 33: 708-14.

31. O’Meara E, Clayton T, McEntegart MB, McMurray JJ, Lang CC, Roger SD, et al. Clinical correlates and consequences of anaemia in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. Circulation 2006; 113: 986-94.

32. Redondo-Bermejo B, Pascual-Figal DA, Hurtado-Martínez JA, Montserrat-Coll J, Peñafiel-Verdú P, Pastor-Pérez F, et al. Clinical determinants and prognostic value of hemoglobin in hospitalized patients with systolic heart failure. Rev Esp Cardiol 2007; 60: 597-606.