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

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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

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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