Impact of Statin Therapy on Systemic Inflammation, Left Ventricular Systolic and Diastolic Function and Prognosis in Low Risk Ischemic Heart Disease Patients without History of Congestive Heart Failure

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Abstract

Objectives The aim of this study was to investigate the impact of statin on systemic inflammation, left ventricular systolic and diastolic function and prognosis in low risk ischemic heart disease (IHD) patients.

Methods A total of 430 consecutive IHD patients without congestive heart failure were enrolled. One hundred and thirtytwo patients (31%) were treated with statin (statin group) and 298 patients (69%) were not (no statin group). Echocardiographic indices, high sensitivity CRP, and prognosis were compared.

Results Ejection fraction (EF) was significantly higher in the statin group ($p < 0.01$). The ratio of the early transmitral flow velocity to early diastolic velocity of the mitral annulus (E/E') was significantly lower in the statin group than in the no statin group ($p < 0.01$). Although LDL-cholesterol level did not differ, high sensitivity CRP level was significantly lower in the statin group (0.3 ± 0.5 vs. 1.1 ± 2.3 mg/dl, $p = 0.005$). Cardiac event-(cardiac death and congestive heart failure)free survival rate was significantly higher in the statin group than in no statin group (Log-rank $p < 0.0001$). By multivariate logistic regression analysis, $E/E' > 15$ ($p = 0.002$), $EF < 50\%$ ($p = 0.003$), lack of statin use ($p = 0.009$), left atrial dimension ($p = 0.02$), use of diuretics ($p = 0.03$) and lack of beta-blockers ($p = 0.04$) were independent predictors of cardiac events. In 248 patients matched by propensity scores, statin remained associated with better event-free survival (Log-rank $p = 0.006$).

Conclusion Statin may improve left ventricular function and thus improve the prognosis in low risk patients with IHD.

Key words: hyperlipidemia, ultrasonics, heart failure

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Introduction

Previous studies have suggested possible cardio-protective effects of statin beyond lipid lowering. Several studies have demonstrated impact of the statin on left ventricular systolic function and prognosis in patients with heart failure (1-3). Moreover, a recent study has shown that statin may also improve the prognosis in patients with diastolic heart failure (4). Therefore, statin may have some favourable impact not only on left ventricular systolic function but also on left

ventricular diastolic function. Although possible mechanisms affecting diastolic function have been suggested based on experimental data, to date the clinical impact of statin on left ventricular diastolic indices have not been well documented. This may be possibly because of the limitation of currently used Doppler-derived indices of left ventricular diastolic function such as the ratio of the early and late transmitral flow velocity (E/A) and the deceleration time of the E (DT), namely pre-load dependency and as a result presence of pseudonormal pattern appears. Recently, the ratio of the early transmitral filling velocity and the early dia-

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stolic mitral annular velocity, E/E', has been introduced as a relatively preload-independent non-invasive Doppler index (5-9).

Despite the previous data supporting the possible efficacy of statin on prognosis in patients with a known history of congestive heart failure, it is unknown whether or not statin also improves cardiac function and lowers the future risk of congestive heart failure in relatively low risk ischemic heart disease (IHD) patients without prior history of congestive heart failure (CHF). Moreover, the role of the anti-inflammatory effect of statin on cardiac function and prognosis has not been well investigated.

Accordingly, we hypothesized that statin may suppress systemic inflammation and improve cardiac function as well as prognosis even in low risk IHD patients without a history of congestive heart failure. To clarify these hypotheses, this study was conducted to evaluate the impact of statin on 1) systemic inflammation, 2) left ventricular systolic and diastolic function including tissue Doppler-derived indices and 3) the prognosis in IHD patients without prior history of CHF.

Methods

Study populations

Between January 2000 and December 2004, the Bell Land General Hospital echocardiography database was probed to find IHD patients without history of congestive heart failure who were referred to the echocardiographic examination and had both transmitral flow velocity and tissue Doppler imaging of the mitral annulus. Patients with atrial fibrillation, prosthetic heart valve, mitral annular ring and severe mitral annular calcification were excluded from this study. Finally, a total of 430 consecutive patients were included. There were 302 men and 128 women with a mean age of 68 years old. Patients were diagnosed as hypertension if one of the following was found: 1) systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg or 2) they are currently treated with antihypertensive medicine. Patients were diagnosed as hyperlipidemia if one of the following was found: 1) total cholesterol level > 240 mg/dl, or 2) they are treated with lipid lowering agents. Patients were diagnosed as diabetes mellitus with one of the followings: 1) fasten blood glucose level > 126 mg/dl, or 2) blood glucose level 2 hours after 75 g oral glucose tolerance test > 200 mg/dl, or 3) they have a known history of diabetes mellitus.

Echocardiographic examination and laboratory data

Two-dimensional and Doppler echocardiography was performed with patients in the left lateral decubitus position using a commercially available echocardiographic machine (Vivid 7, GE Medical, Milwaukee, WI, USA) with a broadband (1.5-4 MHz) phased array transducer. From parasternal long axis view, left atrial dimension was measured as re-

ported previously. Left ventricular end-diastolic volume, end-systolic volume and ejection fraction were measured and calculated based on modified Simpson's rule from apical 2- and 4-chamber views. Transmitral flow velocity signals were recorded from apical 4-chamber view and the early (E) transmitral flow velocity was measured. Deceleration time of the E was also measured.

Similarly, tissue Doppler imaging of the mitral annulus was obtained from apical 4-chamber view. A sample volume of the pulsed wave Doppler was positioned at the septal side of the mitral annulus and then velocity profile of the mitral annular velocity was recorded by pulsed Doppler method. Peak early (E') mitral annular velocity was measured. E/E' was calculated as an index of left ventricular filling pressure.

Laboratory data were obtained from a subset of patients. Serum B-type natriuretic peptide (BNP, n=86), LDL-cholesterol (n=220) and high sensitivity CRP (hsCRP, n=246) levels were measured and compared. For hsCRP comparison, patients with myocardial infarction <14 days after the onset were excluded because of possible impact of acute myocardial inflammation on serum hsCRP level. Both LDL-cholesterol and hsCRP were grouped into quartiles for comparison of EF, E/E', and clinical outcomes.

Clinical outcome

Patients' death and cause of death were confirmed by a medical record review or a telephone contact as of January 2006. Cardiac death was defined as either a death directly related to cardiac disease, mainly congestive heart failure, or sudden death. Similarly, congestive heart failure was identified by a medical record review or a telephone contact.

Statistical analysis

Continuous data were expressed as mean $\pm$ SD. The differences between 2 groups for the parametrical data were tested by use of unpaired t test. Categorical variables between 2 groups were compared using chi-square test or Fisher's exact test. Independent predictors of death were calculated by logistic regression. Differences in EF and E/E' among quartiles of hsCRP were compared by use of ANOVA. Variables with a probability value of < 0.15 were then entered into a multivariate logistic regression analysis. Cumulative event-free survival curves during follow-up in the statin group versus the no statin group were obtained by the Kaplan-Meier method with a log-rank test. Similarly, cumulative event-free survival curves in quartiles of hsCRP and LDL-cholesterol were obtained by the Kaplan-Meier method with a log-rank test. To adjust baseline clinical and echocardiographic differences between patients treated with and without statin, patients without statin were further matched to those treated with statin for other multivariate predictors of cardiac events (LAD, EF, E/E', use of beta blockers and use of diuretics). A propensity score was calculated and 124 patients in each group (total 248 patients) were matched. A p value < 0.05 was considered statistically

Table 1. Clinical Characteristics

	Statin (n=132)	No statin (n=298)	p
Age, y	64.2±10.0	69.1±10.3	<0.0001
Sex, M/F	103/29	199/99	0.02
Diagnosis			
Myocardial infarction (<14days), n (%)	18 (14)	40 (13)	NS
Myocardial infarction (≥14days), n (%)	54 (41)	119 (40)	NS
Angina pectoris, n (%)	60 (45)	139 (47)	NS
CABG, n (%)	27 (20)	58 (19)	NS
Diabetes mellitus, n (%)	41 (31)	71 (24)	NS
Hyperlipidemia, n (%)	128 (97)	34 (11)	<0.0001
Hypertension, n (%)	77 (58)	160 (54)	NS

Table 2. Medications

	Statin (n=132)	No statin (n=298)	p
Statin, n (%)	132 (100)	0 (0)	-
Aspirin, n (%)	114 (86)	218 (73)	0.003
Beta blockers, n (%)	40 (30)	47 (16)	0.0005
ACEI or ARB, n (%)	54 (41)	101 (34)	NS
Ca antagonists, n (%)	40 (30)	102 (34)	NS
Nitrates, n (%)	21 (16)	71 (24)	0.06
Nicorandil, n (%)	19 (14)	51 (17)	NS
Digitalis, n (%)	5 (4)	34 (11)	0.01
Diuretics, n (%)	17 (13)	69 (23)	0.01

significant. A p value < 0.05 was considered statistically significant. Statistical analysis was performed using commercially available software (Statview).

Results

Statin was used in 132 (31%) of 430 IHD patients (statin group). On the other hand, statin was not prescribed in the remaining 298 (69%) patients (no statin group). Baseline clinical characteristics in both statin and no statin groups are shown in Table 1. The statin group was younger and had more men than in the no statin group. As expected, the incidence of hyperlipidemia was significantly higher in the statin than in the no statin group. Medications are summarized in Table 2. Statin group took more aspirin and beta blockers and less diuretics and digitalis.

Echocardiographic indices are shown in Table 3. Although left ventricular end-diastolic volume was similar between the two groups, left ventricular end-systolic volume was significantly smaller in the statin group. As a result, the left ventricular ejection fraction was significantly higher in the statin group. With respect to the Doppler indices, A, E/A, S, D

Table 3. Two-Dimensional and Doppler Echocardiographic Indices

	Statin (n=132)	No statin (n=298)	p value
LAD, mm	38.4±5.3	38.4±6.2	NS
LVEDV, ml	84.2±29.8	85.3±35.8	NS
LVESV, ml	35.0±19.4	39.9±28.4	0.07
LVEF, %	59.6±10.2	56.0±13.3	0.006
E, m/sec	0.64±0.18	0.69±0.23	0.049
A, m/sec	0.79±0.19	0.80±0.23	NS
E/A	0.86±0.37	0.94±0.53	NS
DT, msec	220.6±61.7	210.9±66.4	0.08
S, m/sec	0.60±0.14	0.62±0.16	NS
D, m/sec	0.45±0.12	0.46±0.14	NS
S/D	1.41±0.43	1.45±0.53	NS
E', cm/sec	5.6±1.7	5.0±1.8	0.0003
E/E'	12.4±5.0	15.3±7.0	<0.0001

and S/D were not different between the two groups. On the other hand, E was significantly lower (p=0.049) and deceleration time of E showed a trend toward longer in statin group (p=0.08). By TDI, E' was significantly higher in statin group than in no statin group. As a result, E/E' was significantly lower in statin group than in no statin group (p<0.0001).

LDL-cholesterol level did not differ between the statin and no statin groups (111.2±30.4 vs. 116.6±32.1 mg/dl, p=0.23). On the other hand, serum hsCRP level was significantly lower in statin group than in no statin group (0.3±0.4 vs. 1.1±2.3 mg/dl, p=0.005). BNP level was significantly lower in statin group than in no statin group (54.4±53.8 vs. 368.8±622.5 pg/dl, p=0.02).

During the follow-up period (average 657±369 days), 42 deaths (9.8%) were documented. In addition, 31 patients were hospitalized due to congestive heart failure. There were 21 cardiac deaths and 21 non-cardiac deaths, respectively (Table 4). By multivariate logistic regression analysis, independent predictors of cardiac death and congestive heart failure were E/E'>15 (p=0.002), EF<50% (p=0.003), lack of statin use (p=0.009), left atrial dimension (p=0.02), use of diuretics (p=0.03) and a lack of beta blockers (p=0.04) (Table 5).

Kaplan-Meier plots of cardiac death-free survival curve during follow-up showed a significantly higher survival rate in statin group than in no statin group (Fig. 1). Similarly, Kaplan-Meier plots of congestive heart failure-free survival curve showed a significantly higher survival rate in statin group than in no statin group (Fig. 2). As a result, cardiac event (cardiac death and congestive heart failure)-free survival rate was significantly higher in statin group than in no

Table 4. Clinical Events during Follow-up

	Statin	No statin	p value
CHF, n (%)	3 (2.3)	28 (9.4)	0.008
All-cause death, n (%)	4 (3.0)	38 (12.4)	0.002
Cardiac, n(%)	1 (0.8)	20 (6.7)	0.008
Non-cardiac, n(%)	3 (2.3)	18 (6.0)	0.09
Cardiac death or CHF, n (%)	3 (2.3)	46 (15.4)	<0.0001

Table 5. Multivariate Predictors of Death and Congestive Heart Failure

	chi-square	p value	risk ratio	95% CI
E/E' > 15	9.30	0.002	3.63	1.59-8.31
EF < 50 %	8.63	0.003	3.38	1.50-7.63
No statin	6.88	0.009	5.57	1.54-20.1
LAD	5.51	0.02	1.08	1.01-1.16
Diuretics	4.64	0.03	2.37	1.08-5.20
No beta-blockers	4.14	0.04	3.82	1.05-1.16

statin group (Fig. 3).

Furthermore, Kaplan-Meier plots of cardiac event-free survival curves stratified by EF were also constructed (Fig. 4). Both in patients with EF<50% and in patients with EF≥50%, the event-free survival rate was significantly higher in statin group than in no statin group, suggesting that the favorable effect of statin was independent of cardiac systolic function.

A quartile-dependent increase in the risk of cardiac death and congestive heart failure was seen with increasing plasma hsCRP but not with increasing LDL-cholesterol (Fig. 5). A quartile-dependent decrease in EF and increase in E/E' are shown in Fig. 6.

Between the propensity-matched groups with and without statin, left ventricular systolic function (EF 59.2±10.4 vs. 59.0±10.7 %, p=NS) and diastolic functions (DT 219.2±60.7 vs. 213.7±57.8 msec, E/E' 12.6±5.1 vs. 13.6±5.3, both p=NS) were well matched. Also, baseline medications other than statin such as aspirin (90% vs. 78%), beta blockers (24% vs. 23%), diuretics (16% vs. 15%), digitalis (6% vs. 7%) and nitrates (17% vs. 23%) were well matched (all p=NS) after adjustment. In the propensity-matched group without statin (124 patients), 13 deaths (5 cardiac and 8 non-cardiac) and 10 congestive heart failures were observed during follow-up. As a result, statin remained associated with higher cardiac event-free-survival in these matched patients (Log-rank p=0.006) (Fig. 7).

Discussion

Our study shows that statin may improve left ventricular

Figure 1. Kaplan-Meier plots of cardiac death-free survival curve showing a significantly higher survival rate in the statin group than in the no statin group. **Figure 2.** Kaplan-Meier plots of congestive heart failure-free survival curve showing a significantly higher survival rate in the statin group than in the no statin group. **Figure 3.** Kaplan-Meier plots of cardiac event (cardiac death and congestive heart failure)-free survival curve showing a significantly higher survival rate in the statin group than in the no statin group.

Figure 4. Kaplan-Meier plots of cardiac event free survival rate during follow-up in patients with (A) ejection fraction (EF) < 50% and (B) EF ≥ 50%. The statin group had a significantly higher cardiac event-free survival rate during follow-up.

Figure 5. Kaplan-Meier curves for cardiac events by quartiles of (A) plasma hsCRP and (b) LDL-cholesterol level.

Figure 6. A hsCRP quartile-dependent decrease in EF (A) and increase in E/E' (B) are observed.

systolic and diastolic function assessed by Doppler echocardiography including TDI analysis, which may be related to improved prognosis in low risk IHD patients without history of HF. These favorable effects of statin may in part be explained by its anti-inflammatory effect.

Statin and prognosis in IHD population

Several randomized trials have clearly demonstrated beneficial effects of statin on mortality and morbidity in IHD patients. Results of a randomized controlled trial have shown

Figure 7. Kaplan-Meier plots of cardiac event-(cardiac death and congestive heart failure) free survival curve showing a significantly higher survival rate in the statin group than in the propensity score-matched no statin group.

that fluvastatin significantly reduced major adverse cardiac events including cardiac death, non-fatal myocardial infarction or reintervention procedure following percutaneous coronary intervention (10). These favorable effects of statins come mainly from the lipid lowering effect and as a result an anti-atherosclerotic effect. In fact, intravascular ultrasound trials have demonstrated the impact of statins on suppressing coronary plaque progression (11). Recently, more intensive lipid lowering therapy using atorvastatin has been shown to almost freeze plaque progression compared with intermediate intensity lipid lowering therapy using pravastatin (12). Furthermore, even more aggressive lipid lowering therapy by rosuvastatin has been shown to regress coronary atherosclerotic plaque as assessed by intravascular ultrasound (13).

In addition to its strong effects on coronary arterial wall, statins have been shown to favorably affect cardiac function and subsequent prognosis in not only ischemic but also non-ischemic heart failure patients (1, 2). Node et al reported that short term (3months) statin therapy improved left ventricular systolic function (ejection fraction) in patients with non-ischemic dilated cardiomyopathy (1). Although impact of statins on left ventricular diastolic indices were not been clarified in their study.

Horwich et al. studied a cohort of 551 patients with systolic heart failure ($EF \leq 40\%$) including ischemic and non-ischemic origins and found that statin therapy was an independent predictor of improved survival in both ischemic and non-ischemic heart failure (2).

More recently, Fukuta et al. studied 137 patients with heart failure with preserved systolic function ($EF > 50\%$) or diastolic heart failure (4). They have demonstrated that statin therapy may be associated with lower mortality. In their series, however, improved left ventricular diastolic indices were not demonstrated. In contrast, the present study did show the differences in not only systolic index (EF) but also

diastolic indices (E' and E/E') derived from TDI after statin treatments.

Additionally, the present results further address that even in broad spectrum of IHD patients without prior history of CHF, statin was associated with lower incidence of hospitalization due to CHF and cardiac death. Because LDL-cholesterol level did not differ between those treated with and without statin, this favorable effect may not be directly related to the lipid lowering effect of statin. Lower hsCRP level observed in patients treated with statin suggests that the anti-inflammatory effect of statin may be associated with a favorable prognosis. Systemic inflammation has been reported to be associated with prognosis in patients with HF (14-17). Experimental and clinical studies suggest that statin may improve cardiac function by its anti-inflammatory effects (18-20). In fact, hsCRP level was associated with prognosis in the present study population.

There were other possible mechanisms by which statin improved left ventricular systolic and diastolic function. Statin has been shown to improve endothelial function in an experimental model (21). Also, a clinical study demonstrated that 4 weeks of atorvastatin (10 mg) treatment improved forearm vasodilatory response to reactive hyperemia (22). Endothelial function has been well known as an important indicator of cardiac function as well as prognosis in patients with ischemic heart disease (23). Therefore, the favorable effects of statin on endothelial function may play some role in improved cardiac function and prognosis.

Statin has been shown to prevent cardiac myocyte hypertrophy in a neonatal rat model (24). In addition, statin has been shown to modulate the remodeling process (25). Hayashidani et al have shown, in a murine model of post infarct heart failure, that fluvastatin reduced cardiac myocyte hypertrophy and interstitial fibrosis of the noninfarcted LV after myocardial infarction, which was associated with the attenuation of increased MMP activity (25). Similarly, Bauersachs et al have shown anti-remodeling effect by cerivastatin (26).

Finally, the blood pressure lowering effect of statin has been reported in several clinical investigations (27, 28). Since more than half of the present study population are hypertensive, this mild but significant antihypertensive effect may have contributed to improved LV function and prognosis.

Study limitation

There are limitations to be noted in this study. First of all, because this was a retrospective study, statin was prescribed based on each primary physician's discretion. Therefore, possible selection bias could be present. However, as expected, statin was prescribed basically to patients with hyperlipidemia. Further, we have also performed an additional analysis using a propensity score. Even after adjustment of the baseline cardiac function and other medications (beta blockers and diuretics), statin remained a significant predictor of cardiac death and congestive heart failure. Secondly,

since statins had already been administered at the time of the index echocardiographic examination, serial change in echocardiographic indices of left ventricular systolic and diastolic indices before and after statin treatments have not been investigated. Finally, only 21 cardiac deaths (4.8%) and 31 hospitalizations due to congestive heart failure (7.2%) were documented in our overall study population. These lower incidences of the cardiac event rate may reflect

the “low risk” population of the present study. Despite these relatively lower incidences of the cardiac events among small numbers of the study population, it is noteworthy that statin was significantly associated with a better clinical outcome.

In conclusion, statin may be associated with decreased systemic inflammation and improved left ventricular function and prognosis in low risk IHD patients.

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