Prognostic impact of renal dysfunction on long-term mortality in patients with preserved, moderately impaired, and severely impaired left ventricular systolic function following myocardial infarction

Lidija Savic, Igor Mrdovic, Milika Asanin, Sanja Stankovic*, Gordana Kriljanac, Ratko Lasica

Clinic of Cardiology and Coronary Care Unit, *Center for Medical Biochemistry, Clinical Centre of Serbia, Emergency Hospital; Belgrade-Serbia

ABSTRACT

Objective: The aim of this study was to investigate and compare the prognostic impact of renal dysfunction (RD) at admission in patients with preserved, moderately impaired and severely impaired left ventricular systolic function following ST-elevation myocardial infarction (STEMI).

Methods: We included 2436 patients with STEMI treated with primary percutaneous coronary intervention (pPCI). Patients presenting with cardiogenic shock and those on hemodialysis were excluded. According to the left ventricular ejection fraction (EF), patients were divided in three groups: preserved left ventricular systolic function – EF >50%, moderately impaired – EF=40%-50% and severely impaired left ventricular systolic function-EF <40%. RD was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m² at admission. The follow-up period was 6 years.

Results: Preserved, moderately impaired and severely impaired systolic function were found in 741 (30.5%), 1367 (56.1%) and 328 (13.4%) patients, respectively. RD was present in 105 (14.2%) patients with preserved systolic function, 247 (18.1%) patients with moderately impaired, and 120 (36.5%) patients with severely impaired systolic function.Regardless of the presence of RD, 6-year mortality rates in patients with preserved, moderately impaired, and severely impaired systolic function were 2.7%, 5.2% and 31.1% respectively. Within each LVEF group, patients with RD had a worse outcome, both in the short- and long-term. In the Multivariate Cox Analysis, RD remained an independent predictor of 6-year mortality in patients with moderately (HR 2.52, 95% CI 1.54-3.78) and severely impaired systolic function (HR 2.84, 95% CI 1.68-5.34), but not in patients with preserved left ventricular systolic function (HR 0.59, 95% CI 0.14-1.41).

Conclusion: Although patients with RD had higher 6-year mortality following STEMI regardless of LVEF, RD at admission remained a strong independent predictor for 6-year mortality only in patients with moderately and severely impaired left ventricular systolic function. (Anatol J Cardiol 2018; 20: 21-8)

Keywords: renal dysfunction, left ventricular systolic function, prognosis

Introduction

Renal dysfunction (RD) is a strong independent predictor for adverse cardiovascular outcomes in the general population after ST-elevation myocardial infarction (STEMI) (1-7). Another strong and important predictor of short- and long-term outcome following myocardial infarction is left ventricular systolic function (8-12). Introducing the primary percutaneous coronary intervention (pPCI) in treating of patients with STEMI has significantly reduced mortality and the occurrence of complications (8, 9). The percentage of patients with severely impaired left ventricular systolic function (ejection fraction, EF <40%) is also significantly smaller in the pPCI era than in thrombolytic era, as, generally speaking, establish of a normal blood flow through the infarcted artery leads to a reduction in the myocardial necrotic zone (8). Therefore, majority patients treated with pPCI have preserved (EF >50%) or moderately impaired (EF=40%-50%) left ventricular systolic function (8). The prognostic impact of renal function in patients with STEMI complicated by heart failure and/or severely impaired left ventricular systolic function (EF <40%) is well known. It has been clearly established that coinciding renal function impairment additionally increases the risk mortality and nonfatal adverse events during short- and long-
term follow-up, which is considered to be linked to the development of cardiorenal syndrome (5, 9, 10, 13). The prognostic impact of RD at admission on long-term overall mortality in patients with severely impaired, moderately impaired and preserved left ventricular systolic function following STEMI.

Methods

Study population, data collection and definitions

In the present study, data from the prospective Clinical Center of Serbia STEMI Register, for a subgroup of 2,436 consecutive patients, who were hospitalized between February 2006 and October 2010, were used. The purpose of the prospective Clinical Center of Serbia STEMI Register has been published elsewhere (16). In brief, the objective of the register is to gather complete and representative data on the management and short- and long-term outcomes of patients with STEMI who have undergone primary PCI at the Center. The study protocol was approved by the Local Research Ethics Committee. All consecutive patients with STEMI, aged >18 years, who had been admitted to the Coronary Care Unit after undergoing pPCI at the Center, were included in the Register. For this study, patients with cardiogenic shock at admission and those on haemodialysis were excluded. Coronary angiography was performed via the femoral approach. Aspirin, 300 mg, and clopidogrel, 600 mg, were administered to all eligible patients before pPCI. Selected patients, with visible intracoronary thrombi, were also given the glicoprotein (GP) IIb/IIIa receptor inhibitor tirofiban during pPCI. Flow grades were assessed according to Thrombolysis in Myocardial Infarction (TIMI) criteria. After pPCI, patients were treated according to current guidelines.

Demographic, baseline clinical, angiographic and procedural data were collected and analyzed. Baseline RD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² at admission. The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation.

\[
\text{GFR (mL/min/1.73 m²) = 175 x (S_GFR)^{-1.154} x (\text{Age})^{-0.203} x (0.742 if female)}
\]

Echocardiographic examination was performed within the first 3 days following pPCI. The left ventricular EF was assessed according to the biplane Simpson method, in classical two- and four-chamber apical projections. According to EF, patients were divided into three groups: preserved left ventricular systolic function (EF >50%), moderately impaired left ventricular systolic function (EF=40%-50%) and severely impaired left ventricular systolic function (EF <40%).

Patients were followed-up at 6 years after enrollment. Follow-up data were obtained by scheduled telephone interviews and out-patient visits.

Statistical analysis

Continuous variables were expressed as the median (med), with the interquartile range (IQR) between the 25th and 75th quartiles, whereas categorical variables were expressed as frequency and percentage. Analysis for normality of data (continuous variables) was performed using the Kolmogorov Smirnov test. Baseline differences between groups were analyzed using the Mann-Whitney U test, for continuous variables and the Pearson X² test, for categorical variables. The Kaplan-Meier method was used for constructing probability curves for 6-year survival whereas the difference between the groups was tested with the Log Rank test. Multiple logistic regression analysis was used for identifying independent predictors for RD. Multiple cox analysis (backward method, with p<0.10 for entrance into the model) was used for identifying independent risk factors for the occurrence of 6-year all-cause mortality. SPSS statistical software, version 19.0, was applied (SPSS Inc, Chicago, IL, USA).

Results

Out of a total of 2,436 patients, 1,773 (72.8%) were men and 663 (27.2%) were women. The average age of the examined patients was 57 (50-63) years. Preserved, moderately impaired and severely impaired left ventricular systolic function was registered in 741 (30.5%), 1,367 (56.1%) and 328 (13.4%) patients, respectively. RD at admission was registered in 472 (19.3%) patients, whereas the mean eGFR value was 88.5 (67.7, 108.8) ml/min/1.73 m²; 428 (17.6%) patients had eGFR 30-60 ml/min/1.73 m² and 44 (1.8%) patients had eGFR 15-30 ml/min/1.73 m². RD was registered in 105 (14.2%) patients with preserved left ventricular systolic function, in 247 (18.1%) patients with moderately impaired left ventricular systolic function and in 120 (36.5%) patients with severely impaired left ventricular systolic function. Demographic characteristics, risk factors, previous cardiovascular diseases or procedures, characteristics on admission, as well as angiographic and procedural characteristics in relation to EF and the presence of RD at admission are shown in Table 1.

After adjustment for variables defined as predictors in the univariate analysis (age, female gender, previous infarction, diabetes, hypertension, heart failure at admission, anemia at admission and three-vessel disease) we found that independent predictors for RD regardless of EF category were as follows: age (HR 1.20, 95% CI 1.18-1.30; p<0.001), previous infarction (HR 1.38, 95% CI 1.25-2.57; p=0.018), diabetes (HR 1.29, 95% CI 1.10-2.68; p=0.045), hypertension (HR 1.38, 95% CI 1.28-1.68; p=0.050),
heart failure at admission (HR 1.54, 95% CI 1.25-2.28; p=0.027) and anemia (hemoglobin level <130 g/L in males and <120 g/L in females) at admission (HR 1.24, 95% CI 1.12-1.57; p=0.028).

Therapy at discharge is shown in Table 2.

Over a 6-year follow-up, there were 196 (8.3%) deaths overall. Regardless of the presence of RD, 6-year mortality rates in patients with preserved, moderately impaired and severely impaired left ventricular systolic function were 2.7%, 5.2% and
The present study differs from other studies analyzing the prognostic impact of RD upon STEMI published to date, because it separately identifies and analyzes the subgroup of patients with EF=40%-50%. It is a known fact that mortality upon STEMI rapidly increases in patients with EF <40%, whereas patients with EF >50% have a good prognosis in the short-term and long-term follow-up (8). Therefore, prognostically speaking, there is a “gap” for a large group of patients whose EF is between 40 and 50 percent. These patients were, in earlier studies, commonly attached to the patient group with preserved systolic function (17, 18). Identifying the group of patients with EF=40%-50% as a separate group is something that can only be seen in recent studies dealing with heart failure. Clinical characteristics and prognosis of patients with EF=40%-50% are most commonly somewhere in between that with EF >50% and those with EF <40% (8, 12, 15, 17), this has also been observed in this present study.

With respect to pathophysiology, the EF value of 40%-50% means that there is a primarily moderate systolic dysfunction of the left ventricle, with a lesser impairment of diastolic function (14, 18). Because moderately impaired systolic function is considered to be the initial step toward further deterioration of the said function, simultaneous existence of RD represents the first step toward the development of cardiorenal syndrome (11, 17). This particular conclusion may be the explanation for similar prognostic impact of RD during long-term monitoring of patients in the present study with EF 40%-50% and EF <40%.

In literature, the prognostic impact of renal function in relation to the EF value is most frequently analyzed in patients with heart failure. Accordingly, in a study by Löfman et al. (15), which included patients with heart failure with varying etiology, the prognostic impact of chronic kidney disease (CKD) in patients with preserved EF >50%, mid-range EF (40%-50%) and reduced EF (<40%) was analyzed. In this study, in the absence of CKD, patients with preserved EF had a higher short-term and long-term mortality than those with moderately and severely impaired left ventricular systolic function. The total percentage of patients with RD at admission is similar or somewhat smaller than data found in literature (2, 7), whereas the largest percentage of patients with RD at admission was registered in the group with EF <40%.

**Discussion**

Results of this study have shown that the prognostic impact of RD at admission on the long-term survival of patients with STEMI differs depending on left ventricular systolic function, i.e. in patients with preserved left ventricular systolic function, RD had no prognostic impact, however, in those with moderately or severely impaired left ventricular systolic function it had a strong independent prognostic impact. The prognostic impact of RD was similar, albeit somewhat stronger, in patients with moderately impaired left ventricular systolic function, in whom the presence of RD increased 6-year mortality by three times, whereas in patients with moderately impaired left ventricular systolic function the existence of RD increased the 6-year mortality by approximately 2.5 times. Results of this present study have also confirmed that upon STEMI, in the pPCI era larger percentage of patients have preserved or moderately impaired left ventricular systolic function. The total percentage of patients with RD in literature (2, 7), whereas the largest percentage of patients with RD at admission was registered in the group with EF <40%.

In literature, the prognostic impact of renal function in relation to the EF value is most frequently analyzed in patients with heart failure. Accordingly, in a study by Löfman et al. (15), which included patients with heart failure with varying etiology, the prognostic impact of chronic kidney disease (CKD) in patients with preserved EF >50%, mid-range EF (40%-50%) and reduced EF (<40%) was analyzed. In this study, in the absence of CKD, patients with preserved EF had a higher short-term and long-term mortality than those with moderately and severely impaired left ventricular systolic function. The total percentage of patients with RD at admission is similar or somewhat smaller than data found in literature (2, 7), whereas the largest percentage of patients with RD at admission was registered in the group with EF <40%.

The present study differs from other studies analyzing the prognostic impact of RD upon STEMI published to date, because it separately identifies and analyzes the subgroup of patients with EF=40%-50%. It is a known fact that mortality upon STEMI rapidly increases in patients with EF <40%, whereas patients with EF >50% have a good prognosis in the short-term and long-term follow-up (8). Therefore, prognostically speaking, there is a “gap” for a large group of patients whose EF is between 40 and 50 percent. These patients were, in earlier studies, commonly attached to the patient group with preserved systolic function (17, 18). Identifying the group of patients with EF=40%-50% as a separate group is something that can only be seen in recent studies dealing with heart failure. Clinical characteristics and prognosis of patients with EF=40%-50% are most commonly somewhere in between that with EF >50% and those with EF <40% (8, 12, 15, 17), this has also been observed in this present study.

With respect to pathophysiology, the EF value of 40%-50% means that there is a primarily moderate systolic dysfunction of the left ventricle, with a lesser impairment of diastolic function (14, 18). Because moderately impaired systolic function is considered to be the initial step toward further deterioration of the said function, simultaneous existence of RD represents the first step toward the development of cardiorenal syndrome (11, 17). This particular conclusion may be the explanation for similar prognostic impact of RD during long-term monitoring of patients in the present study with EF 40%-50% and EF <40%.
left ventricular systolic function. However, CKD was an independent predictor of 5-year mortality in all three groups of patients, with a similar prognostic impact in patients with EF=40-50% and EF<40% (15). In addition it was found that CKD was more frequent in patients with preserved EF, but was prognostically least significant, in the sense of a lesser impact on long-term mortality, than in patients with EF <40% and EF=40%-50%. A larger percentage of patients with CKD in the group with EF >50% was attributed by the authors to the fact that the group with EF >50% was older and with a higher percentage of hypertension and diabetes (15). Overall it can be said that data in literature regarding the prevalence and prognostic impact of CKD in pa-

| Table 4. Association between RD and 6-year mortality according to EF (Univariate analysis and Multiple Cox analysis) |
|---|---|---|---|
| **EF >50%** | Univariate analysis | Multiple Cox analysis |
| HR (95% CI) | P-value | HR (95% CI) | P-value |
| RD | 1.61 (0.55-2.90) | 0.367 | 0.59 (0.14-1.41) | 0.461 |
| eGFR 30-60 mL/min/1.73 m² | 1.08 (0.89-1.26) | 0.898 | 0.98 (0.89-1.01) | 0.887 |
| eGFR 15-30 mL/min/1.73 m² | 0.98 (0.89-1.01) | 0.999 | 0.87 (0.85-1.02) | 0.998 |
| Age (years) | 1.05 (1.01-1.09) | 0.027 | 1.05 (1.01-1.08) | 0.025 |
| Diabetes | 2.23 (1.05-5.95) | 0.050 |
| Hypertension | 2.35 (1.05-7.11) | 0.042 |
| Heart failure at admission | 6.29 (1.31-10.17) | <0.001 | 4.79 (1.83-10.12) | 0.038 |
| Peak CK | 1.01 (1.02-1.04) | 0.010 |
| 3-vessel disease | 1.95 (1.10-4.99) | 0.040 |
| **EF 40-50%** | Univariate analysis | Multiple Cox analysis |
| HR (95% CI) | P-value | HR (95% CI) | P-value |
| RD | 2.94 (1.97-1.39) | <0.001 | 2.52 (1.54-3.78) | 0.001 |
| eGFR 30-60 mL/min/1.73 m² | 3.04 (2.34-10.94) | <0.001 | 2.22 (1.52-5.35) | 0.001 |
| eGFR 15-30 mL/min/1.73 m² | 4.32 (3.95-31.5) | <0.001 | 3.64 (1.35-7.57) | <0.001 |
| Age (years) | 1.09 (1.06-1.11) | <0.001 | 1.04 (1.01-1.07) | 0.002 |
| Previous MI | 1.45 (1.10-2.25) | 0.050 |
| Diabetes | 2.68 (1.60-4.40) | 0.001 |
| Hypertension | 1.78 (1.03-2.78) | 0.048 |
| Heart failure at admission | 5.10 (3.04-8.59) | <0.001 | 3.20 (1.93-5.33) | <0.001 |
| Systolic blood pressure at admission (mm Hg) | 1.01 (0.98-1.02) | 0.871 |
| Heart rate admission /min | 1.02 (1.01-1.03) | 0.060 |
| Peak CK | 1.02 (1.01-1.04) | 0.030 |
| 3-vessel disease | 2.14 (1.31-3.50) | 0.002 |
| Post-procedural flow TIMI<3 | 3.45 (1.56-5.64) | 0.001 | 1.90 (0.96-3.05) | 0.097 |
| **EF <40%** | Univariate analysis | Multiple Cox analysis |
| HR (95% CI) | P-value | HR (95% CI) | P-value |
| RD | 6.76 (4.21-10.89) | <0.001 | 2.84 (1.68-5.34) | <0.001 |
| eGFR 30-60 mL/min/1.73 m² | 3.34 (2.15-7.18) | <0.001 | 2.62 (1.95-3.59) | <0.001 |
| eGFR 15-30 mL/min/1.73 m² | 13.01 (3.25-20.9) | <0.001 | 3.72 (2.80-10.14) | <0.001 |
| Age (years) | 1.01 (1.01-1.07) | 0.001 |
| Previous MI | 1.44 (0.92-2.51) | 0.042 |
| Diabetes | 1.39 (1.27-2.35) | 0.037 |
| Hypertension | 1.25 (1.15-2.01) | 0.050 |
| Heart failure at admission | 3.46 (2.11-6.78) | <0.001 | 1.93 (1.29-2.91) |
| Systolic blood pressure at admission (mm Hg) | 1.01 (0.99-1.03) | 0.001 |
| Heart rate at admission/min | 1.01 (1.09-1.03) | 0.002 |
| Peak CK | 1.02 (1.01-1.04) | 0.020 |
| 3-vessel disease | 2.14 (1.32-3.46) | 0.002 |
| Post-procedural flow TIMI<3 | 5.34 (2.87-9.95) | <0.001 | 2.07 (1.36-3.15) | <0.001 |

EF: ejection fraction; MI: myocardial infarction; RD: renal dysfunction (eGFR<60 mL/min/1.73 m²); eGFR: estimated glomerular filtration rate; CK: creatinine kinase
Patients with EF >50% is inconsistent (8, 12, 15). Thus, in a study analyzing the prognostic impact of left ventricular systolic function in patients with STEMI, no significant difference was found in the prevalence of baseline CKD amongst patients with EF >50%, EF=40-50% and EF <40% (8). In the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) it was demonstrated that among patients with EF >50%, there was a smaller percentage of those with CKD and a lesser impact of CKD on mortality than in patients with EF=40%-50% and EF <40 (11).

A study by Moukarbel et al. (9) analyzed the prognostic impact of CKD in high-risk patients with myocardial infarction (EF <40%). The total 23-month mortality was approximately 18%; the reduction in renal function led to an increase in mortality in these patients; whereas CKD was an independent predictor of mortality. This study did not analyze the prognostic impact of CKD in patients with EF >40% (9). Similarly, during the average follow-up of approximately 24.7 months results of a study by Anavekar et al. show CKD to be an independent predictor of mortality and other adverse events in patients who had suffered myocardial infarction complicated by heart failure, systolic dysfunction of the left ventricle, or both, with the risk of occurrence of adverse events increasing with a decrease in eGFR (5). In this study, as well as in the present study, it has been demonstrated that the greatest risk of mortality in patients with CKD is in the first 30-180 days upon infarction. The negative prognostic impact of CKD remains unchanged independently of therapy with ACE inhibitors, i.e., sartans (5).

There are multiple pathophysiological mechanisms that can account for the negative prognostic impact of impaired renal function in patients with acute myocardial infarction and/or heart failure. Firstly, the existence of comorbidities that may be risk factors for coronary disease and RD (hypertension, diabetes, as well as older age). Secondly, complications of advanced RD, such as hypercalcemia, anemia and disorders of the blood coagulation system, increase the risk of atherosclerotic disease progression, when they co-occur with traditional risk factors. Hypervolemia, as a part of advanced RD, may exacerbate symptoms of heart failure, independent of EF values (7). Sympathetic and numerous neurohormonal mechanisms, inflammation, free radicals, and other factors can significantly influence the development and progression of cardiorenal syndrome (17, 19, 20). Consequently, it has often been noted in literature that patients with RD less frequently receive therapy (beta blockers, ACE inhibitors, sartans, aldosterone antagonists, etc.) that improve the prognosis upon STEMI, particularly in patients with EF <40% (7). There are data suggesting that treatments that improve clinical outcome in patients with EF <40% also seem to benefit those with EF 40%-50% (14). Considering that there are studies indicating a strong negative prognostic impact of RD in patients with EF=40%-50%, as well as in patients with simultaneous occurrence of RD and mild to moderate left ventricular systolic function impairment, independent of the cause, it should be insisted that therapy with ACE inhibitors (or sartans), beta blockers and aldosterone antagonists should be introduced as soon as possible (14, 15).

**Study limitations**

This is an observational prospective study - however it has included consecutive patients limiting possible selection bias. We did not use other measures for determining systolic function such as myocardial deformation imaging. However, many cor-
nerstone clinical trials so far have used EF to stratify patients and have demonstrated its benefit in determining the outcome benefit of therapy (8, 9, 11, 17). There are no data on follow-up echocardiographic examinations to show whether there has been a certain degree of recovery or deterioration in the myocardial contractility. Renal (dys)function at admission can be an indicator of a chronic state or acute deterioration. Renal function was not evaluated during follow-up, however, during the 6-year follow-up, development of terminal renal insufficiency did not occur and none of the patients was started on hemodialysis. Renal function was assessed with the use of the MDRD equation which also has its limitations (19, 21). We did not measure the rates of urinary albumin or protein excretion, factors that may influence the independent impact of RD on cardiovascular outcomes. Patients were treated with clopidogrel; there were no patients treated with more recently developed antithrombotic drugs (ticagrelor was not available for routine administration to patients at the time of their entry into the register); this could have influenced the prognosis of the patients, i.e., reduced the occurrence of cardiovascular mortality, as there are data indicating that the efficacy of clopidogrel is decreased in patients with RD (2). The study was not designed to evaluate whether changing pharmacological treatment would have impact on the long-term outcome in analyzed patients.

Conclusion

Patients with STEMI and RD at admission have higher 6-year mortality, independently of EF values, than those with preserved renal function. Approximately half of the patients in the primary PCI era have moderately impaired left ventricular systolic function upon STEMI. RD at admission was an independent predictor of 6-year mortality only in patients with EF=40%-50% and EF <40%. The negative prognostic impact of RD at admission was similar in both groups of patients, although it as somewhat stronger in those with EF <40%.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – L.S.; Design – L.S.; Supervision – L.S., I.M.; Fundings – None; Materials – S.S.; Data collection &/or processing – M.A., G.K., R.L.; Analysis &/or interpretation – L.S.; Literature search – L.S.; Writing – L.S., I.M.; Critical review – L.S., I.M.

References

1. Jose P, Skali H, Anavekar N, Tomson C, Krumholz HM, Rouleau JL, et al. Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction. J Am Soc Nephrol 2006; 17: 2886-91.
2. Hawranek M, Gierlhotka M, Gąsior M, Hudzik B, Desperak P, Cisłak A, et al. Renal function on admission affects both treatment strategy and long-term outcomes of patients with myocardial infarction (from Polish Registry of Acute Coronary Syndromes). Kardiol Pol 2017; 75: 332-43.
3. Choi JS, Kim MJ, Kang YU, Kim CS, Bae EH, Ma SK, et al. Association of age and CKD with prognosis of myocardial infarction. Clin J Am Soc Nephrol 2013; 8: 939-44.
4. Savic L, Mrdovic I, Asanin M, Stankovic, Krljanac G, Lasica R. Gender differences in the prognostic impact of chronic kidney disease in patients with left ventricular systolic dysfunction following ST elevation myocardial infarction treated with primary percutaneous coronary intervention. Hellenic J Cardiol 2016; 57: 109-15.
5. Anavekar NS, McMurray JJ, Velasquez EJ, Solomon SD, Kober L, Rouleau JL, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2004; 351: 1285-95.
6. Kotwal S, Ranasinghe I, Brieger D, Clayton PA, Cass A, Gallagher M. The influence of chronic kidney disease and age on revascularization rates and outcomes in acute myocardial infarction – a cohort study. Eur Heart J Acute Cardiovasc Care 2017; 6: 291-8.
7. Mok Y, Ballew SH, Matsushita K. Prognostic value of chronic kidney disease measures in patients with cardiac disease. Circ J 2017; 81: 1075-84.
8. Ng VG, Lansky AJ, Meller S, Witzenbichler B, Guagliumi G, Peruga JZ, et al. The prognostic importance of left ventricular function in patients with ST-segment elevation myocardial infarction: the HORIZONS-AMI trial. Eur Heart J Acute Cardiovasc Care 2014; 3: 67-77.
9. Moukarbel GV, Yu ZF, Dickstein K, Hou YR, Witten JT, McMurray JJ, et al. The impact of kidney function on outcomes following high risk myocardial infarction: findings from 27 610 patients. Eur J Heart Fail 2014; 16: 289-99.
10. Savic L, Mrdovic I, Perunicic J, Asanin M, Lasica R, Marinkovic J, et al. Impact of the combined left ventricular systolic and renal dysfunction on one-year outcomes after primary percutaneous coronary intervention. J Interven Cardiol 2012; 25: 132-9.
11. Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Eur Heart J 2012; 33: 1750-7.
12. Toma M, Ezekowitz JA, Bakal JA, O’Connor CM, Hernandez AF, Sardar MR, et al. The relationship between left ventricular ejection fraction and mortality in patients with acute heart failure: insight from the ASCEND-HF Trial. Eur J Heart Fail 2014; 16: 334-41.
13. Marenzi G, Moltrasio M, Assanelli E, Lauri G, Marana I, Grazi M, et al. Impact of cardiac and renal dysfunction on inhospital morbidity and mortality of patients with acute myocardial infarction undergoing primary angioplasty. Am Heart J 2007; 153: 755-62.
14. Nauta JF, Hummel YM, van Melle JP, van der Meer P, Lam CSP, Pionkowski P, et al. What have we learned about heart failure with mid-range ejection fraction one year after its introduction? Eur J Heart Fail 2017; 19: 1569-73.
15. Löfman I, Szummer K, Dahlström U, Jernberg T, Lund LH. Association with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. Eur J Heart Fail 2017; 19: 1606-14.
16. Mrdovic I, Savic L, Lasica R, Krljanac G, Asanin M, Brdar N, et al. Efficacy and safety of tiotrofil-supported primary percutaneous coronary intervention in patients pretreated with 600 mg clopidogrel: results of propensity analysis using the Clinical Center of Ser-
bia STEMI Register. Eur Heart J Acute Cardiovas Care 2014; 3: 56-66.
17. Lam CS, Solomon SD. The middle child in heart failure: heart failure with mid-range ejection fraction (40-50%). Eur J Heart Fail 2014; 16: 1049-55.
18. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al.; ESC Scientific Document Group. 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 J Heart Fail 2016; 18: 2129-200.
19. McAlister FA, Ezekowitz J, Tarantino L, Squire I, Komajda M, Bayes-Genis A, et al.; Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) Investigators. Renal dysfunction in patients with heart failure with preserved versus reduced ejection fraction: impact of the new Chronic Kidney Disease-Epidemiology Collaboration Group formula. Circ Heart Fail 2012; 5: 309-14.
20. Ter Maaten JM, Damman K, Verhaar MC, Paulus WJ, Duncker DJ, Cheng C, et al. Connecting heart failure with preserved ejection fraction and renal dysfunction: the role of endothelial dysfunction and inflammation. Eur J Heart Fail 2016; 18: 588-98.
21. Ekmekci A, Uluganyan M, Gungor B, Tufan F, Cekirdekci EL, Ozcan KS, et al. Comparison of Cockroft-Gault and Modification of Diet in Renal Disease Formulas as predictors of cardiovascular outcomes in patients with myocardial infarction treated with primary percutaneous coronary intervention. Angiology 2014; 65: 838-43.