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Effect of High-Dose Statin Loading on Biomarkers Related to Inflammation and Renal Injury in Patients Hospitalized With Acute Heart Failure

– Randomized, Controlled, Open-Label, Prospective Pilot Study –

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Background: High-dose statin loading is known to reduce periprocedural myocardial infarction and contrast-induced acute kidney injury in patients undergoing percutaneous coronary intervention. However, the clinical role of high-dose statin loading in patients with acute heart failure (AHF) remains unknown.

Methods and Results: In a prospective, single-center, randomized, controlled, open-label pilot study, patients hospitalized with AHF were randomly assigned to receive oral high-dose atorvastatin loading (80 mg for 3 days, followed by 10 mg/day until discharge) or no statin therapy, on top of optimal HF treatment. The primary outcome measures were changes to the level of biomarkers related to inflammation and renal injury from admission to hospital day 4. No significant changes in the levels of NT-proBNP (–2,627±4,956 vs. –2,981±6,951 pg/ml, P=0.845), hsCRP (–6.1±16.4 vs. –2.1±16.2 mg/L, P=0.105), cystatin C (0.002±0.185 vs. 0.009±0.216 mg/L, P=0.904), ACR (–886.3±1,984.9 vs. –165.6±825.2 mg/day, P=0.124) were observed in either group. In-hospital mortality (4.3% vs. 3.8%, P>0.999) and all-cause mortality at 90 days (4.3% vs. 3.8%, P>0.999) were not significantly different between groups.

Conclusions: This pilot study showed that oral high-dose atorvastatin loading may be used safely in patients with AHF, but is not effective in reducing the levels of circulating biomarkers related to inflammation and renal injury during hospitalization. (*Circ J* 2014; **78:** 2447–2454)

Key Words: Acute decompensated heart failure; Biomarkers; Statins

Effective and safe decongestion is a primary therapeutic goal in patients hospitalized with acute heart failure (AHF). Adjuvant therapies that enhance decongestion without worsening renal function (WRF) during hospitalization play a key role in the prognosis of AHF patients.[1,2] Numerous clinical studies, such as the Diuretic Optimization Strategies Evaluation (DOSE),[3] the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF)[4] and the Renal Optimization Strategies Evaluation (ROSE),[5] were designed to investigate the optimal decongestive therapy that did not result in WRF in AHF patients.

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High-dose statin loading has been clearly demonstrated to reduce periprocedural myocardial injury in elective percutaneous coronary intervention (PCI).[6–10] Subsequent meta-analysis showed that high-dose statin pretreatment leads to a significant reduction in both periprocedural myocardial infarction (MI) and 30-day adverse events in patients undergoing PCI.[11,12] Recently, it was demonstrated that on-admission high-dose statin loading in patients with acute coronary syndrome (ACS) scheduled for early invasive procedure could prevent contrast-induced acute kidney injury (CI-AKI) and improve short-term clinical outcomes.[13] In addition to arterial inflammation, high-dose statin therapy is lately known to reduce extra-arterial inflammation such as periodontitis.[14] These findings suggested that the early use of high-dose statin loading was associated with anti-inflammatory, anti-thrombotic, and reno-protective effects, resulting in improvement of clinical outcomes. Accordingly, we speculated that on-admission high-dose statin loading may reduce inflammation and renal injury in AHF patients. Even though rosuvastatin 10 mg administration did not reduce all-cause mortality in chronic systolic HF patients,[15] there has

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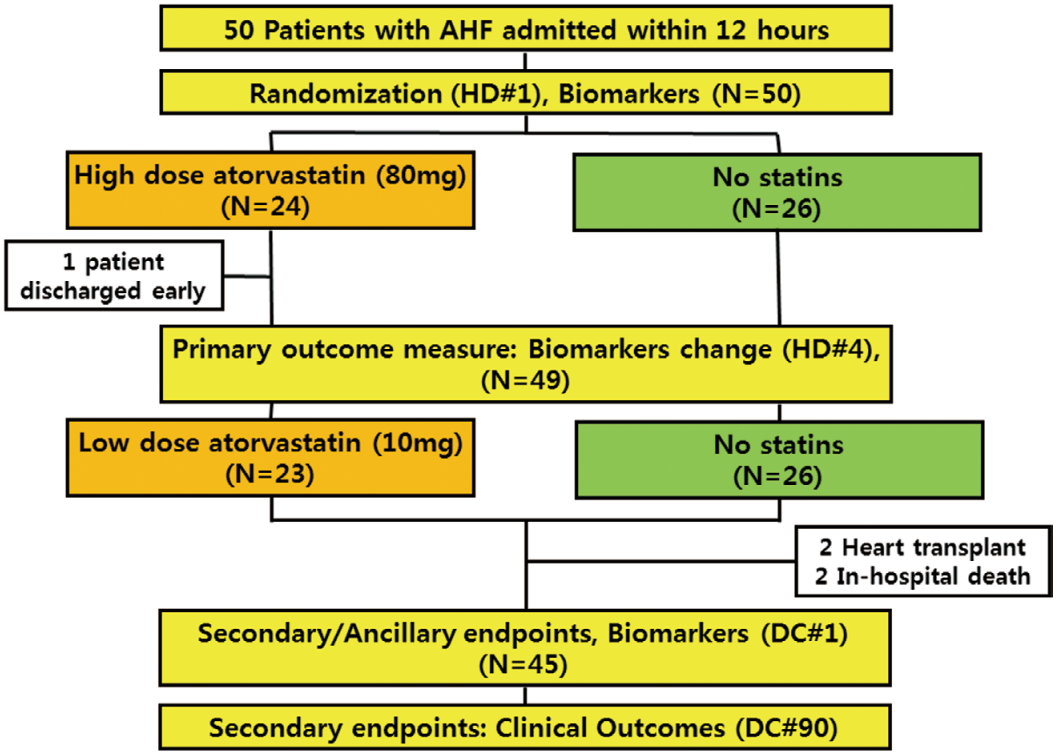

Figure 1. Dataset for the study population. AHF, acute heart failure; HD, hospital day after admission; DC, discharge day.

not been a clinical study of statin therapy in patients with AHF to date.

In the YACHT-LOAD (Yonsei ACute HearT failure - LOADing high dose statin) study, we set out to investigate the effect of high-dose statin loading on surrogate biomarkers related to inflammation and renal injury and also its effects short-term clinical outcomes. To the best of our knowledge, the present study is the first to show the effect of high-dose statin loading in AHF patients.

Methods

Study Population

The YACHT-LOAD trial was a prospective, single-center, randomized, controlled, open-label pilot study. Hospitalized patients with a primary diagnosis of AHF (dyspnea at rest, tachypnea; respiratory rate >20 breaths/min, rales, or pulmonary edema on chest X-ray) according to the current HF guideline[1] were eligible for participation. Exclusion criteria were as follows: ACS diagnosis, hospitalization plan for PCI, coronary artery bypass graft surgery, cardiogenic shock (systolic blood pressure [SBP] <80 mmHg), uncontrolled hypertension (SBP >180 mmHg), allergy, adverse drug reaction, hypersensitivity to statins, troponin >5-fold the upper limit of normal (ULN), creatinine kinase (CK)-MB level >3-fold ULN, aspartate aminotransferase/alanine aminotransferase (ALT) >3-fold ULN or acute hepatitis, current or past history of muscle disease, rhabdomyolysis, life expectancy <6 months (eg, metastatic malignancy, liver cirrhosis), pregnancy, or women of childbearing age.

Patients were screened and randomized between May 2010 and October 2013, and the final patient completed the study in January 2014. All study participants provided written informed consent using documents approved by the Institutional Review of Board at Severance Hospital, Yonsei University College of Medicine (4-2010-0014) (Clinical trial registration; URL: http://www.clinicaltrials.gov, Unique identifier: NCT01127945).

Study Protocol

The study design is presented in Figure 1. After completion of baseline testing in the emergency room (ER), patients were randomly allocated to receive either oral high-dose statin loading (atorvastatin, 80 mg for 3 days, followed by 10 mg/day until discharge, n=24, statin loading group) or no statin loading (n=26, control group) within 12 h of arrival at the ER. A total of 50 AHF patients were enrolled and underwent guideline-recommended optimal HF treatment according to each physician's decision unless contraindicated. One patient with insufficient laboratory data at hospital day 4 (HD4), because of unanticipated early discharge, dropped out of the statin-loading group. During hospitalization, 2 patients underwent heart transplantation, and 2 cases of in-hospital death occurred. Therefore, a total 45 patients (20 in the statin-loading group, 25 in the control group) survived hospitalization and had clinical follow-up after discharge.

The primary outcome measures were the changes in the circulating levels of biomarkers such as N-terminal-pro B-type natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hsCRP), serum creatinine, cystatin C, and the albumin creatinine ratio (ACR) from admission to HD4. The secondary outcome measures were hospital stay, in-hospital death, incidence of WRF (indicated as an increase in serum creatinine at

Table 1. Baseline Characteristics of the Study Population of Patients Hospitalized With Acute HF

	Statin loading (n=23)	Control (n=26)	P value
Clinical			
Male sex, n (%)	11 (47.8)	11 (42.3)	0.778
Age, years	68±10	70±13	0.566
BMI, kg/m^2	22.9±2.4	22.7±4.2	0.816
NYHA III/IV, %	43.5/56.5	30.8/69.2	0.390
Ischemic origin of HF, n (%)	10 (43.5)	8 (30.8)	0.390
HF admission history, n (%)	15 (65.2)	14 (53.8)	0.562
Diabetes, n (%)	12 (52.2)	9 (34.6)	0.257
Hypertension, n (%)	14 (60.9)	11 (42.3)	0.256
Hypercholesterolemia, n (%)	2 (8.7)	4 (15.4)	0.671
Atrial fibrillation, n (%)	6 (26.1)	10 (38.5)	0.382
SBP, mmHg	124±36	121±27	0.772
Heart rate, beats/min	84±21	91±23	0.309
Laboratory			
Hemoglobin, g/dl	12.1±2.4	12.5±2.1	0.538
Glucose, mg/dl	185±104	137±51	0.055
eGFR, ml·min^{-1}·1.73 m^{-2}	48.3±25.7	52.7±26.8	0.565
Sodium, mmol/L	137.4±5.0	137.0±5.5	0.817
hsTnT	0.085±0.093	0.046±0.041	0.075
Echocardiographic			
LVEF, %	35.0±15.5	35.4±17.7	0.936
LVEDD, mm	62.7±8.8	59.8±10.3	0.316
LAVI, ml/1.73 m^2	58.8±39.6	66.9±30.6	0.435
E/E'	24.9±9.8	30.8±13.8	0.130
Medications before hospitalization			
ACE inhibitors/ARBs, n (%)	11 (47.8)	16 (61.5)	0.396
β-blockers, n (%)	5 (21.7)	8 (30.8)	0.220
Spironolactone, n (%)	9 (39.1)	16 (61.5)	0.156
Furosemide, n (%)	14 (60.9)	20 (76.9)	0.352
Statin, n (%)	9 (39.1)	6 (23.1)	0.352
Aspirin, n (%)	11 (47.8)	14 (53.8)	0.778
Warfarin, n (%)	4 (17.4)	8 (30.8)	0.333

Values are mean±SD or n (%).
P-value indicates comparison of statin-loading group vs. control group by t-test, chi-square test.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; E/E', early mitral inflow velocity to early diastolic mitral annular velocity ratio; HF, heart failure; hsTnT, high-sensitivity troponin T; eGFR, estimated glomerular filtration ratio; NYHA, New York Heart Association functional class; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LAVI, left atrium volume index; SBP, systolic blood pressure; SD, standard deviation.

any time during hospitalization >0.3 mg/dl), all-cause mortality, cardiovascular (CV) mortality, and rehospitalization because of HF exacerbation during follow-up (until 90 days after discharge). The ancillary endpoint was assessment of the safety of high-dose statin loading in the setting of AHF (eg, elevated levels of liver enzymes and CK). Clinical outcomes data were collected by a review of the medical records and from telephone interview conducted at the end of the study. Research coordinators guided by documented definitions used standardized reporting forms to collect the follow-up events. The medical records were reviewed whenever possible when patients required repeat hospitalization. In addition to patients' telephone interviews, the referring physicians and institutions were contacted when necessary for additional information.

Statistical Analysis

No formal sample size calculation was performed because there are no previous reports on the effects of high-dose statin loading in patients with AHF. Therefore, we designed this pilot study (25 in statin-loading group vs. 25 in control group) without a sample size calculation. Considering the mean and standard deviation from our study, we could calculate the required sample size for future trials to provide 90% power to detect a treatment difference between the statin-loading and control groups using a 2-sided and 0.025 level of significance. Continuous variables are reported as mean±standard deviation, or median and interquartile range (IQR) for non-normally distributed variables (eg, NT-proBNP, hsCRP, cystatin C). Categorical variables are reported as numbers or percentages. We estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease formula:

$$170\times(\mathrm{SCr})^{-0.999}\times(\mathrm{age})^{-0.176}\times(\mathrm{BUN})^{-0.170}\times(\mathrm{albumin})^{0.318}\times 0.762\ (\text{if female}),$$

where SCr is serum creatinine in mg/dl and BUN is blood urea nitrogen.[16,17] Differences in baseline characteristics between

Table 2. Laboratory Parameters and Primary Outcome Measures of the Study Population of Patients Hospitalized With Acute HF

Variable	Statin loading (n=23)			Control (n=26)			P$ for Δstatin vs. Δcontrol
	Admission	HD4	P value*	Admission	HD4	P value*	
TC (mg/dl)	151±40	132±32#	0.001	159±28	152±27	0.046	0.016
LDL-C (mg/dl)	94±31	73±28#	0.003	101±25	93±24	0.070	0.053
HDL-C (mg/dl)	35±9	38±12	0.068	39±12	37±11	0.517	0.092
ALT (IU/L)	28±23	21±15	0.003	33±26	51±103	0.360	0.227
CK (IU/L)	161±149	99±97	0.007	118±78	95±66	0.111	0.106
NT-proBNP (pg/ml)	8,266 (2,647–35,000)	3,831 (1,789–12,163)	0.002	10,325 (4,153–14,408)	4,544 (1,308–12,528)	0.005	0.845
hsCRP (mg/L)	14.0 (3.8–22.4)	10.3 (3.1–25.8)	0.085	5.0 (3.1–25.6)	6.3 (3.7–26.1)	0.910	0.105
BUN (mg/dl)	30.1±17.2	27.0±20.0	0.086	28.7±15.0	24.0±15.7	0.268	0.564
Creatinine (mg/dl)	1.83±1.26	1.86±1.60	0.836	1.54±0.95	1.41±0.97	0.038	0.197
eGFR (ml·min^{-1}·1.73m^{-2})	48.3±25.7	54.5±31.0	0.014	52.7±26.8	58.0±25.5	0.063	0.652
Cystatin C (mg/L)	1.23 (1.13–2.32)	1.25 (1.08–1.85)	0.171	1.39 (1.14–1.73)	1.42 (1.12–1.62)	0.964	0.904
ACR (mg/day)	206 (32–2,024)	56 (19–1,155)	0.002	188 (60–538)	148 (41–515)	0.028	0.124

Values are mean±SD or median (interquartile range).
*Comparison of admission vs. HD4 by paired t-test, Wilcoxon signed-rank test; $effect of statin loading from generalized linear model; #P<0.05 comparison of statin-loading group vs. control group by t-test, Mann-Whitney U-test.
ACR, urine albumin creatinine ratio; ALT, alanine aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; HD, hospital day after admission; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal-pro B-type natriuretic peptide; TC, total cholesterol. Other abbreviations as in Table 1.

groups were evaluated by chi-square, unpaired t-tests, or the Mann-Whitney U-test for non-normally distributed variables. Within-group changes in the reported variables were evaluated by paired t-test or the Wilcoxon signed-rank test for non-normally distributed variables.

A general linear model (GLM) was used to examine the effect of high-dose statin loading on each primary outcome measure. Kaplan-Meier survival analysis was used to estimate event-free survival, and log-rank tests were used to compare the clinical outcomes in patients with and without high-dose statin loading therapy. A 2-tailed P-value <0.05 was considered significant. All analyses were performed with commercially available statistical analysis packages (SPSS ver. 21.0; SPSS/IBM Corp, Chicago, IL, USA and STATA ver. 12.0; Stata Corp LP, College Station, TX, USA).

Results

Baseline Characteristics

The baseline clinical, laboratory, and echocardiographic parameters of the study population (n=49) are presented in Table 1. The mean age was 69 years and the percentage of men was 44.9%. The percentage of patients graded as New York Heart Association functional classification (NYHA) IV was 63.3%, and 36.7% of the patients had HF of an ischemic origin. The mean left ventricular ejection fraction (LVEF) on echocardiography was 35.2%, and 20.4% of patients were diagnosed with HF with preserved LVEF (HFPEF, LVEF >45%). Atrial fibrillation was present in 32.7% of the patients. The most common comorbid condition was hypertension (51.0%), and 59.2% of the patients had a previous admission history for HF. There were no significant differences between groups in clinical, laboratory, echocardiographic parameters, or medications before hospitalization.

Effect on Changes in Biomarker Levels Between Admission and HD4

The primary outcome measures of the present study (changes in the levels of biomarkers such as NT-proBNP, hsCRP, BUN, creatinine, eGFR, cystatin C, and ACR from admission to HD4) are summarized in Table 2. On admission, no significant differences in biomarkers between the statin-loading and control groups were observed (eg, P=0.509 for hsCRP, P=0.984 for ACR). In the statin-loading group, levels of total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, ALT, CK, and NT-proBNP, as well as the ACR, significantly decreased, while eGFR significantly increased by HD4. Only TC, NT-proBNP, creatinine and ACR significantly decreased in the control group by HD4. There were no significant changes in cystatin C levels in either group during this period.

When we compared the changes in these biomarkers between groups using GLM analysis, only TC (−19.0±23.4 vs. −5.3±11.9 mg/L for control, P=0.016) was statistically different. LDL cholesterol (−16.0±20.1 vs. −5.3±11.9 mg/L for control, P=0.053), high-density lipoprotein (HDL) cholesterol (2.3±5.4 vs. −1.0±6.6 mg/L for control, P=0.092), hsCRP (−6.1±16.4 vs. 2.1±16.2 mg/L for control, P=0.105, Figure 2A), and ACR (−886.3±1984.9 vs. −165.6±825.2 mg/day for control, P=0.124, Figure 2B) were quantitatively different between the 2 groups, but none reached statistical significance. In the subgroup analysis (eg, ischemic vs. non-ischemic HF, HF with reduced EF, HFREF vs. HFPEF, statin-naïve vs. already statin-taking), we could not find any significant differences in biomarkers between groups excepting hsCRP (P=0.053 for HFREF) and ACR (P=0.041 for non-ischemic HF, P=0.054 for statin-naïve) (other data not shown).

Secondary Outcome Measures and Safety of High-Dose Statin Loading

The average length of hospital stay (median 8, IQR 5–10 vs. median 8 days, IQR 6–12 days for control, P=0.522) and the

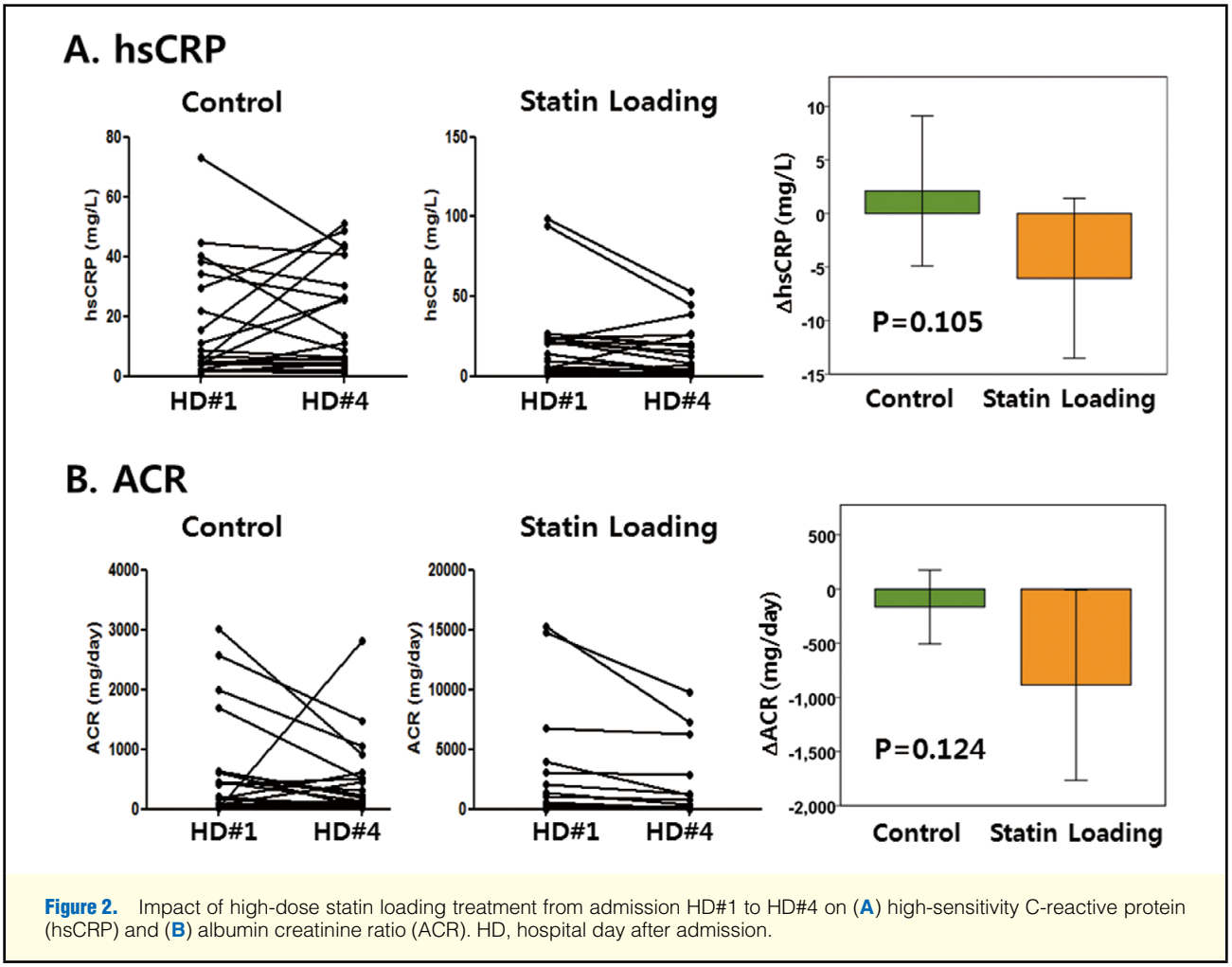

Figure 2. Impact of high-dose statin loading treatment from admission HD#1 to HD#4 on (**A**) high-sensitivity C-reactive protein (hsCRP) and (**B**) albumin creatinine ratio (ACR). HD, hospital day after admission.

in-hospital death rate (4.3% vs. 3.8% for control, P>0.999) were not significantly different between the 2 groups. The occurrence of WRF was not significantly different between groups (17.4% vs. 7.7%, P=0.400). For 90 days after discharge, all-cause mortality, CV mortality, rehospitalization for HF aggravation, and non-CV mortality were not significantly different between groups (**Table 3**). In the statin-loading group, the major side effects of statin therapy, such as elevation of ALT or CK, were not seen during the study period (**Table 2**). There were no cases of rhabdomyolysis in the present study.

Discussion

The principal finding of this study is that high-dose atorvastatin loading is safe, but not effective for reducing surrogate biomarkers related to inflammation and renal injury from admission to HD4 in patients hospitalized for AHF.

Statins are one of the most widely prescribed drugs in the world.[18] The recently published 2013 ACC/AHA guidelines recommend a wider administration of statins to help reduce atherosclerotic CV risk in adults.[19] Statins are pleiotropic and have beneficial pharmacological effects that include well-known lipid-lowering power and also anti-inflammatory, anti-oxidative, anti-thrombotic and reno-protective effects.[20,21] The beneficial effects of high-dose statin loading is mainly assumed to result from these pleiotropic effects. Many studies and their meta-analyses have shown that high-dose statin loading prior to PCI is associated with a reduction in periprocedural MI and favorable short-term clinical outcomes in patients with non-ST-elevation ACS.[7–10,12] Recently, high-dose statin loading in ACS patients who underwent an early invasive procedure was shown to prevent CI-AKI and improve short-term clinical outcomes.[13] Similarly, recent data indicates that 5-day administration of a statin can reduce CI-AKI in patients with diabetes and chronic kidney disease (CKD).[22] However, until the current study, there has not been a report concerning the clinical role of high-dose statin loading in AHF.

According to an updated meta-analysis, CKD and WRF are prevalent and associated with a strongly increased mortality risk across all HF subgroups.[23] For this reason, numerous ongoing research programs are focused on adjuvant therapies that enhance decongestion without WRF during hospitalization. The reno-protective effect of statins has been investigated. In terms of GFR, some studies have reported that statin therapy showed an upward trend in eGFR,[24] while others report no change in eGFR.[25] According to a post-hoc analysis from the JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial, the reduction in eGFR was less in the rosuvastatin group compared with the placebo group in a longitudinal assessment.[26] A recent meta-analysis showed that both rosuvastatin and atorvastatin could improve GFR.[27] In addition, 2 recent studies demonstrated a

Table 3. Clinical and Secondary Outcome Measures for Each Group Comparison of the Study Population of Patients Hospitalized With Acute HF

	Statin loading (n=23)	Control (n=26)	P value
Clinical (HD4)			
SBP, mmHg	116±19	109±17	0.157
Heart rate, beats/min	79±12	82±16	0.517
Decongestion (HD4)			
Body weight change, kg	–3.4±10.4	–2.1±8.1	0.624
Required furosemide IV dose, mg	98±177	72±77	0.508
Required furosemide PO dose, mg	106±93	132±91	0.337
Urine output, L	6.45±2.71	6.53±2.95	0.921
Discharge medications			
ACE inhibitors/ARBs, n (%)	15 (75.0)	19 (76.0)	>0.999
β-blockers, n (%)	5 (25.0)	9 (36.0)	0.525
Spironolactone, n (%)	15 (75.0)	20 (80.0)	0.731
Statin, n (%)	17 (85.0)	6 (24.0)	0.001
Clinical outcomes			
WRF during admission, n (%)	4 (17.4)	2 (7.7)	0.400
In-hospital mortality, n (%)	1 (4.3)	1 (3.8)	>0.999
Heart transplantation, n (%)	2 (8.7)	0	0.215
Hospital stay, days	8 (5–10)	8 (6–12)	0.522
All-cause mortality at 90 days, n (%)	1 (4.3)	1 (3.8)	>0.999
CV mortality at 90 days, n (%)	1 (4.3)	1 (3.8)	>0.999
HF rehospitalization at 90 days, n (%)	3 (13.0)	4 (15.3)	>0.999
Non-CV rehospitalization at 90 days, n (%)	0	0	>0.999

Values are mean±SD or n (%) or median (interquartile range).
P-value indicates comparison of statin loading group vs. control group by t-test, chi-square test.
CV, cardiovascular; WRF, worsening renal function. Other abbreviations as in Tables 1,2.

reno-protective effect of statins on CI-AKI in a randomized clinical trial setting.[13,22] Conversely, other reports showed that statins, especially in high doses, could be related to adverse renal events.[28,29] In our study, we found a significant increase in eGFR in the statin loading group. However, we found no significant differences in the change of cystatin C between the stain-loading and control groups, an important renal biomarker that was a primary endpoint parameter of the recent ROSE study.[5] We also observed no differences in the occurrence of WRF between the 2 groups. At the very minimum, our data suggest that high-dose atorvastatin loading is not related to renal injury in patients with AHF.

Two meta-analyses regarding the effects of statins on albuminuria reported that statins may reduce pathologic albuminuria and proteinuria.[27,30] In particular, Wu et al reported atorvastatin as more effective in reducing proteinuria than rosuvastatin.[27] In chronic HF, large clinical studies have shown ACR to be a prognostic marker.[31,32] In AHF, Koyama et al recently showed that ACR was often increased at admission and decreased significantly within 7 days of treatment. Furthermore, this change in ACR correlated with serum NT-proBNP and bilirubin concentrations but not with eGFR.[33] From our data, we can confirm that ACR was decreased from the point of admission to HD4 in the overall study group. These lines of evidence suggest that ACR could be a multi-pathophysiologic biomarker beyond just a renal marker. However, although ACR tended to be decreased in the statin-loading group compared with control, the data failed to research significance, likely because of the small population. Decreased ACR during hospitalization may be related to better clinical outcomes in AHF. In the sample size calculation from our data, a total of 111 patients would be needed to prove the different effects of statin-loading on ACR. Further prospective clinical trials are warranted to assess this interesting finding.

In the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial, rosuvastatin was safe but did not reduce all-cause mortality in older patients with systolic HF.[15] Through post-hoc analysis from the CORONA study, the investigators identified a subgroup who benefitted from statin therapy by using biomarker such as NT-proBNP (<868 pg/ml) and hsCRP (≥2.0 mg/L).[34,35] In theory then, biomarker-guided statin therapy could be beneficial in HF. In a post-hoc analysis of RELAX-AHF (Relaxin in Acute Heart Failure),[36] changes in biomarkers (eg, NT-proBNP, cystatin C) during admission was associated with 180-day mortality.[37] Recent important clinical trials such as DOSE, CARRESS-HF, and ROSE also used changes in biomarker levels 72 h after admission as endpoints.[3–5] Considering these lines of evidence, we also explored changes in the levels of biomarkers from admission to HD4 during hospitalization as a surrogate for AHF and as a primary outcome measure of our study. Unfortunately, we could find no significant effects of statin loading on the changes in biomarker levels (eg, NT-proBNP). However, it should be noted that hsCRP tended to decrease more in the statin-loading group than in the control group (**Table 2**, **Figure 2A**).

Study Limitations

First, the positive trend in the changes in hsCRP and ACR (especially in the subgroup analysis) should be interpreted cautiously because our study was underpowered to demonstrate differences between the statin-loading and control groups because of the limited sample size. Our findings are not conclusive, but they do allow us to generate hypotheses. Considering the lack of previous studies to calculate sample size, this study

could help future investigations to accurately estimate sample size and to effectively design a prospectively study. Second, the lack of clinical events did not allow us to do a proper survival analysis and draw any conclusions, although we demonstrated clinical outcomes as secondary outcome measures. Further clinical studies are warranted to prove the clinical safety and efficacy of high-dose statin loading therapy in AHF. Third, other unidentified confounding variables such as other medications that can reduce inflammation and β-blocker use at discharge might have influenced outcomes during hospitalization and the post-discharge period. Fourth, we did not measure high-sensitivity troponins serially, which have been given much attention as important biomarkers in HF.[38,39] Finally, we cannot be sure that the statin dosing regimen of this study was adequate to attain the pleiotropic effects of the statin, even though we observed the expected lipid-lowering effect by HD4.

Conclusions

Our pilot study showed that oral high-dose atorvastatin loading in patients with AHF was safe, but not effective for reducing surrogate biomarkers for AHF from admission to hospital day 4. Therefore, further larger clinical trials are required to prove the efficacy of high-dose statin loading in patients with AHF.

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Disclosures

None.

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