

ORIGINAL ARTICLE

Effects of Short-term High Dose Atorvastatin on Left Ventricular Remodeling in Patients with First Time Attack of Anterior Acute Myocardial Infarction

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Key words: atorvastatin; acute myocardial infarction; high-sensitivity C-reactive protein;
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Objects The aim of this trial was to evaluate the effect of short-term high-dose atorvastatin therapy on levels of high-sensitivity C-reactive protein (hs-CRP), malonaldehyde (MDA), endothelin-1(ET-1), matrix metalloproteinases (MMPs), and left ventricular (LV) remodeling in patients with first time attack of acute anterior myocardial infarction (AAMI) .

Methods A hundred and three patients with first time attack of AAMI who underwent successful primary percutaneous coronary intervention were randomized to receive atorvastatin 40 mg once daily for 1 week followed by 20 mg once daily (intensive treatment group, IT group, $n=49$), or atorvastatin 20 mg once daily (standard treatment group, ST group, $n=54$). Plasma levels of hs-CRP, MDA, ET-1, MMP-2 and MMP-9 were measured on admission, at 1 week, 2 weeks and 6 months follow up and compared between the IT group and ST group. Echocardiography was performed on admission, at 2 week, and 1 year follow up. The left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and left ventricular ejection fraction (LVEF) were measured at each echocardiographic examination and compared between the IT group and ST group.

Results Plasma levels of hs-CRP ($F=7.718$, $P=0.009$), ET-1 ($F=7.882$, $P=0.006$), MMP-9 ($F=4.834$, $P=0.028$) and pro-BNP ($F=4.603$, $P=0.032$) were significantly lower at 1 week after initial onset of AAMI in the IT group compared with the ST group. The changes of LVEDV, LVESV, and LVEF at the 1 year follow-up from the admission did not differ between the IT group and the ST group ($t=0.722$, $P=0.444$; $t=1.228$, $P=0.221$; $t=1.354$, $P=0.187$, respectively).

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Conclusions Short-term high-dose atorvastatin treatment for AAMI was associated with lower hs-CRP, ET-1 and MMP-9 levels compared to the standard dose treatment. However, this beneficial effect is not likely to related to the left ventricular remodeling.

LEFT ventricular (LV) remodeling in response to myocardial infarction (MI), defined as changes in geometry, structure and function of the heart, is associated with increased risks of heart failure and cardiovascular death.¹ Some studies have demonstrated that excessive inflammation² and matrix metalloproteinase (MMP) levels³ were associated with adverse LV remodeling. In addition to the decrease of low-density lipoprotein-cholesterol (LDL-C), statins have been recognized to have properties of modifying inflammatory responses, endothelial function and plaque stability, and these pleiotropic lipid-lowering effects of statins may be independent.^{4,5} Statins possess properties of anti-inflammatory⁶ and inhibiting MMPs activity,⁷ which is relevant to their cardioprotective effects. Previous studies have showed that normal dose statins reduce plasma levels of C-reactive protein (CRP)⁸ and endothelin-1 (ET-1),⁹ and appears to beneficially attenuate LV remodeling after MI.^{10,11} As intensive statins therapy lead to a lower CRP level compared with normal dose statins,¹² and anterior MI patients experience more pronounced post-infarction LV remodeling and dysfunction than non-anterior MI patients,¹³ we conducted this trial to explore whether a treatment with intensive statins could affect LV remodeling after anterior MI *via* its effect of anti-inflammatory and activity of inhibiting MMPs.

PATIENTS AND METHODS

Study population and protocol

This study was approved by the institutional ethic committee. Written informed consents were acquired from all patients. Inpatients with first time attack of ST-segment elevated acute anterior MI (AAMI) from March 2013 to July 2016 were candidates for the study. The inclusion criteria were: age ranged from 18 to 75 years; MI was diagnosed based on typical chest pain, cardiac enzyme elevation and persistent ST-segment elevation in 2 contiguous electrocardiographic leads; underwent successful primary percutaneous coronary intervention (PCI) within 12 h after chest pain onset. Exclusion criteria were: history of myocardial

infarction; history of treatment with statins; accompanied with non-sinus rhythm; cardiogenic shock; died during hospitalization; accompanied with hepatic disease, or creatinine level >2.0 mg/dl, or clinical and/or laboratory evidence of inflammatory disease. The eligible patients were randomly assigned into two groups: the intensive treatment (IT) group, who received atorvastatin 40 mg once daily immediately after diagnosis for 1 week, followed by 20 mg once daily; the standard treatment(ST) group, who received atorvastatin 20 mg once daily after the admission.

All PCIs were performed using femoral artery approach with Iopamidol (Bracco Sine, Shanghai, China). All patients were administrated with aspirin 300 mg/day plus clopidogrel 600 mg/day before PCI, and aspirin 100 mg/day plus clopidogrel 75 mg/day after PCI. Successful PCI was identified if angiographic residual stenosis of the involved vessel was <20% by visual estimation, without any in-hospital major complication (acute myocardial infarction, repeat PCI, or death).

Blood sampling and laboratory analysis

Multiple peripheral blood samplings were performed on admission, at 1 week, 2 weeks after initial onset of AAMI, and at 6 months follow-up. Whole blood was immediately collected into tubes containing heparin sodium and ethylene diamine tetraacetate (EDTA). The heparin sodium blood samples were used to examine high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), Creatine kinase-myocardial isoenzyme (CK-MB) by a clinical automatic analyzer (Hitachi 7600, Tokyo, Japan). The EDTA blood was centrifuged at 1500 g for 15 min at room temperature and the plasma were stored at -80°C until use. The plasma levels of high-sensitivity C-reactive protein (Hs-CRP) was quantified using high-sensitivity enzyme-linked immunosorbent assay (ELISA) kit (Yingchuang Biotechnology, Houzhou, China). ELISA kits were used to quantify Malonaldehyde (MDA) (Jiancheng Biotechnology, Nanjing, China), ET-1 (Bangding taiké Biotechnology, Beijing), MMP-2 and MMP-9 (both

Meridian Life Science, Saco USA). N-terminal pro-brain natriuretic peptide (NT-pro-BNP) was measured using an electro-chemiluminescence immunoassay (Roche Cobas E601, Mannheim, Germany). All the measurements followed the manufacturer's instructions.

Echocardiography and measurements

The echocardiographic studies were performed on admission, at 2-weeks follow-up and 1 year follow-up after PCI. Echocardiographic examinations were performed using a commercially available sonographer system (Vivid 7, GE, Milwaukee, WI, USA) with a 3.5-MHz phased array transducer. Performers were blind to the grouping information of each patient. Echocardiographic examinations were performed with the patient taking supine position. Two-dimensional images were recorded and measured. Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) were measured on the apical two-chamber view and apical four-chamber view respectively. Left ventricular ejection fraction (LVEF) was calculated using the Simpson's method.¹⁴

Statistical analysis

Continuous variables were described as mean $\pm$ standard deviation; categorical variables were described

as number and percentage. Normal distribution was tested by the Kolmogorov-Smirnov test. Differences in baseline parameters between the two groups were analyzed using independent-samples *t* test or the Chi-Square test where appropriate. Levels of hs-CRP, MMPs, MAD, ET-1 and the LV remodeling parameters in-group assessments were analyzed by the repeated measures test with the post hoc LSD test. Multivariate analysis of variance (MANOVA) was used in comparison of the data between the two groups with the post hoc LSD test. All probability values were 2-sided, and a *P* value of less than 0.05 was considered significant. All statistical analyses were performed by using SPSS 19.0.

RESULTS

Clinical information of patients

Totally 22 out of 125 illegible patients were excluded for reasons shown in the flowchart (**Fig. 1**), and 103 patients were finally enrolled in the study. There were no significant differences between the two groups in terms of age, gender, hypertension, diabetes Mellitus, smoking, baseline levels of HDL-C, LDL-C, peak CK-MB, time from symptom onset to PCI, single/multi-vessel disease, as well as medications after PCI (**Table 1**).

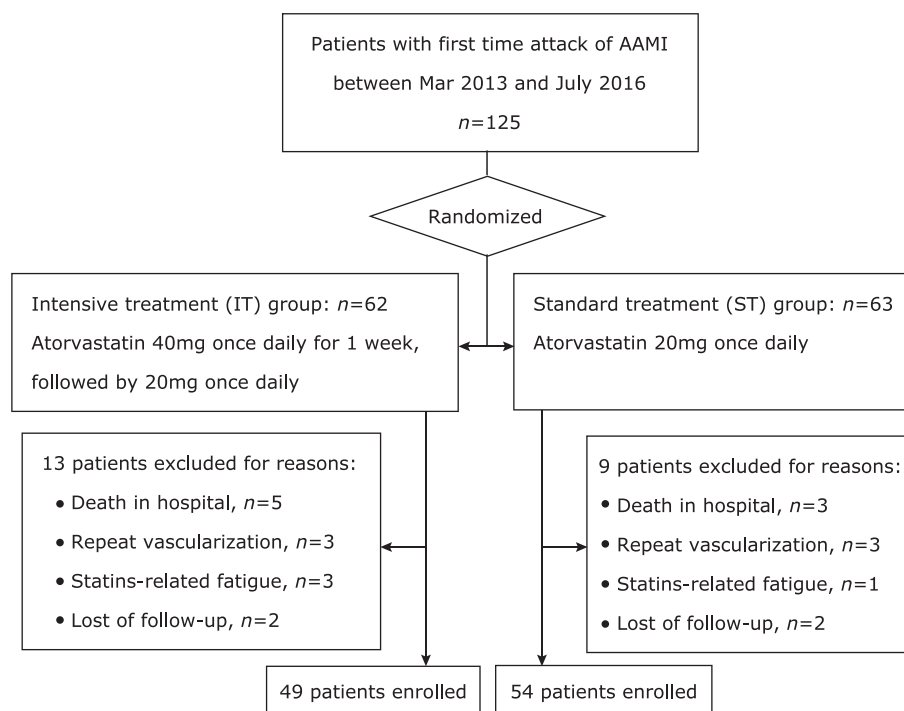


Figure 1. Flowchart of the study cohort.

Table 1. Comparison of clinical characteristics of AAMI patient between the ST group and the IT group[§]

Clinical characteristics	ST group (n=54)	IT group (n=49)	t/ χ^2 value	P value
Age, years	64±11	61±10	1.188	0.239
Gender				
Male, n (%)	35(64.8)	33(67.3)	0.073	0.682
Female, n (%)	19(35.2)	16(32.7)		
Risk factors				
Hypertension, n (%)	15(27.8)	16(32.7)	0.290	0.590
Diabetes Mellitus, n (%)	13(24.1)	10(20.4)	0.199	0.655
smoking, n (%)	21(38.9)	14(28.6)	1.219	0.270
Laboratory parameters				
HDL-C, mmol/L	1.57±0.36	1.66±0.38	1.014	0.315
LDL-C, mmol/L	3.24±0.75	3.11±0.75	0.774	0.466
Peak CK-MB, U/L	188.8±135.5	221.0±141.6)	0.872	0.352
PCI parameters				
Time from onset to revascularization, min	387±174	327±168	0.726	0.161
Single-vessel /multi-vessel	41/13	35/14	0.269	0.604
Contrast media volume, ml	142±29	154±38	1.512	0.135
Medications after PCI				
Aspirin, n (%)	54(100)	49(100)	NA	NA
Clopidogrel, n (%)	54(100)	49(100)	NA	NA
Beta blockers, n (%)	46(85.2)	40(81.6)	0.235	0.628
ACE-I or ARB, n (%)	44(81.5)	38(77.6)	0.245	0.621

§: Plus-minus values are means±SD.

ST: standard treatment; IT: intensive treatment; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; CK-MB: creatine kinase-myocardial isoenzyme; ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; PCI: percutaneous coronary intervention; NA: not available.

Effects of atorvastatin treatment on plasma hs-CRP, ET-1, MDA and MMPs

There were no significant differences in pro-BNP, hs-CRP, ET-1, MDA, MMP-2 and MMP-9 levels at admission between the two groups. Plasma levels of hs-CRP, ET-1, MDA, MMP-2 and MMP-9 in both groups continuously decreased over time after the treatments. In IT group, the levels of pro-BNP, hs-CRP, ET-1 and MMP-9 were significantly lower compared with that of ST group at 1 week after MI onset (all $P < 0.05$) (**Table 2**).

Effects of atorvastatin treatment on LV remodeling parameter

The 1 year echocardiographic follow-up showed that the LVEDV and LVEF in both groups significantly increased compared with that of baseline ($P < 0.01$ for all comparisons). The LVESV at 1 year follow-up did not change significantly compared with that of baseline in both groups. NO differences were found between both groups in LVEDV, LVESV and LVEF on admission, at 2 week and at 1 year follow-up. The changes in LVEDV,

LVESV and LVEF over the follow up time were not significantly different between the two groups either (**Table 3**).

DISCUSSION

Since significant inflammatory response as well as oxidative stress occurs soon after AAMI, and the LV remodeling is developed subsequently, in the study, we aimed to explore whether short-time high-dose atorvastatin can prevent LV remodeling *via* inhibiting inflammation and attenuating oxidative stress. Our study showed that intensive treatment with 40 mg atorvastatin for one week in patients with AAMI could decreased the levels of Pro-BNP, hs-CRP, ET-1 and MMP-9 temporarily, but this beneficial effect did not translate into an improvement of LV remodeling at 1 year follow up.

CRP is a highly sensitive, but nonspecific marker of systemic inflammation. Clinical studies have demonstrated the peak circulating level of CRP after MI is correlated with adverse outcomes such as LV remodeling,

Table 2. Comparison of Pro-BNP and Hs-CRP at different time points and between the IT and ST group[§]

Patient group	Pro-BNP, ng/L				F value	Hs-CRP, mg/L				F value
	admission	1 week	2 weeks	6 months		admission	1 week	2 weeks	6 months	
IT group (n=49)	438±291	298±222*	311±241	305±209	14.875	9.6±3.2	6.1±2.7*	3.6±1.8 [#]	3.0±1.5	81.369
ST group (n=54)	445±236	397±253	344±261	328±245	3.369	9.8±3.6	7.7±3.2*	4.5±2.0 [#]	3.4±1.7 [‡]	73.066
F value	0.382	4.603	1.981	0.413		0.140	7.718	5.532	1.172	
P value	0.510	0.032	0.144	0.368		0.709	0.009	0.021	0.282	

Patient group	ET-1, ng/L				F value	MDA, nmol/l				F value
	admission	1 week	2 weeks	6 months		admission	1 week	2 weeks	6 months	
IT group (n=49)	68.8±12.4	50.6±10.9*	41.1±10.6 [#]	35.7±8.4 [‡]	105.460	12.0±2.6	5.1±2.3*	3.8±1.3 [#]	3.6±1.3	140.583
ST group (n=54)	66.1±11.5	57.7±253*	44.5±10.7 [#]	37.9±9.9 [‡]	97.477	11.2±2.4	5.3±1.8*	4.2±1.5 [#]	4.0±1.5	138.848
F value	1.215	7.882	2.587	1.397		2.557	0.621	0.204	0.164	
P value	0.273	0.006	0.111	0.240		0.113	0.429	0.604	0.782	

Patient group	MMP-2, µg/L				F value	MMP-9, µg/L				F value
	admission	1 week	2 weeks	6 months		admission	1 week	2 weeks	6 months	
IT group (n=49)	270±110	236±103*	241±111	218±88 [‡]	2.635	93±47	57±28*	46±25 [#]	39±20 [‡]	47.039
ST group (n=54)	259±106	240±103*	232±99	210±93 [‡]	1.047	97±47	77±42*	51±28 [#]	41±24 [‡]	15.443
F value	0.218	0.104	0.168	0.142		0.711	4.834	0.434	0.551	
P value	0.688	0.881	0.721	0.771		0.723	0.028	0.501	0.614	

§: Plus-minus values are means±SD.

Pro-BNP: pro-brain natriuretic peptide; Hs-CRP: high-sensitivity C-reactive protein; ET-1: endothelin-1; MDA: malonaldehyde; MMP: matrix metalloproteinase. **P*<0.05 compared to the values on admission; [#]*P*<0.01 compared to the values at 1 week;

[‡]*P*<0.05 compared to the values at 2 week.

Table 3. Comparison of echocardiographic parameters in left ventricular remodeling between the ST group and the IT group on admission, at 2 weeks and 1 year follow-up[§]

Echocardiographic parameter	Time points	ST group (n=54)	IT group (n=49)	t value	P value
LVEDV, ml	Admission	108±17	103±16	1.184	0.241
	2 weeks	109±17	104±17	1.079	0.294
	1 year	119±17*	115±19 [#]	0.722	0.444
	Δ	10.8±5.6	12.3±6.7	1.041	0.311
LVESV, ml	Admission	55±10	51±11	1.081	0.207
	2 weeks	54±11	52±11	1.157	0.287
	1 year	54±9	51±13	1.228	0.221
	Δ	-0.3±4.6	-0.4±3.5	0.092	0.927
LVEF, n(%)	Admission	49±7	50±8	0.734	0.551
	2 weeks	50±7	51±8	0.423	0.693
	1 year	54±7 [‡]	56±8 [‡]	1.354	0.187
	Δ	4.7±3.3	6.0±4.6	1.488	0.154

§: Plus-minus values are means ± SD; Δ: changes of values at the 1 year from the admission.

LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction. Significant changes compared to the values at admission: **t*=11.054, *P*=0.000; [#]*t*=10.364, *P*=0.000; [‡]*t*=8.953, *P*=0.000; [‡]*t*=7.620, *P*=0.000.

development of heart failure, and death.^{15,16} The deleterious effect of CRP on post-MI LV remodeling may be associated with increased MMP-9 activity in the border zone.¹⁶ Extracellular Matrix (ECM) breakdown by MMPs play essential roles in LV remodeling of the post-MI, and changes in expression of MMP-2 and MMP-9 and their activities have been identified in LV remodeling. MDA is a stable end product of lipid peroxidation and serves as a reliable marker for the assessment of free radical induced damages to tissue. Our study showed that short-term high-dose atorvastatin could further decreased hs-CRP and MMP-9 but not MMP-2 and MDA levels, which was consistent with study results of Tousoulis,¹⁷ who demonstrated that short term treatment with 40 mg/day of atorvastatin exerted beneficial impact on MMP-9 level.

This study further investigated whether there is an improvement of LV remodeling which was associated to these beneficial effects. We found that among the patients in the short-time high-dose atorvastatin treatment group, LV remodeling parameters at one-year follow-up were not significantly different compared to patients with standard treatment. There are several possible explanations. Firstly, although short-term high-dose atorvastatin could significantly inhibit the inflammatory response, this effect may be not strong enough to completely correct the inflammatory damage. Secondly, ECM is remodeled by MMPs, which is a large family of zinc-dependent proteases. Previous studies have showed that MMP-3, MMP-8 and Membrane Type 1-Matrix Metalloproteinase (MT1-MMP) were also involved in LV remodeling besides MMP-9 and MMP-2.¹⁸ Inhibiting MMP-9 activity solely may not be enough to prevent ECM degradation and LV remodeling. Thirdly, LV remodeling after MI involves both the infarcted and non-infarcted LV myocardium, therefore, seven days of high-dose atorvastatin may be not sufficient to exert a significant effect on LV remodeling. Finally, LV remodeling is a continuous process that last for months or years, 1 year follow up in this study may not be long enough to appreciate a significant change in LV remodeling.

It has been previously reported that short-term treatment (4 weeks) of atorvastatin at a dose of 40 mg/day in patients with ischemic heart failure exerted beneficial impact on endothelial function, arterial stiffness and LV remodeling.¹⁷ This trial enrolled patients who had suffered from heart failure and been followed up for 4 weeks, and demonstrated that atorvastatin

40 mg/day resulted in significantly decreased level of serum MMP-9, which was a biomarker of left ventricular remodeling. Ours study also confirmed that short-term treatment with atorvastatin at a dose of 40 mg/day in patients with AAMI could significantly reduce MMP-9 levels, but it did not result in an improvement of echocardiographic parameters.

Elevated level of ET-1 has been shown to be associated with post AMI death.¹⁹ Previous study has shown that statin therapy could significantly reduce circulating ET-1 concentrations.⁹ We evaluated the effect of short time high-dose atorvastatin on ET-1 level and found that compared with normal dose, high-dose atorvastatin was further associated with reduced ET-1 levels in patients with MI. Restricted by the costs and length of follow up, this study was not able to investigate whether the reduced ET-1 level could further improve endothelial function or reduce cardiovascular mortality.

The limitations of this study also include: first, the inadequate number of patients limit the power of the results in this study, and prospective study with a larger sample size would help to confirm the present observations. Secondly, the one-year follow-up in the current study may not be long enough to appreciate a significant change in LV remodeling. Thirdly, only plasma MMP-2 and MMP-9 activity were measured, while the tissue inhibitors of metalloproteinases (TIMPs) which specifically inhibit MMPs activity in tissue were not measured in this study.

In conclusion, the present study shows that short-term high-dose atorvastatin treatment in ST-elevation AAMI could significantly decrease hs-CRP, ET-1, MMP-9 and pro-BNP levels. This beneficial effect did not result in improvement of LV remodeling. Our study suggests that large scale clinical trial that observe the long-term effects of high-dose atorvastatin should be carried out to further evaluate the potential benefit of high dose of atorvastatin on LV remodeling.

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