International Journal of Cardiology 266 (2018) 180–186

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Effect of renin-angiotensin system blockade in patients with severe renal insufficiency and heart failure

Se Yong Jang [a], Shung Chull Chae [a,*], Myung Hwan Bae [a], Jang Hoon Lee [a], Dong Heon Yang [a], Hun Sik Park [a], Yongkeun Cho [a], Hyun-Jai Cho [b], Hae-Young Lee [b], Byung-Hee Oh [b], Jin-Oh Choi [c], Eun-Seok Jeon [c], Min-Seok Kim [d], Sang Eun Lee [d], Jae-Joong Kim [d], Kyung-Kuk Hwang [e], Myeong-Chan Cho [e], Sang Hong Baek [f], Seok-Min Kang [g], Dong-Ju Choi [h], Byung-Su Yoo [i], Youngkeun Ahn [j], Kye Hun Kim [j], Hyun-Young Park [k]

[a] Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea
[b] Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea
[c] Department of Internal Medicine, Sungkyunkwan University College of Medicine, Seoul, Republic of Korea
[d] Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[e] Department of Internal Medicine, Chungbuk National University College of Medicine, Cheongju, Republic of Korea
[f] Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[g] Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
[h] Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea
[i] Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea
[j] Department of Internal Medicine, Heart Research Center of Chonnam National University, Gwangju, Republic of Korea
[k] Division of Cardiovascular and Rare Diseases, National Institute of Health, Osong, Republic of Korea

ARTICLE INFO

Article history:
Received 26 September 2017
Received in revised form 12 February 2018
Accepted 5 March 2018

Keywords:
Angiotensin-converting enzyme inhibitors
Angiotensin receptor blocker
Renal insufficiency
Heart failure

ABSTRACT

Background: Renin-angiotensin system blockade (RAB) is the cornerstone in the management of patients with heart failure. However, the benefit of RAB in patients with accompanying severe renal impairment is not clear. We aimed to examine the effect of RAB and the differential effect of RAB depending on renal replacement (RR) in patients with severe renal insufficiency and acute heart failure.

Methods and Results: Among 5625 patients from the Korean Acute Heart Failure registry, 673 in-hospital survivors (70.9 ± 12.8 years, 376 men) who had left ventricular ejection fraction < 40% and estimated glomerular filtration rate < 30 mL/min/1.73 m^2 during hospitalization were analyzed. The inverse probability of treatment weighting (IPTW)-adjusted survival analysis was used to compare the composite of all-cause mortality and rehospitalization between patients with and without pre-discharge RAB. A total of 334 (49.6%) adverse events were observed during the 1-year follow-up. The IPTW-adjusted Kaplan-Meier survival analysis showed that the 1-year event rate was 48.7% and 53.8% for patients with RAB and those without, respectively (log rank p = 0.048). RAB was significantly related to better prognosis in patients receiving RR therapy (hazard ratio [HR] = 0.436 [0.269–0.706], p = 0.001), but not in patients not receiving RR therapy (HR 0.956 [0.731–1.250], p = 0.742) in a weighted cohort (p for interaction = 0.005).

Conclusions: Early RAB treatment in patients with heart failure and severe renal insufficiency was related to better prognosis. The benefit of RAB was particularly prominent in patients receiving RR therapy.

1. Introduction

Renin-angiotensin system blockade (RAB) with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) is the cornerstone in treating patients with heart failure with reduced ejection fraction (HFrEF). Solid evidence supports the effect of RAB in reducing morbidity and mortality of patients with HFrEF [1–7]. However, the study populations in randomized trials testing the effect of RAB on patients with heart failure have been limited to patients with relatively preserved renal function. Therefore, there is a scarcity of data showing the benefit of RAB in patients with HFrEF and severe renal insufficiency. Accordingly, current guidelines for heart failure clearly state that there is insufficient evidence to use RAB in patients with HFrEF and renal insufficiency and that caution is needed to treat such patients with RAB [8,9]. Despite the reno-protective effect of RAB, the use of RAB in patients with impaired renal function alone is controversial. Some data showed significantly reduced left ventricular mass, cardiovascular event, and mortality rate in patients with severe

* Corresponding author at: Department of Internal Medicine, School of Medicine, Kyungpook National University, 680 Gukchaebosang-ro, Daegu 41944, Republic of Korea.
E-mail address: scchae@knu.ac.kr (S.C. Chae).

https://doi.org/10.1016/j.ijcard.2018.03.016
0167-5273/

renal insufficiency by using RAB [10–12], whereas others did not demonstrate favorable results [13–15]. As the effect of RAB on patients with HFrEF is so evident, the rationale for using RAB in patients with HFrEF and concomitant renal insufficiency should be investigated. In patients with impaired renal function, adverse effects such as hyperkalemia or worsening renal function greatly limit the use of RAB. Patients on renal replacement (RR) therapy may be more relieved of those side effects; thus, the presence or absence of RR may affect the use of RAB and the subsequent prognosis of patients having both HFrEF and severe renal insufficiency. To date, few studies have assessed the clinical effect of RR on the RAB treatment in patients with heart failure and impaired renal function. The present study was performed to investigate 1) the effect of early RAB treatment after acute decompensated heart failure in patients with HFrEF and concomitant severe renal insufficiency and 2) the differential effect of RAB on the prognosis of patients on and not receiving RR therapy.

2. Methods

2.1. Study design

The present study included patients from the Korean Acute Heart Failure (KorAHF) registry. The KorAHF registry is a prospective multicenter cohort study based on 10 tertiary university hospitals throughout the Republic of Korea, which enrolled 5625 patients hospitalized for acute heart failure between March 2011 and February 2014 [16]. Information regarding the design, purpose, and population of the study is provided in the clinical trial registration (ClinicalTrial.gov NCT01389843). Baseline characteristics and outcome of the KorAHF registry were previously published [16,17]. The analysis was retrospectively performed with data from the KorAHF registry.

2.2. Patient selection

Among 5625 patients from the registry, patients who had LV ejection fraction (LVEF) < 40% and severe renal insufficiency were included. Those who died or underwent heart transplantation during the index hospitalization period were excluded. Severe renal insufficiency was defined as an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 at any time during the index hospitalization. eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation [18]. The main comparison was between patients who started RAB and those who did not, before discharge during the index hospitalization period. Subgroup analysis was performed between the patients on RR and those not using RR therapy during the index hospitalization period. Patients on RR were defined as those who underwent dialysis at least once during the index admission period. RR included all types of hemodialysis and peritoneal dialysis.

2.3. Follow-up and outcomes

The composite event of all-cause mortality and rehospitalization for heart failure in 1 year was assessed for the prognosis of patients. The association between the use of RAB and all-cause mortality alone was also analyzed. The outcome data were prospectively collected from each hospital. Data of patients who were lost to follow-up were ascertained by telephone contact and national death records. Follow-up data of laboratory test and echocardiography were assessed to evaluate the difference between the patients with and without RAB.

2.4. Statistics

The baseline characteristics were summarized according to the use of RAB. Continuous variables were expressed as the mean ± standard deviation. Categorical variables were presented as frequencies and proportions. To adjust for the selection bias between the groups with and without RAB, the baseline differences between the two groups were approached by the standardized difference [19]. A standardized difference ≥ 10% indicated significant imbalance for a given variable between the groups. The observed differences were controlled with the inverse probability of treatment weighting (IPTW)-adjusted analysis [20]. Missing values were handled by multivariate imputation before IPTW adjustment [21]. The balance between the variables in the weighted population was also assessed by using a standardized difference approach. IPTW-adjusted Kaplan-Meier survival curve analyses were performed to examine the effect of RAB, and IPTW-adjusted log-rank test was used to compare the prognosis of the weighted population [22].

To examine whether there is a difference in RAB effect on the prognosis between the groups on RR and those not on RR therapy, the interaction between RAB and RR therapy was assessed by the Cox proportional hazard model. The interaction was tested in a crude population model, weighted population model, and adjusted model, which included significant confounders from univariate analyses based on unweighted population. The hazard ratio (HR) and 95% confidence interval (CI) estimating the effect of RAB were derived from each model using the Cox regression analyses.

All statistical analyses were performed with R for Windows (version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value < 0.05 was considered as statistically significant.

3. Results

3.1. Baseline characteristics

Among the patients from the KorAHF registry, 2954 were in-hospital survivors with reduced LVEF after excluding patients who died or underwent heart transplantation during hospitalization. Among these, 673 patients with severe renal insufficiency were finally included in the analysis. The numbers of patients with pre-discharge RAB were 423 among 673 patients. Among patients with RAB, 37.1% and 63.6% were taking ACEI and ARB, respectively. Data on types of drugs used can be found in Supplementary Fig. 1. The median hospital stay was 13 days (interquartile range [IQR], 8–22 days). At planned 1-year follow-up, 76.6% of the patients with RAB at discharge continued RAB, and 34.4% of those without RAB at discharge also were taking RAB (Supplementary Fig. 2). The median follow-up was 291 days (IQR, 56–360 days). During the 1-year follow-up, 334 (49.6%) composite events (death/rehospitalization for heart failure) and 216 (32.1%) deaths were recorded. The baseline characteristics are presented in Table 1. Estimated GFRs of the patients at admission and discharge are shown in Supplementary Fig. 3.

3.2. Effect of RAB in the unweighted and weighted population

In patients with severe renal insufficiency, the composite event rates of all-cause mortality and rehospitalization for heart failure were 46.8% and 54.4% for the groups with and without RAB, respectively. The survival difference between the two groups was significant in the Kaplan-Meier curve analysis (log rank p = 0.012) (Fig. 1). With respect to mortality alone, the group with RAB also showed significantly better outcome than the group without RAB (event rate, 27.7% vs. 39.6%; log rank p < 0.001). Although baseline LVEF was not significantly different between the two groups, LVEF tended to be higher in patients with RAB at 1 year (37.9 ± 14.5% vs. 35.0 ± 13.5%, p = 0.064, Supplementary Table 2). Distributions of baseline characteristics before and after IPTW adjustment are presented in Table 1. After IPTW adjustment, all standardized differences for the given variables except body mass index (BMI) were ≤10%, indicating that the distribution of baseline characteristics, in-hospital treatment, and medication at discharge was similar between the groups with and without RAB. The mean follow-up of the weighted population was 216 ± 149 days. The IPWT-adjusted Kaplan-Meier survival analysis (Figs 1) revealed that the group with RAB showed significantly better prognosis than the group without RAB (event rate, 48.7% vs. 53.8%; log rank p = 0.048). In the analysis of all-cause mortality alone, patients with RAB also presented with a better prognosis than those without RAB (event rate, 28.5% vs. 38.0%; log rank p = 0.005).

To investigate the effect of RAB in patients with chronic status of renal insufficiency, a subgroup analysis was done with the patients with eGFR < 30 mL/min/1.73 m^2 at discharge (n = 401). The Kaplan-Meier survival analysis revealed that the patients with RAB were associated with a better prognosis than those without RAB in terms of composite outcome (45.5% vs. 55.4%; log rank p = 0.019) and all-cause mortality (29.3% vs. 41.7%; log rank p = 0.006) (Supplementary Fig. 6), which was consistent with overall population analysis.

3.3. Effect of RAB depending on RR therapy

A total of 172 (25.6%) patients received RR during the index hospitalization. The baseline characteristics and differences between the groups with and without RR are presented in Supplementary Table 1. To examine the effect of RAB depending on RR therapy, survival analysis

Table 1
Baseline characteristics of the patients before and after IPTW-weighting.

	Unweighted population n, (%) or mean ± standard deviation					Weighted population % or mean ± standard deviation			
Group	Missing values (n)	No RAB (n = 250)	RAB (n = 423)	p-Value	SD (%)	No RAB	RAB	p-Value	SD (%)
Demographic data									
Age	0	70.6 ± 12.4	71.2 ± 13.0	0.501	5.3	71.1 ± 12.1	70.9 ± 13.2	0.879	1.2
Male	0	147 (58.8)	229 (54.1)	0.240	9.4	55.4	55.7	0.945	0.6
Body mass index (kg/m^2)	6			0.073	18.8			0.349	12.4
<23		145 (59.2)	228 (54.0)			54.1	56.7		
23–25		52 (21.2)	78 (18.5)			23.3	18.3		
≥25		48 (19.6)	116 (27.5)			22.6	24.9		
Past medical history									
Hypertension[a]	0	185 (74.0)	328 (77.5)	0.298	8.3	76.6	75.9	0.837	1.7
Diabetes[a]	0	148 (59.2)	248 (58.6)	0.884	1.2	58.7	58.6	0.976	0.2
Chronic lung disease	0	30 (12.0)	54 (12.8)	0.772	2.3	13.7	12.5	0.695	3.5
Cerebrovascular disease	0	47 (18.8)	79 (18.7)	0.968	0.3	19.4	18.9	0.894	1.1
Clinical data									
Admission via ED	0	199 (79.6)	350 (82.7)	0.310	8.0	81.3	81.4	0.982	0.2
NYHA class	0			0.505	9.4			0.973	2.0
II		22 (8.8)	41 (9.7)			9.6	9		
III		77 (30.8)	146 (34.5)			33.7	33.9		
IV		151 (60.4)	236 (55.8)			56.7	57.1		
Systolic blood pressure (mm Hg)	3	131.5 ± 31.2	135.4 ± 31.5	0.120	12.4	134.2 ± 32.8	133.7 ± 31.8	0.851	1.7
Heart rate (bpm)	3	95.0 ± 24.6	95.4 ± 24.9	0.802	2.0	94.6 ± 24.6	95.1 ± 25.0	0.792	2.2
LVEF (%)	0	27.4 ± 7.3	27.6 ± 7.2	0.789	2.1	27.7 ± 7.2	27.6 ± 7.3	0.865	1.4
Etiology of heart failure									
Ischemic disease	0	144 (57.6)	223 (52.7)	0.220	9.8	55.8	54.8	0.797	2.2
Cardiomyopathy	0	46 (18.4)	105 (24.8)	0.054	15.7	22.1	22.5	0.924	0.8
Valvular disease	0	19 (7.6)	30 (7.1)	0.807	1.9	7.5	7.4	0.950	0.5
Laboratory data									
Hemoglobin (g/dL)	0	11.4 ± 2.2	11.3 ± 2.1	0.639	3.8	11.3 ± 2.2	11.3 ± 2.2	0.888	1.2
Sodium (mEq/L)	0	137.0 ± 4.6	136.7 ± 4.9	0.402	6.6	136.7 ± 4.6	136.8 ± 4.8	0.839	1.7
Potassium (mEq/L)	0	4.7 ± 0.9	4.7 ± 0.8	0.786	2.2	4.7 ± 0.9	4.7 ± 0.8	0.925	0.8
eGFR (mL/min/1.73 m^2)	0	27.8 ± 19.7	27.5 ± 16.5	0.937	0.6	27.3 ± 18.9	27.6 ± 16.5	0.847	1.6
In-hospital treatment									
ICU care	0	154 (61.6)	236 (55.8)	0.141	11.8	58.0	57.9	0.994	0.1
IV vasodilators	0	107 (42.8)	189 (44.7)	0.635	3.8	43.9	44.0	0.993	0.1
IV inotropic agents	0	121 (48.4)	168 (39.7)	0.028	17.6	43.1	43.0	0.975	0.3
Transfusion	0	85 (34.0)	125 (29.6)	0.229	9.6	32.8	31.8	0.786	2.3
IABP	0	16 (6.4)	15 (3.5)	0.089	13.2	4.7	4.8	0.971	0.3
ECMO	0	9 (3.6)	13 (3.1)	0.711	2.9	3.9	3.5	0.818	2.0
ICD	0	7 (2.8)	9 (2.1)	0.581	4.3	2.5	2.4	0.897	1.1
CRT	0	2 (0.8)	6 (1.4)	0.475	5.9	0.8	1.1	0.681	3.3
Renal replacement therapy	0	68 (27.2)	104 (24.6)	0.453	6.0	25.2	25.2	0.984	0.2
Medication at discharge									
β-Blocker	0	119 (47.6)	250 (59.1)	0.004	23.2	56.3	55.2	0.787	2.2
MRA	0	67 (26.8)	146 (34.5)	0.038	16.8	32.9	31.9	0.819	2.0
Loop diuretics	0	164 (65.6)	303 (71.6)	0.102	13.0	69.7	69.8	0.980	0.2
Thiazide diuretics	0	10 (4.0)	28 (6.6)	0.156	11.7	6.7	5.8	0.675	4.0
Warfarin	0	56 (22.4)	97 (22.9)	0.874	1.3	22.3	22.8	0.885	1.2
Statin	0	114 (45.6)	194 (45.9)	0.947	0.5	46.0	45.8	0.968	0.3

CRT, cardiac resynchronization therapy; ECMO, extracorporeal membrane oxygenation; ED, emergency department; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; ICD, implantable cardioverter-defibrillator; ICU, intensive care unit; IV, intravenous; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RAB, renin-angiotensin blockade; SD, standardized difference.

[a] Including the newly diagnosed disease during the index admission.

was performed in subgroups of patients who received RR therapy and those who did not. Kaplan-Meier survival analyses of these subgroups in the unweighted population demonstrated that the survival gap between patients with and without RAB was more distinct in patients who received RR therapy (event rate, 32.7% vs. 61.8%; log rank $p < 0.001$) than in those who did not (event rate, 51.4% vs. 51.6%; log rank $p = 0.508$) (Fig. 2A). A similar trend was also observed in the analysis performed for mortality alone. A significant prognostic difference was observed between patients with and without RAB in the subgroup receiving RR therapy (event rate, 25.0% vs. 52.9%; log rank $p < 0.001$), whereas the difference was not significant in the subgroup that did not receive RR therapy (event rate, 28.6 vs. 34.6%; log rank $p = 0.105$) (Fig. 2B).

To estimate the effect of RAB depending on RR therapy, HR was calculated in the unweighted and IPTW-adjusted populations, which are described in Table 1. The adjusted HR was additionally obtained using the Cox regression analysis in the unweighted population. The adjustment was performed for age, sex, systolic blood pressure, New York Heart Association (NYHA) class, hemoglobin level, β-blocker use, and inotropic agent use, which were significantly associated with the composite outcome among the variables of baseline characteristics in the univariate analyses. Overall, in the models described above, the use of RAB was significantly associated with better prognosis in patients receiving RR, but not in patients without RR (Figs 3). There were significant interactions between the effect of RAB and RR in all models,

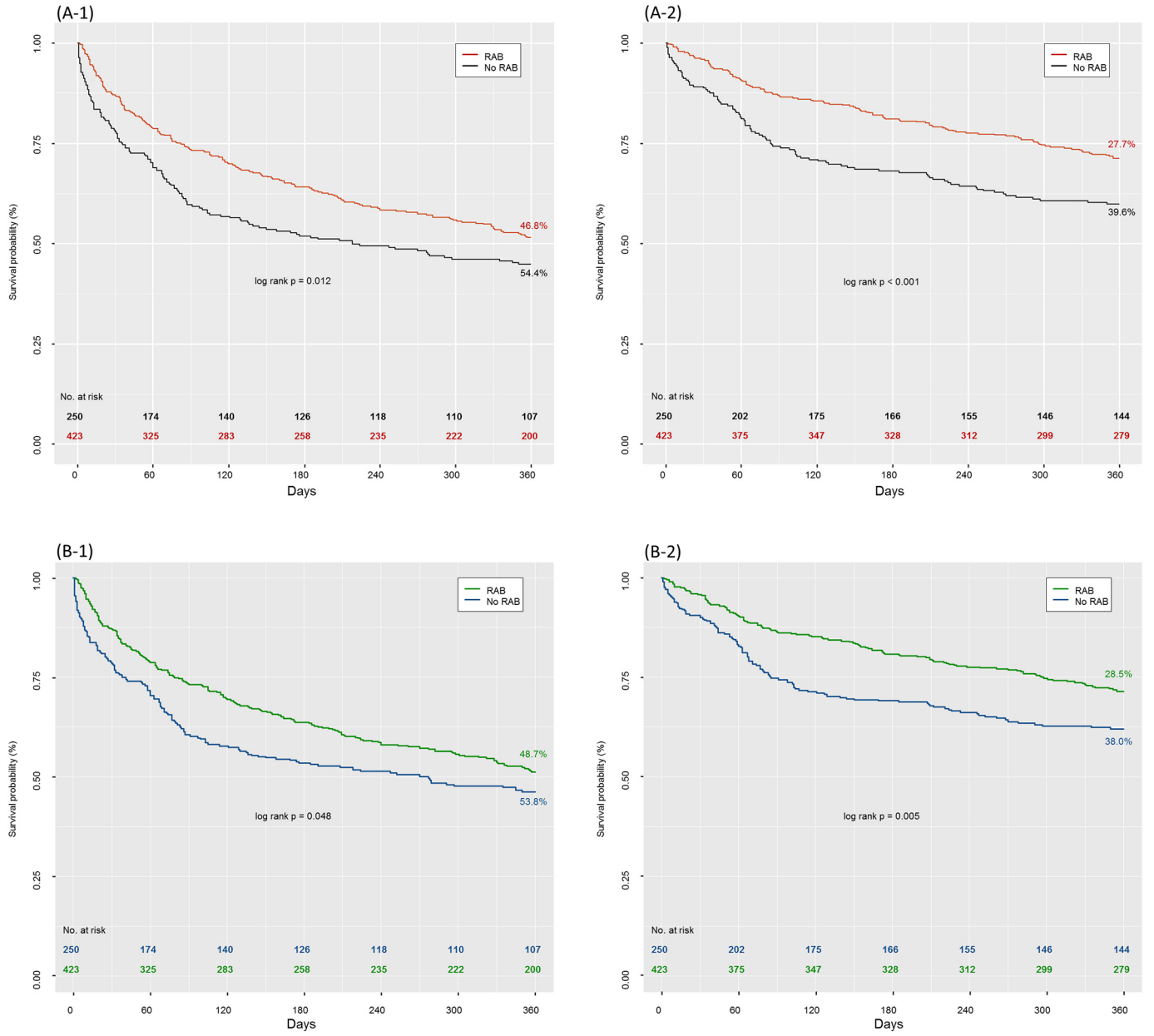

Fig. 1. Kaplan-Meier survival analysis of patients with HFrEF who received pre-discharge RAB versus those who did not; Unadjusted analysis for composite outcome of all-cause mortality and hospitalization for heart failure (A-1) and all-cause mortality alone (A-2) and IPTW-adjusted Kaplan-Meier survival analysis for composite outcome (B-1) and all-cause mortality alone (B-2). HFrEF, heart failure with reduced ejection fraction; RAB, renin-angiotensin system blockade.

indicating that RAB was more distinctively effective in patients receiving RR therapy than in those who did not.

In the analysis of the subgroup of patients with eGFR < 30 mL/min/1.73 m^2 at discharge (n = 401), the effect of RAB was also more prominent in patients receiving RR therapy than in those who did not (Supplementary Fig. 7). The results were consistent in both composite outcome (45.5% vs. 55.4%; log rank p = 0.019) and all-cause mortality (29.3% vs. 55.4%; long rank p = 0.006).

3.4. Factors interfering with the use of RAB

Possible factors that can interfere with the use, maintenance, and dosage of RAB were assessed in patients receiving and not receiving RR therapy. Analyses were limited to patients who were taking RAB at discharge (104 and 319 patients with and without RR, respectively), and all the parameters used were the values at discharge. Potassium level was significantly lower in patients with RR than those without RR (median, 4.1 [IQR, 3.9–4.5] vs. 4.3 [IQR, 3.9–4.7] mEq/L; p = 0.033). There was a tendency toward stronger intensity of RAB in patients with RR than those without (41.4 ± 38.4% vs. 34.4 ± 29.3% of the maximum dose of ACEI/ARB; p = 0.085). The distribution of the potassium levels and intensity of RAB in patients receiving and not receiving RR therapy is presented in Supplementary Fig. 5. The serum creatinine level was significantly higher in patients with RR compared to those without RR (median, 4.6 [IQR, 2.3–7.6] vs. 1.7 [IQR, 1.34–2.4] mg/dL; p < 0.001). There was no significant difference in the systolic blood pressure at discharge between the two groups (120.6 ± 20.3 and 117.8 ± 17.7 mm Hg for the groups with and without RR, respectively). Prescription rates of ACEI/ARBs between the patients receiving and not receiving RR therapy were not significantly different throughout the 1-year follow-up (Supplementary Fig. 8). Although proportions of the patients with ≥50% of the maximum ACEI/ARB dose were

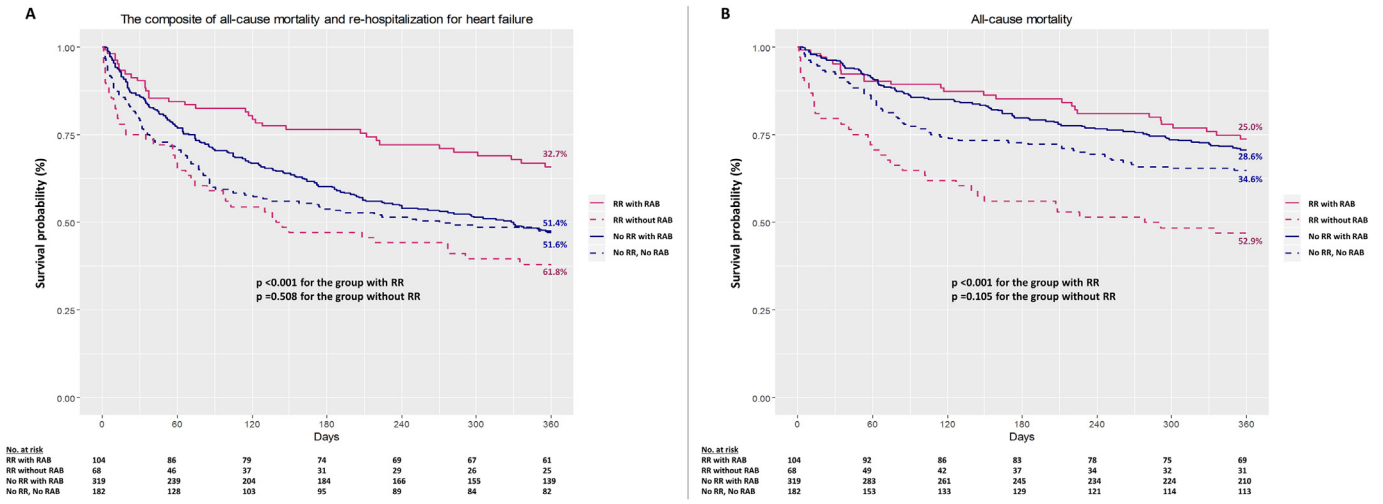

Fig. 2. Kaplan-Meier survival analysis of RAB depending on the presence and absence of renal replacement (RR) therapy in patients with heart failure and severe renal insufficiency RAB, renin-angiotensin system blockade.

not different between the two groups at discharge (34.6% vs. 27.9%, p = 0.192), a significantly larger number of the patients were taking ≥50% of the maximum ACEI/ARB dose in the group with RR than in those without (43.5% vs. 22.4%, p = 0.004, Supplementary Fig. 9).

4. Discussion

The results of the present study demonstrated that the use of RAB was associated with better outcomes in patients with acute heart failure

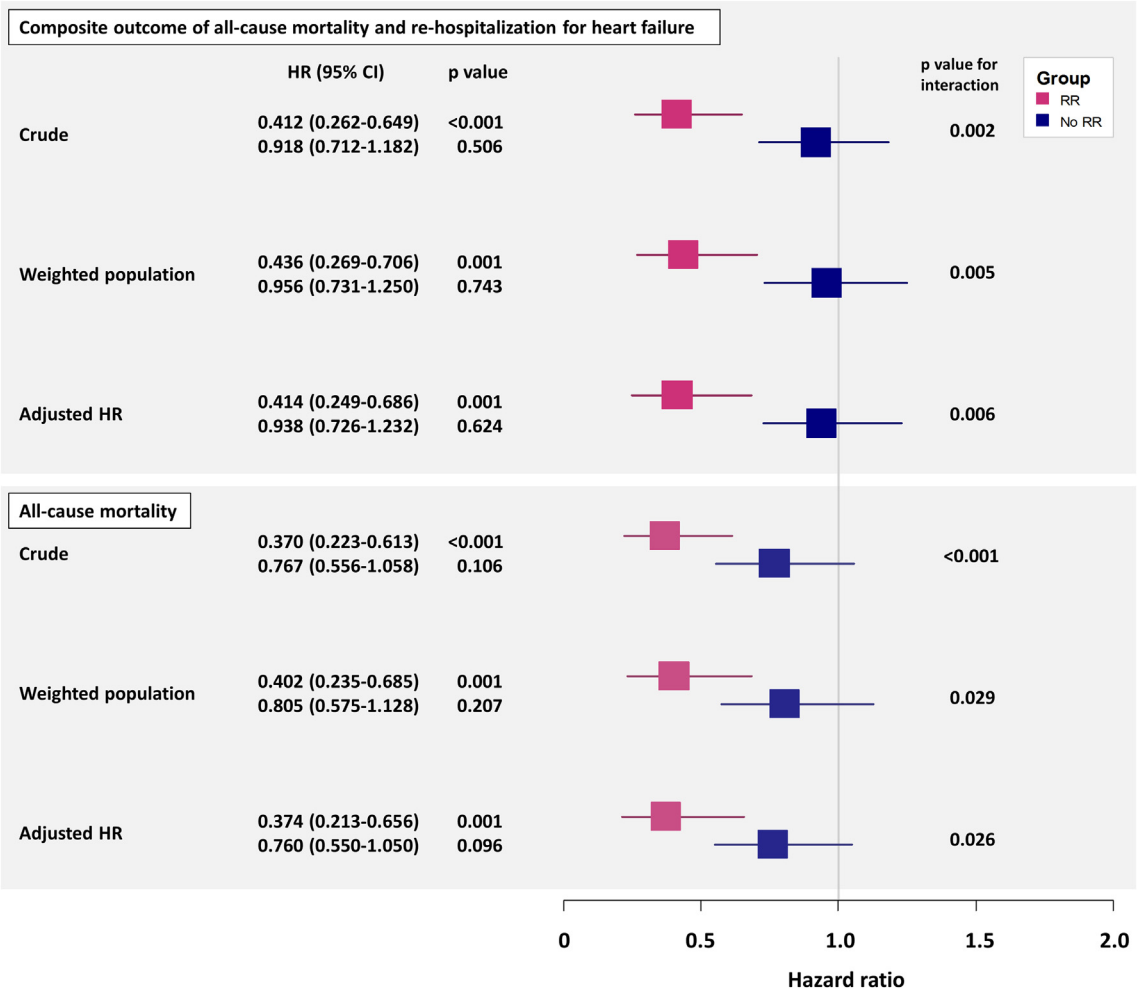

Fig. 3. Differential impact of renin-angiotensin system blockade depending on the absence and presence of renal replacement (RR) therapy in patients with heart failure and severe renal insufficiency

and severe renal insufficiency. Those benefits were more distinctively seen in patients receiving RR than in those not receiving RR. Furthermore, the present data showed a lower potassium level despite the tendency for the stronger intensity of RAB in patients receiving RR, which may suggest that the titration and maintenance of RAB can more relieved the side effects after discharge in those receiving RR than in those who did not. The results were consistent in both the composite outcome and mortality alone.

4.1. RAB in patients with severe renal insufficiency and heart failure

Although the beneficial effect of RAB in patients with HFrEF was well known [1–3,6,7], the rationale for using RAB in patients with HFrEF and severe renal insufficiency is yet to be established. Since enalapril improved the symptoms and prognosis of patients with congestive heart failure in the CONSENSUS trial [1], many randomized trials have shown the benefits of ACEI/ARB in patients with HFrEF [2–6]. However, those trials excluded patients with moderate to severe renal insufficiency. Despite that severe renal impairment is a frequent accompanying condition in patients with heart failure [23], limited data are currently available with respect to the benefits of RAB in those patients. A study investigating the relationship between renal insufficiency and pharmacotherapy in 6427 patients with ischemic heart failure reported that, unlike in patients with preserved renal function (creatinine clearance level ≥ 60 mL/min), ACEI was not associated with better survival in patients with impaired renal function (creatinine clearance level < 60 mL/min) [24]. On the other hand, one registry data showed 20% and 24% of relative risk reduction in all-cause mortality and cardiovascular mortality in 3 years with RAB in patients with hemodialysis [25]. More recently, the Swedish Heart Failure Registry data presented 24% of relative risk reduction for 1-year mortality in patients with severe renal insufficiency (creatinine clearance level < 30 mL/min), and the effect was similar to that in patients without severe renal insufficiency [26]. However, there is a scarcity of studies that assessed the effect of RAB depending on the presence and absence of RR in a single cohort, which may be an important clinical factor in the initiation and maintenance of RAB.

Although the effect of RAB is markedly observed in patients receiving RR, it should not be assumed that RAB is ineffective in patients with HFrEF and severe renal insufficiency who are not receiving RR therapy. At 1-year follow-up, the patients receiving RR were taking higher doses of ACEI/ARB than those without RR. It may imply that uptitration and maintenance of ACEI/ARB can be less difficult in patients receiving RR than those without, which can be related to the better outcome of the patients with RR.

4.2. Adverse effect of RAB in patients with heart failure and severe renal insufficiency

There are difficulties in using RAB in patients with severe renal insufficiency, because major side effects limiting the use of RAB, such as hyperkalemia and deterioration of renal function, are closely related to the renal function. Those side effects can aggravate the prognosis of the patients and caution should be needed when prescribing ACEI/ARB especially in patients with severe renal insufficiency. The reason for the low prescription rate of RAB in those patients may be related to physicians' concerns about the adverse reactions and unproven benefits [27]. The effect of RAB in patients with severe renal insufficiency and HFrEF may depend on the balance between the intensity of the treatment and tolerability of the drug. In patients with maintenance hemodialysis, deteriorating renal function is no longer a significant problem. Furthermore, RAB may barely increase the risk of hyperkalemia [28]. As in the present study, patients with RR can be treated with higher intensity with fewer side effects, and it may be linked to better prognosis. The effect of RAB in patients with severe renal dysfunction and HFrEF should be investigated further, and future studies need to consider these differences between patients with and without RR.

4.3. RAB in patient with acute heart failure and cardiorenal syndrome

Organ-to-organ interactions between the heart and kidney, which is called cardiorenal interaction, is frequently observed in a clinical practice. Worsening renal function in heart failure is commonly seen in patients with acute heart failure, as well as those with chronic heart failure [29]. The population of the present study is based on acute heart failure and can include the patients with acute kidney injury caused by acute cardiorenal syndrome. To date, there is insufficient evidence to use RAB in patients with those conditions. Based on the results of the presents study, early initiation of RAB in patients with heart failure and related acute kidney injury can be a better strategy and need to be validated in a larger well-organized clinical trial.

4.4. Limitations

The KorAHF is a registry with meticulous data management with a wide spectrum of variables. However, the present study has some limitations. First, the IPTW adjustment was performed for possible baseline characteristics though we cannot exclude the possibility of residual confounding factors. Second, detailed data on RR is limited. Timing and duration of RR during the index admission and data on the maintenance of RR after discharge were not available in this analysis. Third, natriuretic peptide (NP) was not included in the present analysis. It is well known that NP is associated with disease severity and prognosis of patients with heart failure. However, as the method of NP measurement was unified among the 10 tertiary hospitals, there was a limitation for NP level to be included in the current analysis.

5. Conclusions

In patients with HFrEF and accompanying severe renal insufficiency, RAB was associated with lower composite events of mortality and rehospitalization for heart failure. The result was consistent with mortality alone. However, the benefit of RAB was more noticeable in patients receiving RR than in who did not. Further studies on RAB in patients with HFrEF and severe renal insufficiency, especially in patients receiving and not receiving RR, will be needed to establish an appropriate treatment in those patients.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

Funding

The KorAHF registry was supported by the Research of Korea Centers for Disease Control and Prevention [2010-E63003-00, 2011-E63002-00, 2012-E63005-00, 2013-E63003-00, 2013-E63003-01, 2013-E63003-02, 2016-ER6303-00].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.03.016.

References

[1] The 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. 316 (1987) 1429–1435.
[2] The SOLVD Investigators, Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure, N. Engl. J. Med. 325 (1991) 293–302.
[3] The SOLVD Investigators, Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions, N. Engl. J. Med. 327 (1992) 685–691.

[4] M.A. Pfeffer, E. Braunwald, L.A. Moye, L. Basta, E.J. Brown Jr., T.E. Cuddy, et al., Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators, N. Engl. J. Med. 327 (1992) 669–677.
[5] M. Packer, P.A. Poole-Wilson, P.W. Armstrong, J.G. Cleland, J.D. Horowitz, B.M. Massie, et al., Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group, Circulation 100 (1999) 2312–2318.
[6] J.N. Cohn, G. Tognoni, Valsartan Heart Failure Trial I, A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure, N. Engl. J. Med. 345 (2001) 1667–1675.
[7] C.B. Granger, J.J. McMurray, S. Yusuf, P. Held, E.L. Michelson, B. Olofsson, et al., Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial, Lancet 362 (2003) 772–776.
[8] P. Ponikowski, A.A. Voors, S.D. Anker, H. Bueno, J.G. Cleland, A.J. Coats, et al., 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. 37 (2016) (2016) 2129–2200.
[9] C.W. Yancy, M. Jessup, B. Bozkurt, J. Butler, D.E. Casey Jr., et al., ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines, Circulation 128 (2013) (2013) e240–327.
[10] A. Takahashi, H. Takase, T. Toriyama, T. Sugiura, Y. Kurita, R. Ueda, et al., Candesartan, an angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients on chronic haemodialysis–a randomized study, Nephrol. Dial. Transplant. 21 (2006) 2507–2512.
[11] M. Ikeda, M. Nakao, K. Hirano, K. Yokoyama, T. Yokoo, N. Joki, et al., Possible prevention of dialysis-requiring congestive heart failure by angiotensin-II receptor blockers in non-dialysis Japanese patients with stage 5 chronic kidney disease, J. Renin-Angiotensin-Aldosterone Syst. 16 (2015) 1175–1184.
[12] Y. Yang, R. Wang, M.X. Li, Y. Xing, W.G. Li, Effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on left ventricular mass index and ejection fraction in hemodialysis patients: a meta-analysis with trial sequential analysis of randomized controlled trials, Int. J. Cardiol. 219 (2016) 350–357.
[13] F. Zannad, M. Kessler, P. Lehert, J.P. Grunfeld, C. Thuilliez, A. Leizorovicz, et al., Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies, Kidney Int. 70 (2006) 1318–1324.
[14] T.I. Chang, D. Shilane, S.M. Brunelli, A.K. Cheung, G.M. Chertow, W.C. Winkelmayer, Angiotensin-converting enzyme inhibitors and cardiovascular outcomes in patients on maintenance hemodialysis, Am. Heart J. 162 (2011) 324–330.
[15] R.R. Bajaj, R. Wald, D.G. Hackam, T. Gomes, J. Perl, D.N. Juurlink, et al., Use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and cardiovascular outcomes in chronic dialysis patients: a population-based cohort study, Arch. Intern. Med. 172 (2012) 591–593.
[16] S.E. Lee, H.J. Cho, H.Y. Lee, H.M. Yang, J.O. Choi, E.S. Jeon, et al., A multicentre cohort study of acute heart failure syndromes in Korea: rationale, design, and interim observations of the Korean Acute Heart Failure (KorAHF) registry, Eur. J. Heart Fail. 16 (2014) 700–708.
[17] S.E. Lee, H.Y. Lee, H.J. Cho, W.S. Choe, H. Kim, J.O. Choi, et al., Clinical characteristics and outcome of acute heart failure in Korea: results from the Korean Acute Heart Failure Registry (KorAHF), Kor. Circ. J. 47 (2017) 341–353.
[18] A.S. Levey, L.A. Stevens, C.H. Schmid, Y.L. Zhang, A.F. Castro 3rd, H.I. Feldman, et al., A new equation to estimate glomerular filtration rate, Ann. Intern. Med. 150 (2009) 604–612.
[19] P.C. Austin, Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples, Stat. Med. 28 (2009) 3083–3107.
[20] P.C. Austin, The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments, Stat. Med. 33 (2014) 1242–1258.
[21] S. van Buuren, Multiple imputation of discrete and continuous data by fully conditional specification, Stat. Methods Med. Res. 16 (2007) 219–242.
[22] S.R. Cole, M.A. Hernan, Adjusted survival curves with inverse probability weights, Comput. Methods Prog. Biomed. 75 (2004) 45–49.
[23] A. Michel, M. Martin-Perez, A. Ruigomez, L.A. Garcia Rodriguez, Incidence and risk factors for severe renal impairment after first diagnosis of heart failure: a cohort and nested case-control study in UK general practice, Int. J. Cardiol. 207 (2016) 252–257.
[24] J. Ezekowitz, F.A. McAlister, K.H. Humphries, C.M. Norris, M. Tonelli, W.A. Ghali, et al., The association among renal insufficiency, pharmacotherapy, and outcomes in 6,427 patients with heart failure and coronary artery disease, J. Am. Coll. Cardiol. 44 (2004) 1587–1592.
[25] C.H. Tang, T.H. Chen, C.C. Wang, C.Y. Hong, K.C. Huang, Y.M. Sue, Renin-angiotensin system blockade in heart failure patients on long-term haemodialysis in Taiwan, Eur. J. Heart Fail. 15 (2013) 1194–1202.
[26] M. Edner, L. Benson, U. Dahlstrom, L.H. Lund, Association between renin-angiotensin system antagonist use and mortality in heart failure with severe renal insufficiency: a prospective propensity score-matched cohort study, Eur. Heart J. 36 (2015) 2318–2326.
[27] P. Roy, J. Bouchard, R. Amyot, F. Madore, Prescription patterns of pharmacological agents for left ventricular systolic dysfunction among hemodialysis patients, Am. J. Kidney Dis. 48 (2006) 645–651.
[28] S.W. Han, Y.W. Won, J.H. Yi, H.J. Kim, No impact of hyperkalaemia with renin-angiotensin system blockades in maintenance haemodialysis patients, Nephrol. Dial. Transplant. 22 (2007) 1150–1155.
[29] L. Di Lullo, A. Bellasi, D. Russo, M. Cozzolino, C. Ronco, Cardiorenal acute kidney injury: epidemiology, presentation, causes, pathophysiology and treatment, Int. J. Cardiol. 227 (2017) 143–150.