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Effects of angiotensin receptor blocker at discharge in patients with heart failure with reduced ejection fraction: Korean Acute Heart Failure (KorAHF) registry☆

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ABSTRACT

Background: After introduction of up-titration strategy, there are limited data on comparison between the effects of angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blocker (ARB) in patients with heart failure with reduced ejection fraction (HFrEF). The study sought to investigate the association between treatment with ARB at discharge and clinical outcomes in patients with HFrEF compared with treatment with ACEI or no renin angiotensin system blocker (RASB).

Methods: The KorAHF registry is a prospective multicenter cohort and included patients who were hospitalized for acute heart failure (AHF). We studied 3005 patients with HFrEF (<40%), and divided into ARB ($n = 1190$), ACEI ($n = 1090$), and no RASB ($n = 725$) groups. Propensity score matching was performed.

Results: All-cause death occurred in 346 patients (29.1%) in the ARB group, 315 patients (28.9%) in the ACEI group, and 305 (42.1%) in the no RASB group. After propensity score matching (ARB vs. ACEI, 827 pairs), there was no significant difference between the two groups in the rate of death (HR 0.91, 95% CI 0.76–1.09, $p = 0.32$). All-cause death was significantly lower in the ARB group than in the no RASB group (ARB vs. no RASB, 538 pairs, HR 0.69, 95% CI 0.56–0.83, $p < 0.001$). The ARB group had a significantly lower discontinuation rate than the ACEI group (20.8% vs. 33.6%, $p < 0.001$).

Conclusions: For treatment of AHF with reduced EF after hospitalization, ARB at discharge shows a mortality benefit comparable to that of ACEI. In addition, tolerability of medication was greater for ARB than for ACEI.

1. Introduction

Heart failure (HF) is a chronically progressive disease and one of the most important causes of morbidity and mortality worldwide despite recent improvements in its treatment [1–3]. The mortality and morbidity benefits of angiotensin converting enzyme inhibitor (ACEI) are well established in HF with reduced ejection fraction (HFrEF) [4–6]. Previous studies have also shown beneficial effects of angiotensin receptor blocker (ARB) in HFrEF patients who cannot tolerate ACEI [7,8]. In the OPTIMAAL study, a randomized controlled trial to compare the effects of losartan 50 mg and captopril 150 mg, the captopril group had more

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; AHF, acute heart failure; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CKD, chronic kidney disease; GFR, glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; RASB, renin angiotensin system blocker.

☆ Trial registration: KorAHF registry, ClinicalTrial.gov, NCT01389843.

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favorable outcomes compared with the losartan group [9]. However, since the introduction of accelerated up-titration of renin angiotensin system blocker (RASB) to maximum tolerated dosages there are limited data directly comparing the beneficial effects between ACEI and ARB in HFrEF patients. Although current guidelines recommend that ARB could be used as an alternative treatment in HFrEF patients who are intolerant to ACEI, in real clinical practice ARB is widely prescribed as first-line therapy for HF instead of ACEI because of the side effects of the latter, such as cough and angioedema [10,11]. We performed the present study using multicenter prospective registry data in Korea to evaluate the beneficial effects of ARB compared with ACEI or no use of RASB.

2. Methods

2.1. Study population and data collection

The Korean Acute Heart Failure (KorAHF) registry is a prospective, multicenter observational study. Between March 2011 and February 2014, 5625 consecutive patients from 10 tertiary hospitals in Korea who were hospitalized for acute heart failure (AHF) were recruited. Detailed information on the study design and results of the KorAHF registry have been documented previously [12,13]. In brief, patients who have signs or symptoms of HF and one of the following criteria are eligible for the study: 1) lung congestion or 2) objective findings of left ventricular systolic dysfunction or structural heart disease. The attending physician filled up a web-based case report form in the Clinical Data Management System (iCReaT) from the National Institute of Health (NIH) of Korea. Information about patient demographics, medical history, signs, symptoms, results of laboratory tests, electrocardiogram, echocardiography, medications, hospital course, and outcomes was collected at admission, at discharge, and during the follow-up (at 30 days, 3 months, 6 months, and annually from 1 to 5 years). Follow-up of the patients is planned until 2018. Mortality data for patients who were lost to follow-up were collected from the National Insurance data or National Death Records. All clinical events were monitored and verified by a Clinical Event Committee, which was composed of independent experts in HF who have not participated in patient enrolment for this study. The flow chart of study distribution is depicted in Fig. 1. For the present study, we excluded 211 patients with missing data on left ventricular ejection fraction (LVEF) and 2232 patients with HF with preserved ejection fraction (HFpEF). In addition, for evaluation of the effect of each RASB agent at discharge, we excluded 164 patients who died in the hospital and 13 patients with concomitant use of ACEI and ARB. Finally, 3005 consecutive AHF patients with HFrEF were enrolled in the present study. The Institutional Review Board of each hospital approved the study protocol.

2.2. Definitions and outcomes

HFrEF was defined as LVEF <40% according to the recent guideline [11]. LVEF was assessed by the biplane Simpson technique, M-mode, or visual estimation [14]. Renal function was assessed based on estimated glomerular filtration rate (GFR) according to the Modification of Diet in Renal Disease (MDRD) equation [15]. A total of 3005 patients were divided into the ACEI group ($n = 1090$), ARB group ($n = 1190$), and no RASB group ($n = 725$) according to the use of ARB or ACEI at discharge. The primary end point of the present study was the occurrence of all-cause death during follow-up.

2.3. Statistical analysis

Continuous variables were compared using the Student *t*-test or Wilcoxon rank-sum test as applicable. Chi-squared test or Fisher's exact test were performed to compare categorical data. Survival curves were assessed by Kaplan–Meier analyses and significance level was evaluated with the log-rank test. To compare the risk of mortality between ARB and ACEI groups or between ARB and no RASB groups, we used a Cox proportional hazards model. In multivariable models,

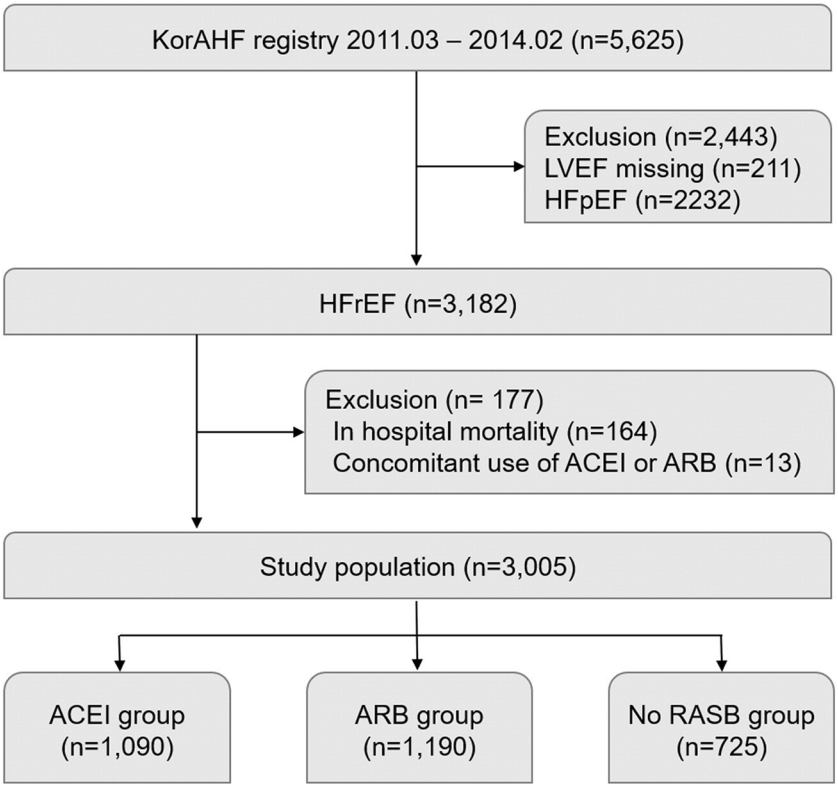

Fig. 1. Flow chart of study population. ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; RASB = renin angiotensin system blocker.