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Trial Design

Rationale and Study Design of the Withdrawal of Spironolactone for Heart Failure with Improved Left Ventricular Ejection Fraction

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ABSTRACT

It is unclear if guideline-directed medical therapy (GDMT) should be maintained in patients who have heart failure (HF) with improved ejection fraction (HFiEF). Of the medications recommended for HF, mineralocorticoid receptor antagonist (MRA) is associated with heterogeneous results and considerable adverse events. We wish to evaluate whether MRA withdrawal is safe or associated with deterioration of left ventricular ejection fraction (LVEF). We will select 60 patients with HFiEF of a New York Heart Association functional class I–II who are receiving GDMT and randomize them in a 1:1 fashion into 2 groups: one that will continue treatment and one that will have spironolactone administration withdrawn. All patients will receive standard medical therapy other than MRA. The primary outcome is the proportion of patients with declining LVEF ≥10%. Secondary outcomes include a change in LVEF, the estimated glomerular filtration rate, B-type natriuretic peptide or N-terminal pro-brain natriuretic peptide levels, and adverse clinical events, including death, re-hospitalization, or an emergency department visit for HF. This trial will provide important evidence on whether MRA in addition to other standard therapy, should be maintained or withdrawn in patients with HFiEF.

Keywords: Heart failure; Left ventricular ejection fraction; Spironolactone; Management; Outcomes

INTRODUCTION

Medical therapy is a mainstay in the management of heart failure (HF) with reduced ejection fraction (HFrEF), and current guidelines recommend angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), beta-blockers (BBs), and mineralocorticoid receptor antagonists (MRA) in combination,[1-3] which has improved patient survival.[4][5] Recently, angiotensin receptor neprilysin inhibitors (ARNIs) have been preferentially recommended in place of ACEIs or ARBs. Strict adherence to this guideline-directed medical therapy (GDMT) is a cornerstone in the management of HFrEF and is directly associated with better clinical outcomes. Thus, it is strongly recommended that a patient start this GDMT promptly, as left ventricular function reportedly improves in up to 50% of cases.[6][7]

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Lee SE; Data curation: Hyun J; Formal analysis: Lee SE; Funding acquisition: Lee SE; Investigation: Hyun J, Lee SE, Lee SA, Hong JA, Kim MS, Kim JJ; Methodology: Hyun J, Lee SE; Project administration: Hyun J; Resources: Lee SE; Supervision: Lee SE; Validation: Hyun J, Lee SE; Visualization: Hyun J; Writing - original draft: Hyun J; Writing - review & editing: Hyun J, Lee SE.

However, data about whether to maintain or interrupt GDMT in patients whose left ventricular function has improved is limited. In patients who permanently recover, continuing these treatments may be unnecessary or even harmful, while relapse could occur in others if treatment is withdrawn. Many HF patients are older and have comorbidities, including chronic kidney disease, diabetes, and chronic airway disease.[8] Importantly, many people with HF have polypharmacy (using more than 5 drugs in combination), resulting in a low HF management efficacy, a decreased quality of life, and other clinical problems, including inappropriate prescriptions, low compliance, drug interactions, adverse events, and increased net costs.[9]

Recently, a small pilot study with 51 participants reported significant deterioration of left ventricular function or dimension within 6 months of interrupting all GDMT. In particular, the cessation of BB is a possible mechanism of decreased left ventricular ejection fraction (LVEF).[10] However, it remains unknown if all the GDMT prescribed before improvement should be maintained.

Aldosterone receptor antagonists reportedly improved survival in patients with HFrEF in 2 randomized controlled trials (RCTs).[11][12] However, Juurlink et al.[13] reported that a significant proportion of patients who were on aldosterone receptor antagonist therapy experienced re-hospitalization due to hyperkalemia, and subsequently had increased mortality after the RALES trial was published. Furthermore, real-world clinical data that MRA was not associated with benefit on survival or re-hospitalization, in contrast with ACEIs, ARBs, and BBs.[14][15] Subsequently, some suggested MRA use might not be generalizable to real-world practice or the entire HF population solely based on the results of RCTs in which participants were strictly selected and managed.

Accordingly, we aim to evaluate the efficacy and safety of spironolactone withdrawal in patients with HF with improved ejection fraction (HFiEF; defined as LVEF ≤35% previously, but recently improved to LVEF ≥50%) and to identify predictors of worsening HF after spironolactone withdrawal.

STUDY DESIGN

This study is a single-center, prospective, open-label, randomized pilot trial to be conducted at Asan Medical Center (Seoul, Korea). The purpose of the study is to evaluate the clinical impact of withdrawal or continuation of MRA for people with improved LVEF after GDMT, including ACEIs/ARBs/ARNI, BBs, and MRA.

Trial population

Adult patients will be eligible for the study if they have a prior diagnosis of HFrEF (LVEF ≤35%) and have documented LVEF improvement (LVEF ≥50%) by echocardiography after GDMT. After the screening phase, a total of 60 patients who meet the inclusion criteria without any exclusion criteria will be randomized in a 1:1 fashion to either a withdrawal or continuation of spironolactone treatment group (**Tables 1** and **2**). Subjects should receive all GDMT before study entry, according to the recommended guidelines, including ACEIs/ARBs/ARNIs, BBs, and MRA. After randomization, patients will receive medical therapy according to their assigned group, either continuation or withdrawal of spironolactone. GDMT other than spironolactone will continue during the study period.

Table 1. Inclusion criteria

No.	Inclusion criteria
1	Subjects willing and capable of providing informed consent, and who agree to follow the study protocol and clinical follow-up schedule
2	Those between the ages of 19 and 80
3	People with a prior diagnosis of heart failure with reduced LVEF (HFrEF; LVEF ≤35%) who are on medical therapy, including spironolactone combined with ACEIs, ARBs, ARNI, or BBs
4	Subjects with LVEF ≥50%, as documented with echocardiography performed within the last month
5	Those with BNP or NT-proBNP levels that have been documented in the last 3 months

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BB = beta-blocker; BNP = B-type natriuretic peptide; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-brain natriuretic pepti

Table 2. Exclusion criteria

No.	Exclusion criteria
1	Those with dyspnea ≥ New York Heart Association functional class III
2	Patients who need to discontinue spironolactone due to a prior adverse event
3	Those with primary valvular heart disease of at least a moderate degree
4	Patients with an estimated glomerular filtration rate <30 mL/min/1.73 m^2
5	Those with uncontrolled hypertension, defined as blood pressure >140/90 mmHg
6	Subjects with other clinical reasons to continue spironolactone, such as myocardial infarction, primary aldosteronism, or liver cirrhosis
7	Those with hypo- or hyperkalemia, defined as serum potassium levels <3.5 mmol/L or >5.5 mmol/L
8	Pregnant and/or lactating women
9	Those with a life expectancy of less than 1 year
10	Patients who are not suitable for enrollment at the investigator's discretion

Study flow

Patients assigned to the continuation group will be prescribed spironolactone as an MRA and other MRA, eplerenone is not being considered for this study because it is not available in Korea. The acceptable dose range of spironolactone is 12.5–50 mg once or twice daily. At the time of randomization, baseline demographics, physical examination, laboratory tests, including measuring B-type natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP), 12-lead electrocardiography, and echocardiography will be performed. All patients will be followed-up at 6 months, including an assessment of clinical events, laboratory testing, and echocardiography (**Figure 1**). The follow-up window is allowed a month before and 3 months after 6-month. Patients with any symptoms or signs of HF aggravation within 6 months will be allowed to receive echocardiographic and laboratory evaluation and to resume spironolactone, at a physician's discretion. Patients assigned to the continuation group who have adverse events related to spironolactone will be able to discontinue the drug. Adherence to the study drug as assigned and to other medications will be evaluated at every visit.

Endpoints

The primary endpoint of this study is to evaluate the efficacy and safety of spironolactone withdrawal in patients with HFiEF. Detailed endpoints will include a comparison of the proportion of patients with LVEF rates that have declined ≥10% after the discontinuation of an aldosterone receptor antagonist. Secondary endpoints include changes in BNP or NT-proBNP, the estimated glomerular filtration rate, and a comparison of the change in LVEF as a continuous variable. Adverse clinical events, including death, re-hospitalization, or an emergency department visit for HF will also be accessed. Participant blood samples will be collected, and biomarkers such as soluble ST-2 and galectin-3 will be measured at the time of enrollment and at the 6-month follow-up to predict LVEF deterioration.

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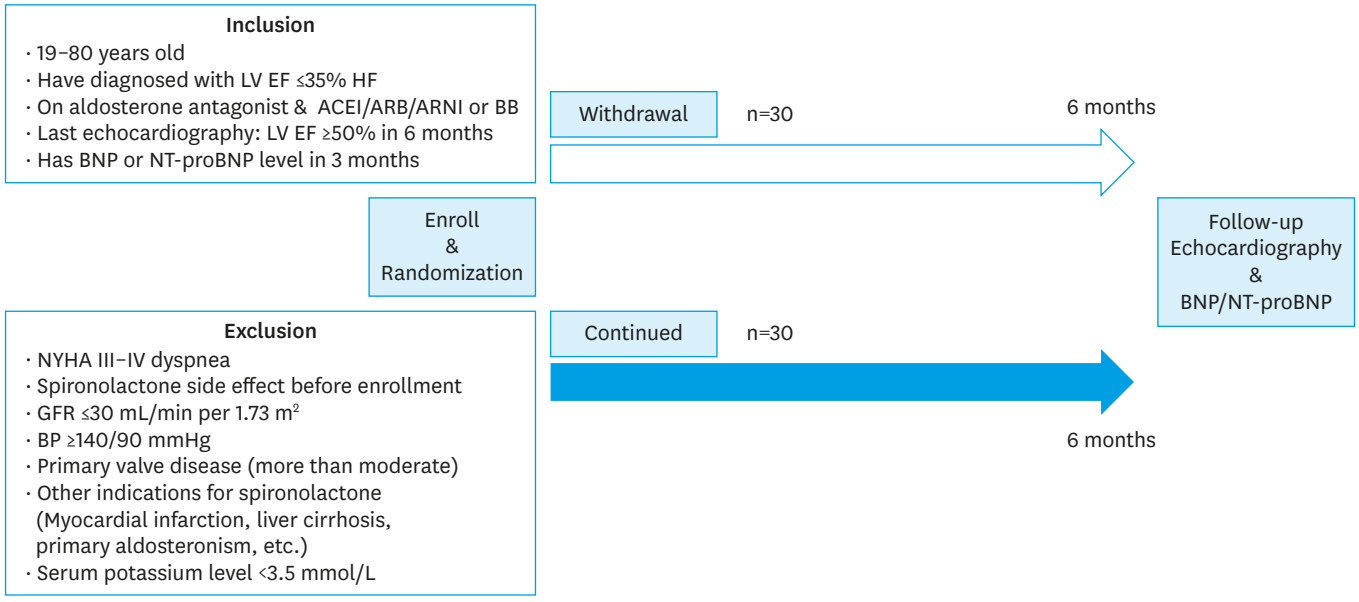


Figure 1. Study flow.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BB = beta-blocker; BP = blood pressure; BNP = B-type natriuretic peptide; GFR = glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association.

Statistical analysis

Overall analyses are based on the intention-to-treat population. The comparison of the proportion of patients with LVEF that has declined ≥10% will be evaluated with chi-square or Fisher's exact test. Adverse clinical events, including death, re-hospitalization, or an emergency department visit for HF will be compared by χ^2 or Fisher's exact test. Changes in BNP or NT-proBNP levels will be transformed with a log value, and the baseline value will be calibrated to perform a covariance analysis. Change in LVEF is a continuous variable, and the estimated glomerular filtration rate will be compared with a paired t-test.

Since there is no study to benchmark to estimate the exact sample size, and this study is aimed at getting the data for a more definitive future study, it was not prospectively powered to detect a difference in the outcome. A retrospective power calculation will be provided in the final report.

DISCUSSION

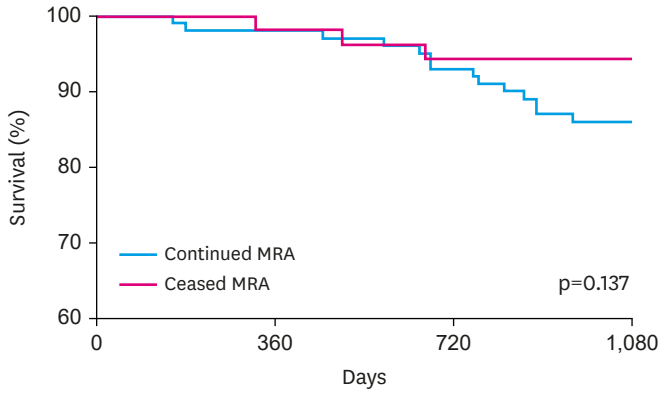
While LVEF can improve in HF patients with or without therapy,[16][17] there is no consensus on the definition of this status, which differs according to guideline and paper. The American College of Cardiology/American Heart Association guidelines define the patients who have LVEF >40%, but who previously had an LVEF ≤40%, as "HF with preserved ejection fraction, improved".[18] Other investigators define those with an LVEF ≥50% but with a previously documented LVEF <50% as HF with recovered EF or HF with better EF.[19][20] HFiEF was used by Florea et al.[21] to define patients with an LVEF >40% and a previously documented LVEF <35%. Here, we adopted the term "HFiEF" based on the recommendation by Gulati and Udelson,[16] but we used more strict LVEF improvement criteria: LVEF ≤35% to LVEF ≥50% to follow the indication for MRA and to be conservative for drug withdrawal. Based on the results from this study, we will further evaluate the lenient criteria for withdrawing MRA.

Previous studies reported different frequencies of LVEF improvement according to the causes of HF, its duration, and co-morbidities. LVEF can better improve in patients with cardiomyopathy that is related to peripartum, tachycardic arrhythmia, stress, fulminant myocarditis, or hyperthyroidism and with a shorter duration of HF. There is less improvement in patients with ischemic cardiomyopathy or left ventricular dysfunction with left bundle branch block and in those with a longer duration of HF.[6)22-25)] In addition, age, duration of HF, chamber size, and global longitudinal strain are reportedly related to the recurrence of LV dysfunction in HFiEF patients.[26-28)] Thus, the heterogeneity of the population can affect the response to withdrawing MRA. We will collect relevant data about the possible cause and duration of HF and underlying medical conditions. The possible cause of HF will be independently and blindly adjudicated by 2 different physicians according to a predetermined definition.

Several prospective studies support the continuation of BBs and ACE inhibitors in HFiEF patients. Swedberg et al.[29)] first reported that BB withdrawal in a small number of patients with congestive cardiomyopathies resulted in pronounced deterioration of both clinical condition and ejection fraction.[30)] Withdrawal of quinapril in a RCT was related to a decrease in exercise tolerance, a higher New York Heart Association functional class, and more frequent worsening of HF.[31)] However, there is no study on withdrawal of MRAs so far. Recently, a small pilot study with 51 participants with dilated cardiomyopathy reported significant deterioration of left ventricular function or dimension within 6 months of interrupting medications, including diuretics, ACEI, BB, and MRA.[10)] When we closely examine the data, diuretics, MRA, BBs, and ACEI/ARBs were sequentially reduced or stopped every 4 weeks, and only after MRA withdrawal was there no increase in the primary outcome.

The primary endpoint, duration and the sample size would be limitation of this study. MRA has been reported to benefit HF patients in various mechanisms, and thus, it would be best to test had clinical endpoint such as survival and rehospitalization, which requires a large sample size and long-term follow-up. The goal of our study is to get such evidence for more definitive further study. Therefore, we are planning to collect data on clinical parameters such as rehospitalization, an unexpected visit, dyspnea severity, new HF symptom and sign development, laboratory parameter such as changes in levels of BNP/NT-proBNP, and echocardiographic parameters including LVEF, global longitudinal strain, and so on. Since TRED-HF trial,[10)] the only RCT testing withdrawal of GDMT in HFiEF evaluated LVEF deterioration at 6 months as the primary endpoint and demonstrated that 44% of those assigned to the withdrawal group met the primary endpoint, we considered LVEF deterioration at 6 months as a reasonable primary endpoint of our trial.

Our preliminary analysis from the Korean Acute Heart Failure Registry, which anticipated the clinical impact of aldosterone receptor antagonist withdrawal, demonstrates that there was no significant difference between continuation (n=100) and cessation (n=53) of the aldosterone receptor antagonist in 153 patients with HFiEF (**Figure 2**). Therefore, evaluating the results of this study will guide true optimal medical therapy, including determining which essential drugs should be maintained and which unnecessary drugs can be safely withdrawn in patients who have impaired LVEF that has improved after HF medication.



No. at risk				
Continued MRA	100	99	94	85
Ceased MRA	53	53	50	48

Figure 2. Preliminary analysis from the Korean Acute Heart Failure Registry demonstrating cessation of spironolactone was not associated with worse outcomes in patients with HFiEF.
HFiEF = heart failure with improved ejection fraction; MRA = mineralocorticoid receptor antagonist.

CONCLUSION

Current pilot study will access the feasibility and safety of spironolactone withdrawal on the top of contemporary medical therapy in patients with HFiEF. We believe the results of this trial will provide crucial evidences for optimal medical therapy and future direction of clinical trial in these population.

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