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Prognostic Effect of Guideline-Directed Therapy Is More Noticeable Early in the Course of Heart Failure

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ABSTRACT

Background: There have been few studies to evaluate the prognostic implications of guideline-directed therapy according to the temporal course of heart failure. This study assessed the relationship between adherence to guideline-directed therapy at discharge and 60-day clinical outcomes in *de novo* acute heart failure (AHF) and acute decompensated chronic heart failure (ADCHF) separately.

Methods: Among 5,625 AHF patients who were recruited from a multicenter cohort registry of Korean Acute Heart Failure, 2,769 patients with reduced ejection fraction were analyzed. Guideline-directed therapies were defined as the use of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor II blocker (ARB), β-blocker, and mineralocorticoid receptor antagonist.

Results: In *de novo* AHF, ACEI or ARB reduced re-hospitalization (hazard ratio [HR], 0.57; 95% confidence interval [CI], 0.34–0.95), mortality (HR, 0.41; 95% CI, 0.24–0.69) and composite endpoint (HR, 0.52; 95% CI, 0.36–0.77) rates. Beta-blockers reduced re-hospitalization (HR, 0.62; 95% CI, 0.41–0.95) and composite endpoint (HR, 0.65; 95% CI, 0.47–0.90) rates. In ADCHF, adherence to ACEI or ARB was associated with only mortality and β-blockers with composite endpoint.

Conclusion: The prognostic implications of adherence to guideline-directed therapy at discharge were more pronounced in *de novo* heart failure. We recommend that guideline-directed therapy be started as early as possible in the course of heart failure with reduced ejection fraction.

Keywords: *De Novo* Acute Heart Failure; Acute Decompensated Heart Failure; Guideline-Directed Therapy

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INTRODUCTION

The American College of Cardiology (ACC)/American Heart Association (AHA) and the European Society of Cardiology (ESC) have developed evidence-based guidelines for the treatment of heart failure (HF) to assist clinicians in clinical decision-making by describing acceptable approaches to the diagnosis, management, and prevention of specific diseases or conditions.[1,2] In chronic HF with reduced ejection fraction (HFrEF), evidence-based benefit on outcome is documented for angiotensin-converting enzyme inhibitors (ACEI), angiotensin-receptor II blockers (ARB), β-blockers, mineralocorticoid receptor antagonists (MRA), angiotensin receptor neprilysin inhibitors (ARNI), and ivabradine. However, acute heart failure (AHF) is characterized by rapid worsening of symptoms and signs of HF. Although survival rates have improved, mortality is still high, typically greater than 4%. However, most morbidity and mortality of hospitalized AHF occurs early after index hospital discharge.[3,4] Hospitalized HF patients have 30-day readmission rates from 20% to 27%, with mortality rate reaching up to 12.2% at 30-days.[5,6] Once the patient is stabilized, the priority should transition to initiation of chronic medical therapy. Modalities initiated in the hospital engender increased outpatient adherence and improved outcomes. Therefore, comprehensive strategies must focus on factors during hospitalization and during the early recovery period soon after discharge to target stressors that contribute to patient vulnerability. The guideline-directed therapy in HF inpatient is associated with post-discharge mortality or re-hospitalization.[7-9] AHF has two forms according to the time course of heart failure: newly arisen ("*de novo*") AHF and acutely decompensated chronic heart failure (ADCHF).[1,2] Acute and chronic HF differ both in their temporal course and treatment.[3,10] However, there are limited data regarding the prognostic implications of guideline-directed therapy according to the temporal course of HF. We assessed the relationship between guideline-directed therapy at discharge and 60-day relevant patient clinical outcomes, including all-cause mortality, re-hospitalization because of aggravated HF, and composite endpoint of mortality or HF hospitalization in *de novo* AHF and ADCHF separately.

METHODS

Study population
We used the registry of Korean Acute Heart Failure (KorAHF), which is a multicenter prospective cohort study. Between March 2011 and February 2014, the registry prospectively enrolled 5,625 consecutive patients admitted for treatment of AHF from 10 tertiary university hospitals. Patients were followed-up until 2018. The registry included patients with signs or symptoms of HF who met at least one of the following inclusion criteria: 1) lung congestion or 2) objective findings of left ventricular systolic dysfunction (LVSD) or structural heart disease. Detailed information on the study design and results of the KorAHF registry have been described previously.[11]

Adherence to guideline-directed therapy
Guideline-directed therapy was defined by ACC/AHA and ECS guidelines.[1,2] Numerators were defined as HF patients who were prescribed each medication and denominator as HF patients with LVSD and without contraindication for medication. The adherence to guideline-directed therapy was assessed by the ratio of the numerator to the dominator.[12,13] Of these guideline-directed therapies, we excluded ARNI and ivabradine because this therapy was not available in Korea during the study period.

The adherence to guideline-directed therapy was defined as follows: 1) β-blocker therapy for LVSD: percentage of patients who were prescribed β-blocker therapy with bisoprolol, carvedilol, sustained-release metoprolol succinate, or nebivolol at hospital discharge. Because the 2016 ESC guidelines for HF recommend β-blockers, including nebivolol, for the treatment of HFrEF, patients prescribed nebivolol were defined as numerators.[14] Patients not eligible for β-blocker therapy were those with systolic blood pressure < 90 mmHg or resting heart rate < 60 bpm at discharge.[2] An equivalent dose of carvedilol was calculated for bisoprolol- and nebivolol-treated subjects (dose × 5), and for metoprolol-treated subjects (dose/4), again taking into account several possible confounders[15]; 2) ACEI or ARB therapy for LVSD: percentage of patients who were prescribed ACEI or ARB therapy at hospital discharge. Patients not eligible for ACEI or ARB therapy were those with systolic blood pressure < 90 mmHg or serum creatinine > 2.5 mg/dL or serum K ≥ 5.0 mmol/L at discharge.[2] Equivalent doses of ramipril were calculated for ACEI, and equivalent doses of candesartan were calculated for ARB.[16]

An additional performance measure for MRA was developed, excluding patients with documented MRA contraindications or intolerance (serum K ≥ 5.0 mmol/L or creatinine > 2.5 mg/dL at discharge).[2]

Clinical outcomes

The follow-up data were collected from the patients by the attending physician and stored in a web-based case report form. The outcome data of subjects who had not been followed-up were ascertained by telephone interview. In addition, the outcome data of patients lost to follow-up were collected from the National Death Records. All clinical events, such as death and re-hospitalization were monitored and verified by a Clinical Event Committee comprising independent experts in HF who did not participate in patient enrolment for the study.[11] The outcomes were 60-day all-cause mortality, re-hospitalization because of aggravated HF, and composite endpoint of mortality or HF hospitalization.

Statistical analysis

Statistical analyses were conducted by the Center of Biomedical Data Science, Yonsei University, Wonju College of Medicine. Continuous variables are expressed as mean ± SD and categorical variables as percentages. For continuous variables, the independent t-test was used, and for dichotomous variables, the χ^2 test was adopted, as appropriate. The Kaplan-Meier method was used to report survival curves and estimate the mean survival, and the 95% confidence interval (CI) and the log rank test were applied. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and their 95% CIs. Models were adjusted for gender; age; history of hypertension, diabetes mellitus, ischemic heart disease, and chronic obstructive pulmonary disease; New York Heart Association functional class; systolic blood pressure; heart rate; creatinine; presence of atrial fibrillation at admission; and LVEF. Model discrimination was assessed using Harrell's C-statistic. In all cases, a *P* value < 0.05 was considered statistically significant. Statistical analyses were performed using SAS 9.4 (SAS Inc., Cary, NC, USA) and R software version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

Ethics statement

The study protocol was approved by the ethics committee at each hospital and the Wonju Christian Hospital, Wonju College of Medicine, Yonsei University (Wonju, Korea; Approval No. CR311003), and written informed consent was obtained from each patient or their relative or legal representative.

RESULTS

Baseline characteristics of the study population and clinical outcomes

Of 5,625 patients, we selected patients with LVSD, which was defined as LVEF < 40% using echocardiography. After excluding 272 patients without quantitative LVEF data and 83 heart transplantation candidates, 2,769 patients were analyzed (**Fig. 1**). Patients were classified by the attending physician according to the contemporary guidelines on AHF, based on the clinical presentation at admission. ADCHF was defined as worsening of HF in patients with a previous diagnosis or hospitalization for HF. *De novo* AHF, defined as AHF in patients with no prior history of HF[14] included 1,417 patients. There were 1,352 patients with ADCHF. Demographic characteristics were significantly different between the 2 groups. Patients with ADCHF were older and had lower body weight, blood pressure, and heart rate than did patients with *de novo* AHF. ADCHF patients had higher rates of comorbid disease. Electrocardiographically, atrial fibrillation and left bundle branch block were more prevalent in ADCHF. At admission, sodium and hemoglobin levels were lower and creatinine and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were higher in patients with ADCHF. On echocardiography, patients with ADCHF had a more deteriorated heart function (**Table 1**). In patients with ADCHF, 60-day rehospitalization (14.3% vs. 6.8%; $P < 0.001$), mortality (8.2% vs. 5.9%; $P = 0.02$), and composite endpoint (20.6% vs. 11.8%; $P < 0.001$) rates were higher compared with those in patients with *de novo* HF (**Supplementary Table 1**).

Discharge medication and guideline adherence

Compliance rates for performance measures ranged from high for ACEI or ARB (84.5%) to low for β-blocker (64.5%) and MRA therapy (58.1%) in patients with *de novo* AHF. Compliance with ACEI or ARB (75.2%), β-blocker (52.9%), and MRA (56.1%) decreased in patients with
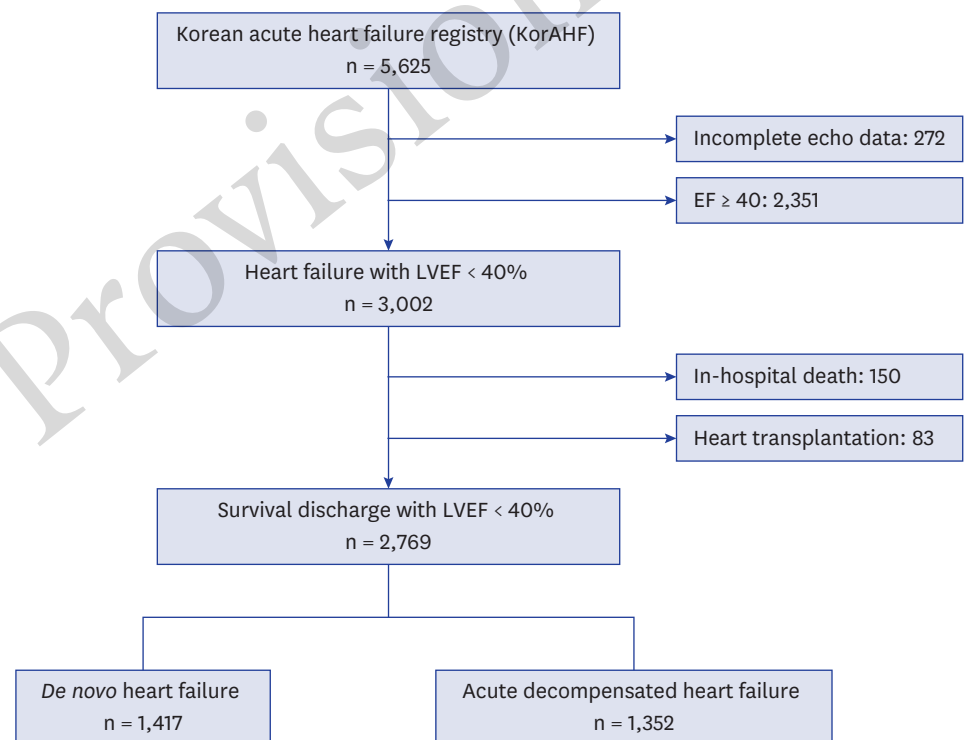
Fig. 1. Flow diagram of patients included.
LVEF = left ventricular ejection fraction.

Table 1. Baseline characteristics of the study population

Characteristics	*De novo* AHF (n = 1,417)	ADCHF (n = 1,352)	*P* value
Demographic characteristic at admission			
Gender, men	873 (61.6)	816 (60.4)	0.50
Age, yr	63.9 ± 15.6	69.0 ± 13.2	< 0.001
Height, cm	162.6 ± 9.2	161.2 ± 9.3	< 0.001
Weight, cm	62.5 ± 14.1	59.9 ± 12.6	< 0.001
Body mass index, kg/m²	23.5 ± 4.0	22.9 ± 3.7	< 0.001
Systolic blood pressure, mmHg	133.9 ± 30.1	125.7 ± 28.2	< 0.001
Diastolic blood pressure, mmHg	83.9 ± 20.0	76.8 ± 17.1	< 0.001
Heart rate, beat/min	99.3 ± 25.1	92.5 ± 24.5	< 0.001
NYHA functional class			0.13
Class II	206 (14.5)	182 (13.5)	
Class III	503 (35.5)	530 (39.2)	
Class IV	708 (50.0)	640 (47.3)	
Comorbidity			
Hypertension	725 (51.2)	817 (60.4)	< 0.001
Diabetes mellitus	460 (32.5)	566 (41.9)	< 0.001
Ischemic heart disease	227 (16.0)	604 (44.7)	< 0.001
Chronic kidney disease	137 (9.7)	271 (20.0)	< 0.001
Chronic obstructive pulmonary disease	123 (9.0)	165 (12.2)	0.01
Medication at admission			
ACEI	96 (26.0)	273 (74.0)	< 0.001
ARB	243 (17.0)	494 (36.5)	< 0.001
β-blocker	188 (13.3)	561 (41.5)	< 0.001
MRA	110 (7.8)	437 (32.3)	< 0.001
Etiology of heart failure			< 0.001
Ischemic heart disease	538 (38.0)	598 (44.2)	
Valvular heart disease	63 (4.4)	137 (10.1)	
Cardiomyopathy	447 (31.5)	402 (29.7)	
ECG characteristics at admission			
Atrial fibrillation at admission	362 (25.5)	454 (33.6)	< 0.001
Left bundle branch block	90 (6.4)	128 (9.5)	< 0.001
Right bundle branch block	64 (4.5)	93 (6.9)	0.01
Laboratory characteristics at admission			
Na, mmol/L	138.2 ± 4.2	136.9 ± 4.8	< 0.001
K, mmol/L	4.3 ± 0.7	4.5 ± 0.7	< 0.001
Albumin, g/dL	3.7 ± 0.5	3.7 ± 0.5	0.91
Hemoglobin, g/dL	13.1 ± 2.4	12.4 ± 2.2	< 0.001
Creatinine, mg/dL	1.4 ± 1.6	1.6 ± 1.6	< 0.001
hs-CRP, mg/dL	2.1 ± 3.5	2.1 ± 4.1	0.96
NT-proBNP, pg/mL	9,308.9 ± 11,845.1	11,506.2 ± 11,171.0	< 0.001
BNP, pg/mL	1,597.9 ± 1,466.3	1,636.0 ± 1,381.7	0.67
CK-MB, ng/mL	9.4 ± 27.8	5.2 ± 12.0	< 0.001
Troponin I, mg/mL	3.2 ± 22.2	0.6 ± 2.8	< 0.001
Echocardiographic characteristics			
LVEF, %	27.3 ± 7.9	26.2 ± 7.9	< 0.001
LVEDV, mL	166.5 ± 68.2	188.0 ± 76.5	< 0.001
LVESV, mL	119.6 ± 55.6	138.2 ± 64.1	< 0.001
LA dimension, mm	46.1 ± 8.0	49.9 ± 9.2	< 0.001

Values are presented as number (%) or mean ± standard deviation, unless otherwise indicated.
AHF = acute heart failure, ADCHF = acutely decompensated chronic heart failure, NYHA = New York Heart Association, ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin-receptor II blocker, MRA = mineralocorticoid receptor antagonists, ECG = electrocardiography, hs-CRP = high-sensitivity C-reactive protein, NT-proBNP = N-terminal-proBNP, BNP = B-type natriuretic peptide, CK-MB = creatinine kinase-MB, LVEF = left ventricular ejection fraction, LVEDV = left ventricular end diastolic volume, LVESV = left ventricular end systolic volume, LA = left atrium.

ADCHF (**Supplementary Table 2**). With regard to medication at discharge, the calculated equivalent doses for ACEI, ARB, β-blockers, and MRA were compared, and they did not differ between the 2 groups (**Table 2**).

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