Synergistic Effect of Combined HMG-CoA Reductase Inhibitor and Angiotensin-II Receptor Blocker Therapy in Patients With Chronic Heart Failure
– The HF-COSTAR Trial –
Yasuhiro Maejima, MD, PhD; Kiyoshi Nobori, MD, PhD; Yuichi Ono, MD, PhD; Susumu Adachi, MD, PhD; Jun-ichi Suzuki, MD, PhD; Kenzo Hirao, MD, PhD; Mitsuaki Isebe, MD, PhD; Hiroshi Ito, MD, PhD; for the Heart Failure by Coadministration of Statin and Angiotensin-II Receptor Blocker (HF-COSTAR) Trial Investigators

**Background:** It is known that HMG-CoA reductase inhibitors (statins) may have a therapeutic benefit in patients with heart failure (HF). However, no studies have yet evaluated the possible interaction of statins and angiotensin-II receptor blockers (ARBs) on left ventricular (LV) function in patients with HF. We hypothesized that statins might alter the effect of ARBs on cardiac function in patients with HF.

**Methods and Results:** We prospectively randomized patients with chronic HF who received the ARB, losartan (LOS group), or the statin, simvastatin (SIM), in combination with LOS (SIM+LOS group) at our hospitals and assessed before and after treatment for 6 months. Although no significant improvement of HF symptoms as evaluated by the New York Heart Association (NYHA) classification was observed in the LOS group, HF symptoms in the SIM+LOS group significantly improved. The percent increase of LV ejection fraction after treatment in the SIM+LOS group was significantly larger than in the LOS group. Furthermore, the plasma brain natriuretic peptide level was significantly lower after treatment in the SIM+LOS group than in the LOS group.

**Conclusions:** Combined statin and ARB therapy significantly improves both symptoms and LV function over time in patients with HF. Thus, the combination of an ARB with a statin may be a useful therapeutic strategy for HF.

*Circ J 2011; 75: 589–595*

**Key Words:** Angiotensin; Heart failure; Pharmacology; Statin

Hydroxymethyl glutaryl coenzyme-A reductase inhibitors (statins) effectively reduce the low-density lipoprotein cholesterol level and therefore they are widely used to treat patients with hypercholesterolemia. However, increasing attention has focused on evidence that statins are not only effective for lowering cholesterol, but also have various other favorable actions.1,2 For example, statins reduce the levels of inflammatory factors, show an antithrombotic effect, may induce angiogenesis by recruiting bone marrow stem cells, and can improve endothelial function.3-5 Furthermore, it is known that statins can improve heart failure (HF). A subanalysis of the Scandinavian Simvastatin Survival Study, a large randomized, placebo-controlled clinical trial of simvastatin (SIM) therapy, led to the first report that statins are effective for treating chronic HF.6 This analysis showed that the prognosis of chronic ischemic HF patients receiving statin therapy was better compared with that of patients without statin therapy. In recent years, the results of a number of clinical trials have suggested that statins reduce the risk of mortality and hospitalization in patients with both ischemic and non-ischemic HF.7-9 Node et al reported that cardiac function of non-ischemic dilated cardiomyopathy (DCM) patients improved markedly for those undergoing SIM therapy in comparison to placebo control.10 They also found that...
plasma concentrations of inflammatory cytokines were lower for patients undergoing SIM therapy, suggesting that statins attenuate HF by suppressing inflammation.

**Editorial p540**

One of the most important physiologic factors involved in exacerbation of chronic HF is the renin-angiotensin-aldosterone system (RAAS). Angiotensin-receptor blockers (ARBs) potently suppress the RAAS, and several recent large-scale clinical trials have provided evidence that ARBs improve symptoms and decrease the mortality and morbidity of patients with HF.11–13 Furthermore, several recent studies have documented that ARBs not only block the RAAS system but also have pleiotropic effects, such as antiinflammatory and antifibrotic effects.14,15 Taken together, these findings suggested to us that the beneficial effect of statins and ARBs on HF partially overlap, and that combining these drugs may lead to a synergistic effect in the treatment of HF. However, there have been no studies evaluating the effects of combined statin and ARB therapy on HF. Accordingly, the present study was performed as a prospective randomized trial to investigate the hypothesis that combined treatment with a statin and an ARB is more effective than monotherapy in patients with chronic HF.

**Methods**

**Study Design**

This study was a prospective, randomized multicenter trial. The design features of HF-COSTAR have been registered on the www.umin.ac.jp/ctr website (Identifier: UMIN000000622). One of the investigators supervised the study by acting as a safety and data monitor.

**Subjects**

The study included 32 patients with HF and echocardiographic evidence of left ventricular (LV) systolic dysfunction (LV ejection fraction (LVEF) <40%), whose symptoms were stable in New York Heart Association (NYHA) functional classes I–III for 1 month before starting standard therapy for HF. NYHA classification was assessed by 1 investigator based on the patients’ reported functional limitation without knowledge of the laboratory results. Patients with severe HF requiring mechanical support (intraaortic balloon pumping, LV assist device, or cardiac resynchronization therapy) and patients requiring heart transplantation were excluded. Patients with acute coronary syndrome, stroke, chronic lung disease, liver dysfunction, chronic kidney disease (defined as a serum creatinine >3.0 mg/dl), peripheral vascular disease, or hypotension (defined as a systolic blood pressure <100 mmHg) were also excluded. The local ethics committee approved the study protocol and the study was

<table>
<thead>
<tr>
<th>Table 1. Patients’ Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan (n=16)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Prior diagnosis</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Combined drugs</td>
</tr>
<tr>
<td>β-blockers</td>
</tr>
<tr>
<td>Loop diuretics</td>
</tr>
<tr>
<td>Spironolactone</td>
</tr>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>Digoxin</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
</tbody>
</table>

Values are the mean±SEM, n=16 per group.

<table>
<thead>
<tr>
<th>Table 2. Comparison of Hemodynamics and Various Markers Before and After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan (n=16)</td>
</tr>
<tr>
<td>BP</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
</tr>
<tr>
<td>Biochemical markers</td>
</tr>
<tr>
<td>Total cholesterol</td>
</tr>
<tr>
<td>Creatinine</td>
</tr>
<tr>
<td>eGFR</td>
</tr>
<tr>
<td>Uric acid</td>
</tr>
<tr>
<td>Creatine kinase</td>
</tr>
<tr>
<td>GPT</td>
</tr>
<tr>
<td>Pottasium</td>
</tr>
<tr>
<td>Hemoglobin</td>
</tr>
<tr>
<td>hsCRP</td>
</tr>
<tr>
<td>Angiotensin II</td>
</tr>
<tr>
<td>Renin</td>
</tr>
<tr>
<td>Aldosterone</td>
</tr>
</tbody>
</table>

Values are mean±SEM, n=16 per group.

*P<0.05 vs. Baseline.
performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

**Study Protocol**

In the acute phase of HF, all patients were treated with standard therapy including intravenous vasodilators and diuretics. All patients received an oral ARB (losartan, LOS). Patients who had remained stable on oral medications alone for 6 months were randomly assigned to either LOS alone (LOS group; n=16) or combined LOS + SIM (SIM + LOS group; n=16). LOS was started at a dose of 25 mg/day in all patients, and the dose was increased to 50 mg/day at 6 months in the LOS group. In the SIM + LOS group, SIM was added at a dose of 5 mg/day at 6 months. All medications were then continued unchanged during the study. No patient received any other cholesterol-lowering agents, angiotensin-converting enzyme inhibitors, or other ARBs. Assessment was performed before and after treatment for 6 months.

**Echocardiography**

Echocardiography was performed in a blinded manner using standard methods by experienced, independent echocardiographers who had no knowledge of the study. The LV diastolic diameter (LVDd) and LV systolic diameter (LVDs) were measured, and then LVEF was calculated by using the modified method of Simpson. The percent change of LVEF was calculated as follows: post-LVEF – pre-LVEF / post-LVEF × 100.

**Biochemical Analyses**

Blood samples were collected into tubes containing disodium ethylenediaminetetraacetic acid after each patient had rested in the supine position for at least 30 min. Plasma was separated by centrifugation and frozen at −80°C. Then the plasma concentrations of various biochemical markers were measured with specific assays.

**Patient Power Calculation**

From previous reports, the estimated effect on EF was 7.0±3.0% in the LOS group and 9.8±3.0% in the SIM + LOS group (2.8% additive effect of SIM). To detect statistically significant differences with 80% power and with α=0.05, a total of 40 patients (20 patients per group) is required with 5% drop-out patients.

**Statistical Analysis**

All statistical analyses were performed with Prism for Macintosh software (Version 4; Graphpad Inc, San Diego, CA, USA). All values are reported as the mean±SEM. Comparison of baseline categorical data between 2 groups was done by the 1-sided contingency table method, and differences between continuous variables were evaluated with the unpaired t-test. Using the Wilcoxon matched pairs signed rank test, we assessed changes of NYHA functional class. In patients who underwent repeated assessment, changes from baseline were evaluated within each treatment group by the paired t-test and changes were compared between 2 groups using 2-way ANOVA. In all analyses, P<0.05 was considered statistically significant.

**Results**

**Clinical Characteristics**

There were no significant differences of age, gender, or cardiac medications between the 2 groups upon entry into the study. The cause of HF was idiopathic dilated cardiomyopathy (DCM) (n=23), ischemic cardiomyopathy (n=4), or other diseases (post-aortic valve replacement (n=2), post-mitral valve replacement (n=1), dilated phase hypertrophic cardiomyopathy (n=1), and post-myocarditis (n=1)). At baseline, the other medications (β-blockers, loop diuretics, spironolactone, amiodarone, digoxin, calcium channel blockers, and aspirin) were similar in both groups (Table 1). No patient was admitted for deterioration of HF, and no patient died of a cardiac event in either group.

**Comparison of Hemodynamics and Blood Examination Before and After Treatment**

After 6 months, the systolic blood pressure shared a significant decrease in both groups (LOS group: 133±3.7 vs. 122±3.4 mmHg; SIM + LOS group: 140±4.5 vs. 127±4.1 mmHg, respectively), and there was no significant difference between the 2 groups. The diastolic blood pressure did not decrease significantly in either group (LOS group: 76±2.2 vs. 73±2.9 mmHg; SIM + LOS group: 81±3.2 vs. 76±3.2 mmHg, respectively).
respectively). Moreover, the heart rate was not significantly different after 6 months in either group (LOS group: 76±3.7 vs. 70±2.3 beats/min; SIM+LOS group: 79±3.5 vs. 74±3 beats/min). Over the follow-up period, serum total cholesterol decreased significantly in the SIM+LOS group and creatine kinase increased significantly. There were no significant changes in other biochemical parameters, such as creatinine, estimated glomerular filtration rate, uric acid, glutamic-pyruvic transaminase, potassium, hemoglobin, high-sensitive C-reactive protein (hsCRP), angiotensin II, renin, and aldosterone levels, in either group (Table 2).

NYHA Functional Class Before and After Treatment
The NYHA functional class of the patients is shown in Figure 1. Patients from both groups showed improvement after 6 months of treatment relative to the baseline status. After 6 months, the NYHA functional class of the SIM+LOS group was significantly improved, but that of the LOS group was not significantly improved (SIM+LOS group; P<0.05, LOS group; NS).

Echocardiographic Findings Before and After Treatment
The LVEF data are shown in Figure 2. In both groups, LVEF was significantly greater after 6 months compared with the baseline value (Figures 2A,B). Although there were no significant differences between the 2 groups at baseline or after follow-up (Figure 2C), the percent change of LVEF was significantly larger in the SIM+LOS group than in the LOS group (Figure 2D, SIM+LOS group; P<0.05, LOS group; NS). LVDd and LVDs shared no significant differences between the 2 groups at either baseline or follow-up (data not shown).

Comparison of Brain Natriuretic Peptide (BNP) Levels Before and After Treatment
Plasma BNP concentrations are shown in Figure 3. In both
groups, the plasma BNP concentration was significantly lower after 6 months compared with the baseline value (LOS group, P<0.05; SIM+LOS group, P<0.05). However, the actual BNP of the SIM+LOS group was significantly lower than that of the LOS group after 6 months (P<0.05).

Discussion

The present study demonstrates that the addition of SIM to LOS therapy achieves superior improvement of symptoms and LV function than treatment with LOS alone in patients with HF. The combination of SIM and LOS decreased the plasma BNP level and improved cardiac function (percent change of LVEF) compared with LOS therapy alone. These effects were associated with improvement of symptoms (NYHA class), and suggest that statins may be useful for patients with HF in whom these medications may not be indicated for the treatment of dyslipidemia.

Although we did not address the mechanism by which combined therapy with a statin and an ARB improved LV function in this study, some of the improvement could be explained by the synergism between the additional effects of statins and ARB on HF. First, both ARBs and statins inhibit hypertrophy of cardiomyocytes. It is well known that ARBs inhibit cardiac hypertrophy by inhibiting the RAAS, and we have shown that statins prevent angiotensin II-induced cardiac hypertrophy via inhibition of cyclin D1 expression. Next, both ARBs and statins also inhibit activation of RhoA, a low-molecular-weight G protein, and its primary effector Rho kinase. Previous studies showed that stimulation by stretching activates RhoA in cardiomyocytes and that inhibition of Rho kinase suppresses stretch-induced cardiac hypertrophy. They also showed that Rho kinase plays an important role in angiotensin II-induced hypertrophy of cardiomyocytes. Furthermore, both ARBs and statins may modulate the remodeling process in HF patients through effects on matrix metalloproteinases (MMPs). Fibrosis of the myocardium leads to HF via induction of diastolic failure and cardiac remodeling. MMP-9 plays a central role in this pathologic process, and its activity is regulated by the RhoA/Rho kinase pathway. Thus, a strategy of synergistic treatment for the failing heart with the combination of SIM and LOS appears rational. We recently confirmed that the combination of SIM and LOS inhibits Rho kinase and MMP-9 activity more strongly and has a greater cardioprotective effect compared with LOS alone in Dahl salt-sensitive rats (unpublished data). To our knowledge, this is the first report regarding a synergistic effect of combined statin and ARB therapy in patients with HF compared with ARB monotherapy.

The plasma BNP level is a useful prognostic indicator in patients with HF, because BNP is a hormone produced by the LV. The plasma BNP level is correlated with LV mass, as well as with abnormalities of LV end-diastolic pressure and LVEF. Therefore, a decrease of plasma BNP during combined therapy with SIM and LOS may be due to improvement of LV remodeling, a decrease of LV filling pressure, or both. Treatment of CHF guided by the response of plasma BNP has been reported to reduce cardiovascular events, so a decrease of BNP may be associated with a better outcome, as was indicated by previous studies.

Statins have been shown to decrease the incidence of new onset HF. However, the benefit of statins in patients with chronic non-ischemic HF is controversial. The CORONA study, a randomized, double-blind, placebo-controlled clinical study, showed that treatment of HF patients with rosuvastatin did not have any beneficial effect on clinical outcomes. The result of the GISSI-HF trial also indicated that administration of rosuvastatin is not effective for the treatment of HF patients. Conversely, accumulated lines of evidence based on small- to medium-scale clinical trials suggest that statin treatment in HF patients improves cardiac function parameters such as LVEF and BNP levels. Furthermore, the CORONA study also showed beneficial effects of statin therapy for HF patients, including reduced hospitalization due to exacerbation of HF. It is possible that the effectiveness of statins for HF treatment may depend on their solubility. Rosuvastatin, which was used for both the CORONA study and the GISSI-HF trial, is water-soluble. On the other hand, the statins that indicated favorable effects for HF in some clinical studies, such as SIM, are fat-soluble. For the purpose of clarifying this issue, a large-scale clinical study that aims to evaluate the effect of pitavastatin, a fat-soluble statin, for HF patients (the PEARL study) is now underway. Alternatively, statins may have a beneficial effect when they used in combination for HF therapy, while the administration of statins alone may not improve the outcome of HF patients. Indeed, because most drugs used in HF therapy can cause lowered blood pressure, combination therapy for HF treatment has the potential risk of an exaggerated hypotensive response. In this regard, statins are favorable drugs as combined medicine to treat HF because statins have little influence on blood pressure.

Previous reports showed that the anti-HF effect of statins is closely related with their antiinflammatory actions. However, in this study, there was no significant decrease in hsCRP value following administration of SIM. To determine whether an antiinflammatory action of SIM is involved in the anti-HF effect observed in the combination therapy with LOS, it may be necessary to evaluate other inflammatory markers, such as TNF-α, IL-6, and PAI-1.

There are some limitations in this study. First, the ratio of the cause of HF observed in this study differed somewhat from that of epidemiological investigation-based data. Therefore, concern exists that our results may not apply directly to usual medical examination and treatment for HF patients. Second, it is possible that the predominance of LOS.
and SIM combined therapy against the monotherapy of LOS in patients with HF could simply be a supplemental effect of SIM compensating for the insufficient dose or effect of LOS for the treatment of HF. Currently, we can use 100 mg/day of LOS under strict blood pressure observation and several other ARBs are available. Future work should determine the effectiveness of increased dosage of LOS and/or other ARBs in combination with LOS for treatment of HF. Finally, the relatively small number of patients and examinations used to evaluate cardiac function (ie, LVEF, anaerobic threshold, and Mets number) included in our study were also limiting factors. Thus, we suppose that our findings require confirmation by large-scale randomized clinical trial.

Conclusion

The present findings suggest that combined statin and ARB therapy is more effective than ARB monotherapy for the treatment of HF. Although further investigations are still needed, this may be a novel therapeutic option for patients with chronic HF.

Acknowledgments

This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan, a Research Grant for Diseases from the Ministry of Health and Welfare of Japan, and a Grant from the Japan Cardiovascular Research Foundation.

References


**Appendix**

**HF-COSTAR Trial Investigators**

Yasuhiro Maejima, Kenzo Hirao and Mitsuaki Isobe at Department of Cardiovascular Medicine, Tokyo Medical and Dental University; Jun-ichi Suzuki at University of Tokyo; Susumu Adachi at Shuwa General Hospital; Toshihiko Takamoto at Souka Municipal Hospital; Eijirou Hattori at Hokushin General Hospital; Kenichi Nanba at Sanraku Hospital; Yuichi Ono at Oume Municipal General Hospital; Ken Kadowaki at Akita Seijinyou Medical Center; Toru Nakanishi at Yuri Kumiiai General Hospital; Gen Teru and Mitsuaki Katsuta at Akita Red-Cross Hospital; Yasushi Suzuki at Honjyou Daichi Hospital; Toshifumi Nemoto at Yokote Municipal Hospital; Kiyoshi Nohori, Masaru Ishida, Takashi Koyama and Hiroshi Ito at Second Department of Internal Medicine, Akita University.