Effects of Statins on Left Ventricular Diastolic Function in Patients with Dyslipidemia and Diastolic Dysfunction (Stat-LVDF Study)

Tatsuya Morimoto,*a,b,c Yasufumi Katanasaka,a,b,c Yoichi Sunagawa,a,b,c Sac Hirano,a,d Yusuke Miyazaki,a Masafumi Funamoto,a Yuya Hojo,a Hidetoshi Suzuki,a Eriko Morimoto,b Morio Ueno,c Akira Shimatsu,a Noriko Satoh-Asahara,f Hajime Yamakage,f Hiromichi Wada,c and Koji Hasegawa,c

*Division of Molecular Medicine, School of Pharmaceutical Sciences, University of Shizuoka; Shizuoka 422-8526, Japan; †Shizuoka General Hospital; Shizuoka 420–8527, Japan; ‡Division of Translational Research, Kyoto Medical Center, National Hospital Organization; Kyoto 612–8535, Japan; §Shizuoka Saiseikai General Hospital; Shizuoka 422–8527, Japan; †Department of Ophthalmology, Kyoto Prefectural University of Medicine; Kyoto 602–8566, Japan; and ‡Clinical Research Institute, Kyoto Medical Center, National Hospital Organization; Kyoto 612–8555, Japan.

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Statins, 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors, are potential drugs for chronic heart failure treatment in clinical studies. However, there may be differences in the effects on heart failure between lipophilic and hydrophilic statins. In this study, we investigated whether hydrophilic rosuvastatin (RSV) and lipophilic pitavastatin (PTV) exert different effects on the left ventricular diastolic function. Subjects were hypercholesterolemia patients with left ventricular diastolic dysfunction. This was an open-label, randomized, parallel, comparative, prospective study. The subjects received treatment with RSV or PTV for 24 weeks, and their low density lipoprotein (LDL)-cholesterol levels were controlled by these statins according to the guideline. The primary endpoint was defined as the change in left ventricle (LV) diastolic function (E/E’/uni2032.bold) estimated by echocardiography, and the secondary endpoint was the plasma B-type natriuretic peptide (BNP) level. No serious adverse effects were observed during the entire study period in any patient, nor were there any significant differences in changes in the body mass index, blood pressure, or heart rate. Statin treatment did not significantly alter the primary endpoint, E/E’. The change ratio of BNP was not significantly different between PTV and RSV groups. However, BNP was significantly increased in the RSV group. Observation for a longer period is necessary to clarify the different effects of these statins on LV diastolic dysfunction. (UMIN-ID: UMIN000003571).

Key words lipophilic statin; hydrophilic statin; diastolic function; dyslipidemia

Heart failure is the end stage of various forms of heart disease and exhibits common clinical symptoms, regardless of the underlying pathology.1,2,3 Heart failure severely impacts a patient’s daily life and shortens the patient’s life-span. 3-Hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors are drugs that inhibit cholesterol synthesis in the liver and that lower serum cholesterol. Previous large-scale clinical trials have found that HMG-CoA reductase inhibitors provide primary and secondary prophylaxis against cardiovascular events. Moreover, the latest studies have reported that statins exhibit a range of actions unrelated to lowering cholesterol (such as anti-inflammatory action, anti-oxidant action, and action to inhibit the renin-angiotensin system).3,4 Hydrophilic statins have difficulty entering tissue because of their physical characteristics, but lipophilic statins readily penetrate tissue. Thus, lipophilic statins may be better able to exhibit a range of actions (i.e., pleiotropic effects). Rosuvastatin (RSV) is a hydrophilic statin, and large-scale clinical trials have found that RSV did not improve the prognosis for patients with heart failure.4,5 In contrast, other trials have suggested that lipophilic statins such as simvastatin and pitavastatin (PTV) are effective at treating heart failure.5,6 Nevertheless, studies have not examined differences in how effectively (or ineffectively) hydrophilic statins and lipophilic statins treat left ventricular diastolic dysfunction (LVDD).

Studies have reported that a high proportion of patients with heart failure (40–50%) preserve left ventricular systolic function, and interest in treating heart failure due to LVDD (or diastolic heart failure) has increased.6,7 LVDD has a prognosis that is almost as poor as that of systolic heart failure, but the pathology of diastolic heart failure differs from that of systolic heart failure, and strategies for treatment of diastolic heart failure have yet to be established. Thus, the current study examined differences in the effects of hydrophilic and lipophilic statins on left ventricular diastolic function (LVDF) in patients with LVDD and hypercholesterolemia.

MATERIALS AND METHODS

This clinical study was jointly conducted by Shizuoka Prefectural General Hospital and the Kyoto Medical Center, National Hospital Organization. This study was approved by the ethics committee of Shizuoka Prefectural General Hospital and the ethics committee of the Kyoto Medical Center. The registration of this study started on May 2010, and finished on October 2012. The study was fully explained verbally and in writing to potential subjects. Patients who voluntarily consented to participate in this study in writing were enrolled.

*To whom correspondence should be addressed. e-mail: morimoto@u-shizuoka-ken.ac.jp © 2015 The Pharmaceutical Society of Japan
Subjects were patients with hypercholesterolemia and LVDD. LVDD was defined as an ejection fraction (EF) $\geq 45\%$ according to Doppler echocardiography and the presence of abnormal left ventricular relaxation (E/A $< 1$ and DT $\geq 210$ ms or E/E’ $\geq 10$).

This study was a randomized, open-label, parallel-group study. Patient eligibility was verified and consent was obtained. Subjects were then randomly assigned to 1 of 2 groups that were both administered a statin. One group was administered RSV, a potent hydrophilic statin, while the other group was administered PTV, a lipophilic statin. Both groups were orally administered a statin (RSV or PTV) after dinner for 24 weeks until their low density lipoprotein (LDL)-cholesterol levels reached target levels according to criteria of the Japan Atherosclerosis Society. The primary endpoint was LVDF (gauged using E/E’) according to Doppler echocardiography and the secondary endpoint was the level of B-type natriuretic peptide (BNP) in the blood.

Continuous data that were parametric were expressed as the mean $\pm$ standard deviation (S.D.) and those that were non-parametric were expressed as the median [inter-quartile range (IQR)]. In statistical analysis, a Mann–Whitney U-test was used for comparison of continuous data between 2 groups. For analysis of 3 or more matched groups, Friedman’s test was performed and then a Wilcoxon signed-rank test with Bonferroni correction was performed as a post-hoc test.

A $p<0.05$ was considered statistically significant. All analyses were performed using SPSS version 22.0 for Windows (IBM Japan, Ltd., Tokyo, Japan).

RESULTS

Eighty-three patients were enrolled in this study, and subsequent withdrawals left 53 evaluable patients. Patients in the RSV group consisted of 15 men and 14 women (mean age: 65.3 $\pm$ 9.4 years, body mass index (BMI): 24.8 $\pm$ 2.9 kg/m$^2$), and patients in the PTV group consisted of 13 men and 11 women (mean age: 64.7 $\pm$ 9.4 years, BMI: 24.0 $\pm$ 2.8 kg/m$^2$). There are no differences between the 2 groups in terms of age, sex, or BMI. The average dose of RSV was 1.7 $\pm$ 1.1 mg/d and that of PTV was 1.4 $\pm$ 0.9 mg/d. Serious adverse reactions were not observed in any of the patients, and all of the patients completed the study. E/E’ data were missing for 3 patients in the RSV group, and BNP data were missing for 1 patient in the RSV group.

Changes in individual parameters as a result of statin administration are shown in Table 1. There were no changes in the BMI, systolic blood pressure, diastolic blood pressure, or pulse rate before and after taking a statin in either group. As shown in Table 2, there were no significant differences in the accompanied medications between PTV and RSV groups. These treatments were continued and unchanged during the 24-week follow-up period.

E/E’, an index of LVDF, was the primary endpoint in this study. Significant changes in E/E’ before and after statin administration were not noted, and there were no differences in the E/E’ of either group. The level of BNP was the secondary endpoint in this study. A significant increase in BNP from the level prior to statin administration to the level after 24 weeks of statin administration was observed in the RSV group (15.4 pg/mL prior to administration vs. 16.9 pg/mL after ad-

<table>
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<tr>
<th>RSV</th>
<th>n</th>
<th>0-month</th>
<th>3-month</th>
<th>6-month</th>
<th>p-Value for all group</th>
<th>p-Value (Bonferroni correction)</th>
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</thead>
<tbody>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>28</td>
<td>24.8 $\pm$ 2.9</td>
<td>24.6 $\pm$ 3.0</td>
<td>24.7 $\pm$ 3.0</td>
<td>0.360</td>
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<tr>
<td>SBP (mmHg)</td>
<td>27</td>
<td>127.9 $\pm$ 12.2</td>
<td>127.5 $\pm$ 12.5</td>
<td>127.1 $\pm$ 13.5</td>
<td>0.884</td>
<td>&gt;0.999</td>
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<td>DBP (mmHg)</td>
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<td>73.0 $\pm$ 9.5</td>
<td>72.5 $\pm$ 10.0</td>
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<td>0.877</td>
<td>&gt;0.999</td>
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<tr>
<td>PR (bpm)</td>
<td>27</td>
<td>72.8 $\pm$ 10.6</td>
<td>70.5 $\pm$ 10.4</td>
<td>71.3 $\pm$ 9.5</td>
<td>0.321</td>
<td>0.467</td>
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<td>LDL-C (mg/dL)</td>
<td>28</td>
<td>138.9 $\pm$ 30.2</td>
<td>96.6 $\pm$ 22.6</td>
<td>100.3 $\pm$ 20.5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<td>TG (mg/dL)</td>
<td>28</td>
<td>186.1 $\pm$ 123.2</td>
<td>167.7 $\pm$ 103.8</td>
<td>155.5 $\pm$ 115.8</td>
<td>0.019</td>
<td>0.332</td>
</tr>
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<td>HbA1c (%)</td>
<td>28</td>
<td>5.5 $\pm$ 0.3</td>
<td>5.5 $\pm$ 0.3</td>
<td>5.5 $\pm$ 0.3</td>
<td>0.935</td>
<td>&gt;0.999</td>
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<tr>
<td>Cre (mg/dL)</td>
<td>28</td>
<td>0.7 $\pm$ 0.2</td>
<td>0.7 $\pm$ 0.2</td>
<td>0.7 $\pm$ 0.2</td>
<td>0.683</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>E/E’</td>
<td>26</td>
<td>10.8 (9.54, 12.57)</td>
<td>10.9 (9.71, 12.63)</td>
<td>10.5 (8.95, 12.20)</td>
<td>0.760</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>28</td>
<td>15.4 (7.10, 33.25)</td>
<td>18.2 (8.85, 48.18)</td>
<td>16.9 (7.88, 52.53)</td>
<td>0.023</td>
<td>0.082</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>PTV</th>
<th>n</th>
<th>0-month</th>
<th>3-month</th>
<th>6-month</th>
<th>p-Value for all group</th>
<th>p-Value (Bonferroni correction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>24</td>
<td>24.0 $\pm$ 2.8</td>
<td>23.8 $\pm$ 2.8</td>
<td>23.9 $\pm$ 3.0</td>
<td>0.326</td>
<td>&gt;0.999</td>
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<tr>
<td>SBP (mmHg)</td>
<td>24</td>
<td>128.7 $\pm$ 17.1</td>
<td>123.9 $\pm$ 15.8</td>
<td>126.3 $\pm$ 16.9</td>
<td>0.263</td>
<td>0.318</td>
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<tr>
<td>DBP (mmHg)</td>
<td>24</td>
<td>74.9 $\pm$ 9.9</td>
<td>71.5 $\pm$ 9.2</td>
<td>72.3 $\pm$ 11.0</td>
<td>0.600</td>
<td>0.255</td>
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<td>PR (bpm)</td>
<td>24</td>
<td>75.5 $\pm$ 12.1</td>
<td>78.1 $\pm$ 12.7</td>
<td>75.9 $\pm$ 9.9</td>
<td>0.504</td>
<td>0.992</td>
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<tr>
<td>LDL-C (mg/dL)</td>
<td>23</td>
<td>155.5 $\pm$ 19.2</td>
<td>105.3 $\pm$ 24.9</td>
<td>101.2 $\pm$ 22.6</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>24</td>
<td>195.2 $\pm$ 96.6</td>
<td>162.1 $\pm$ 98.8</td>
<td>145.3 $\pm$ 81.7</td>
<td>&lt;0.001</td>
<td>0.041</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>24</td>
<td>5.6 $\pm$ 0.7</td>
<td>5.6 $\pm$ 0.6</td>
<td>5.7 $\pm$ 0.8</td>
<td>0.421</td>
<td>&gt;0.999</td>
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<td>Cre (mg/dL)</td>
<td>24</td>
<td>0.7 $\pm$ 0.2</td>
<td>0.8 $\pm$ 0.2</td>
<td>0.8 $\pm$ 0.2</td>
<td>0.007</td>
<td>0.124</td>
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<td>E/E’</td>
<td>24</td>
<td>9.8 (8.68, 11.95)</td>
<td>10.5 (8.31, 12.34)</td>
<td>9.0 (7.88, 12.43)</td>
<td>0.464</td>
<td>&gt;0.999</td>
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<td>BNP (pg/mL)</td>
<td>24</td>
<td>14.7 (5.40, 31.35)</td>
<td>16.4 (4.80, 26.00)</td>
<td>14.6 (7.10, 31.43)</td>
<td>0.160</td>
<td>&gt;0.999</td>
</tr>
</tbody>
</table>

Data are presented as the mean $\pm$ S.D. or the median (IQR). A p-value was calculated by repeated measures ANOVA, unpaired t-test with Bonferroni correction in parametric data (BMI, SBP, DBP, PR, LDL-C, TG, Cre, and HbA1c), and by Friedman’s test, Wilcoxon signed-rank test with Bonferroni correction in non-parametric data (E/E’ and BNP). RSV: Rosuvastatin, PTV: Pitavastatin, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PR: Pulse rate.

Table 1. Changes in BMI, SBP, DBP, E/E’ and BNP in Patients with Left Ventricular Diastolic Dysfunction and Hypercholesterolemia Treated with Statin
ministration for 6 months, \( p=0.030 \). No changes whatsoever in BNP from the level prior to statin administration to the level after 24 weeks of statin administration were noted in the PTV group (14.7 pg/mL prior to administration vs. 14.6 pg/mL after administration for 6 months, \( p=0.999 \)). Comparison of the percent change in BNP in the RSV group and the PTV group revealed no differences at 6 months (39.2% vs. 19.5%, \( p=0.607 \)). However, significant differences were observed at 3 months (34.2% vs. -3.4%, \( p=0.035 \)).

As shown in Table 1, after 24 weeks of treatment with statins, we observed a significant reduction of LDL-C and triglyceride (TG) levels in the RSV (LDL-C: \( p=0.001 \) and TG: \( p<0.018 \)) and PTV (LDL-C: \( p<0.001 \) and TG: \( p=0.001 \)) groups. Although serum creatinine levels in the RSV group were unchanged (\( p>0.999 \)), those in the PTV group were increased (\( p=0.017 \)). There were no significant differences in the changes of HbA1c levels between these two groups.

DISCUSSION

In this study, statins did not improve LVDF by Doppler echocardiography to assess LVDF. However, RSV increased BNP, a marker of left ventricular wall stress, while PTV did not. Moreover, long-term observation may indicate that the effects of the 2 statins on LVDF differ. Further studies should be conducted in the future.

A subanalysis of large-scale clinical studies and trials such as the 4S study,\(^{10}\) the PRAISE trial,\(^{11}\) and the VAL-HeFT trial\(^{12}\) has suggested that statins improve the prognosis for patients with heart failure. This improvement is noted in patients who do not have hypercholesterolemia and in those who have non-ischemic heart failure. This improvement is related to some pleiotropic effect of statins besides their cholesterol-lowering action. The CORONA trial\(^{13}\) and the GISSI-HF trial\(^{15}\) are large-scale clinical trials that prospectively examined amelioration of chronic heart failure by statins. In these trials, RSV did not significantly improve the prognosis for patients with heart failure in terms of cardiovascular mortality or overall mortality. Statins are hydrophilic or lipophilic. RSV is a hydrophilic statin, so amelioration of heart failure may differ depending on the type of statin. The PEARL study was conducted to examine amelioration of heart failure by PTV, a lipophilic statin.\(^{19}\) In that study, the primary endpoint was admission or cardiac death due to worsening heart failure. The PEARL study demonstrated no significant differences in admission or cardiac death for a group that was administered PTV and a group that was not administered a statin. Significant differences between the 2 groups in terms of secondary endpoints were not noted, either. Nevertheless, an analysis of patients with a left ventricular EF of 30% or more revealed a significant decrease in risk (close to 50%).\(^{10}\) Thus, PTV may be effective in treating mild heart failure. Moreover, patients who have heart failure with mild systolic dysfunction may include a number of patients who have diastolic dysfunction. PTV would presumably improve LVDD in these patients over the long term.

Although BNP was significantly increased in the RSV group, BNP levels at baseline and after statins treatment were all within a normal range. Increased plasma BNP or serum NT-proBNP levels are useful biomarkers for prediction of high risks for any cause mortality in the general population.\(^{15–17}\) However, few clinical studies have shown significant relationship between low plasma BNP and CVD risk. A community-based study indicated that BNP levels, even if these are within a normal range, predicted the risk of death and cardiovascular events including heart failure in a population consisting of mainly Caucasian and living in Framingham.\(^{18}\) Moreover, plasma BNP is well-correlated with the risk of future development of heart failure within an apparently healthy population in Japan.\(^{19}\) Further, an Ohkuma cohort study indicated that the risk of stroke in the subjects with normal NT-proBNP (30–55 pg/mL) tends to be higher than those with lower NT-proBNP (< 30 pg/mL). These observations indicated that testing of BNP or NT-proBNP may be useful for predicting the risk of cardiovascular events in relatively low risk populations. Further studies are awaited to evaluate the precise relationships between BNP or NT-proBNP levels and cardiovascular events in the general population with their normal levels.

RSV is shown to be hydrophilic based on the octanol–water partition coefficient. This compound is hardly soluble in water, extremely insoluble in octanol, but easily soluble in other organic solvents such as ethyl acetate, acetone, and tetrahydrofuran, in quite contrast to the typical hydrophilic statin pravastatin that is freely soluble in water but insoluble in organic solvents. As such, classical clarifications of statins as either “hydrophilic” or “lipophilic” are misleading. The atomic electrostatic potentials calculated by the CHELPG method have been shown to be sensitive indicators of the gas phase and solution properties of the statins.\(^{20}\) Bioavailability of statins, such as absorption efficiency, transferability to tissues, and retentive property by pharmacokinetics studies should be considered in addition to the classification of “hydrophilic” or “lipophilic.”

Statins lower serum lipid levels, but they are also reported to reduce inflammation, exhibit anti-oxidant activity, improve vascular endothelium, and inhibit cell growth. A host of studies have examined the detailed mechanisms whereby statins slow the progression of heart failure. The mevalonate pathway leads to cholesterol production, and metabolites in that pathway activate signaling molecules such as Ras, Rho, and Rac.\(^{21}\) Ras is involved in cell proliferation and growth, Rho is involved in the production of inflammatory cytokines and chemokines, and Rac is involved in the generation of oxidative stress. Statins decrease the activity of Ras, Rho, and Rac by blocking the mevalonate pathway. A decrease in the activity of these molecules is reported to inhibit cardiac hypertrophy,
reduce inflammation, and inhibit oxidative activity, potentially alleviating heart failure.\(^{22}\)

Plasma BNP levels have been demonstrated to be affected by several factors such as BMI, renal function, age, gender, and medications.\(^{23–25}\) In this study, there was no difference in BMI, age and medications other than statins between the RSV and PTV groups. However, creatinine, a representative marker of renal function, was significantly increased in the PTV group but not in the RSV group. While association of high potency statins with acute renal failure has been reported,\(^{26}\) both PTV and RSV are high potency statins, and reasons of creatinine rises in the PTV but not in the RSV group are unclear. As creatinine and BNP have a positive correlation, the BNP level usually rises when the creatinine level increases. However, the BNP level did not increase while the creatinine level increased in the PTV group. In contrast, despite no increase in the creatinine level, the BNP level did increase in the RSV group. Therefore, there is a possibility that no increase of BNP in the PTV group is caused by one of its pleiotropic effects on the heart rather than by changes in creatinine levels or by differences in patient characteristics.

Until recently, most large-scale clinical trials on treatment of heart failure focused on systolic heart failure, and there is no evidence regarding the effective treatment of LVDD. Left ventricular hypertrophy and fibrosis are thought to be the principal pathological features of LVDD. Drugs that inhibit or delay cardiac hypertrophy and fibrosis would presumably be effective in treating LVDD. At present time, however, no studies have reported drugs that delay left ventricular hypertrophy, improve diastolic function, or alleviate subjective symptoms and exercise tolerance. Such drugs should be studied in the future. Several reports indicated that statins may have beneficial effects on LVDF, mainly by attenuating the development of cardiac hypertrophy and fibrosis in murine hypertensive heart disease (HHD) models.\(^{27–29}\) Although there are several experimentally confirmed benefits of statins in LVDF, few data exist concerning the underlying mechanisms.\(^{50}\) Since myocardial hypertrophy leads to LVDD, the anti-hypertrophic effects may contribute to the restoration of LVDD. Statins are reported to improve LVDF by down-regulating expression of genes such as collagen I, transforming growth factor-beta, matrix metalloproteinase (MMP)-2 and -3, atrial natriuretic factor, interleukin (IL)-6, tumor necrosis factor (TNF)α, and Rho kinase 1, inhibiting the renin-angiotensin system (RAS), and up-regulating eNOS gene expression.\(^{28–31}\) Studies should be fully performed to investigate the underline mechanisms affecting LVDF. A number of clinical studies have evaluated LVDF in patients with various etiologies. Statins play a protective role in LVDF of patients with ischemic heart disease (IHD) but not in those with other types of cardiomyopathies.\(^{27,30,32,33}\) This may be attributable to the fact that LVDD is a heterogeneous pathological state. Therefore, more extensive clinical trials by selecting the types of statins and basal diseases such as IHD, HHD, and valvular heart diseases are needed to clarify whether statins improve LVDF.

The current authors conducted an experiment using cultured cells in order to examine the protection against heart failure that statins provide. Statins were administered to reach levels found in the blood when usual doses of statins are actually taken. Cultured cardiomyocytes stimulated with phenylephrine exhibited hypertrophy. This change was inhibited by PTV but not RSV. Moreover, cell growth of cardiac fibroblasts was inhibited by PTV but not by RSV (unpublished data). Cardiomyocytes hypertrophy and the proliferation of cardiac fibroblasts play a role on the progression of heart failure. Since PTV inhibits these hypertrophy and cell proliferation, this drug may be expected to be used as a treatment for LVDD.

LIMITATIONS

Firstly, the small sample size could be a limitation of this study. Secondly, more than 20% of patients was receiving angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, which have been reported to reduce cardiovascular events and mortality in not only high risk but also low risk patients.\(^{34,35}\) These types of drugs have also been reported to reduce BNP levels.\(^{36}\) Thirdly, BNP levels in majority of our subjects are normal. It is possible that we obtained more significant results, if the study were performed in patients with higher BNP levels. Fourthly, our follow-up period was only six month. Longer duration of follow-up on the patients may be required to obtain significant conclusions. Finally, we did not obtain information regarding medication purchased over-the-counter. The control of blood pressure is most important to suppress cardiac hypertrophy. Since blood pressures of patients in this study are well-controlled by anti-hypertensive therapy, the precise role of statins on cardiac hypertrophy in addition to blood pressure control requires further investigation.

CONCLUSION

To clarify whether or not PTV and RSV affect LVDF differently, further studies are needed in different subjects.

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Conflict of Interest The research facilities where the authors work have cooperative research agreement with Kowa Company, Ltd., and received funding.

REFERENCES


