HMG CoA reductase inhibition and left ventricular mass in hypertrophic cardiomyopathy: a randomized placebo-controlled pilot study

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Abstract

Background Statins reduce cardiomyocyte hypertrophy in animal models of hypertrophic cardiomyopathy, aortic banding and heart failure after myocardial infarction. We investigated the effect of the hydroxymethylglutaryl coenzyme A reductase inhibitor atorvastatin on left ventricular (LV) mass in patients with hypertrophic cardiomyopathy in a randomized placebo-controlled double-blind pilot study.

Materials and methods Patients with hypertrophic cardiomyopathy were randomized to be treated once daily by atorvastatin 80 mg or placebo for nine months. LV mass was assessed by serial cardiac magnetic resonance imaging. LV systolic and diastolic function was determined by echocardiography. Markers of collagen metabolism and inflammation were also assessed.

Results Out of 78 screened patients with hypertrophic cardiomyopathy 28 (2 × 14) patients were eligible for randomization. Eleven patients in each group completed the study with cardiac magnetic resonance imaging assessments meeting the evaluation standards at baseline and at follow-up. Low-density lipoprotein cholesterol levels in the atorvastatin group decreased from 3·24 ± 1·14 mmol L\(^{-1}\) (125 ± 44 mg dL\(^{-1}\)) at baseline to 1·37 ± 0·49 mmol L\(^{-1}\) (53 ± 19 mg dL\(^{-1}\)) at follow-up (\(P<0·001\)), but were unchanged in the placebo group. Baseline LV mass was 228 ± 51 g in the placebo and 232 ± 67 g in the atorvastatin group. The primary endpoint of change in LV mass from baseline to follow-up was 2 ± 10% in the atorvastatin group versus 0 ± 13% in the placebo group (\(P = NS\)). Parameters of LV volumes and diameters, systolic and diastolic function, and markers of collagen metabolism were also unchanged in both groups.

Conclusion In patients with hypertrophic cardiomyopathy, this randomized placebo-controlled double-blind pilot study did not demonstrate an effect of 9-month treatment with atorvastatin 80 mg on LV mass reduction.

Keywords Cholesterol, HMG CoA reductase inhibition, hypertrophic cardiomyopathy, left ventricular mass.


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Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetically determined cardiomyopathy. The disease is caused by multiple mutations in the various genes coding for sarcomeric proteins and associated with cardiomyocyte hypertrophy, fibre disarray and interstitial fibrosis. To establish the diagnosis of HCM, several other causes for left ventricular (LV) hypertrophy must be excluded such as hypertensive heart disease, aortic stenosis, or Fabry disease [1]. HCM is a common cause of sudden cardiac death and leads to the development of heart failure signs and symptoms as the disease progresses [2]. While surgical myectomy or catheter-guided septum embolization can effectively reduce hypertrophied tissue in patients with obstructive HCM, medical therapy of HCM consisting mainly of beta-blockers or calcium antagonists mostly aims at improving clinical symptoms and haemodynamics. So far, none of the existing pharmacological therapies for HCM has been shown to impact on hypertrophy or fibrosis.

The primary abnormality in HCM appears to be impaired myocardial function resulting from alterations of the contractile apparatus [3]. The molecular mechanism of HCM is not quite clear but myocyte stress is considered to activate intracellular signalling similar to the induction of LV hypertrophy in pressure overload. In animal models of LV hypertrophy either induced by aortic banding or by angiotensin II-infusion, hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibition attenuated LV hypertrophy [4]. Furthermore, LV remodelling and function was improved in rats and mice with heart failure after myocardial infarction by statin treatment with concomitant reduction of LV hypertrophy and fibrosis [5–8]. As recently reviewed in detail [9], pleiotropic cardiac effects of statin treatment may also reduce LV mass in patients with hypertension and angina [10,11], and a retrospective analysis showed an association between statin use and lower mortality in diastolic heart failure [12]. In a rabbit model of HCM, statin treatment lowered LV mass by 37% and improved diastolic function [13]. However, the effects of statins on LV mass in patients with HCM are unknown.

Atorvastatin is a very effective and well-tolerated HMG-CoA reductase inhibitor [14,15]. The hypothesis for the present randomized placebo-controlled double-blind pilot study was that atorvastatin 80 mg once daily for nine months would reduce LV mass and improve LV function in patients with HCM.

Patients and methods

Study design

We conducted a single centre, randomized, double-blind, placebo-controlled pilot study in patients with HCM to evaluate the effects of a nine month treatment with atorvastatin 80 mg, or placebo, once daily on LV mass assessed by cardiac magnetic resonance imaging (CMR) at baseline and after nine months. The primary endpoint was defined as the percent (%) change of LV mass from baseline to follow-up. Secondary endpoints were percentage change of LV volume and LV function measured by CMR, % change of LV mass, LV volume and LV function measured by echocardiography. In addition, the effects of atorvastatin on high sensitivity C-reactive protein, serum lipids, and safety parameters were determined. Patients were randomized 1 : 1 after a two week safety run-in phase with atorvastatin 40 mg once daily after which a venous blood sample was analysed for troponin T, creatinine kinase, myoglobin, and liver enzymes. Drug and placebo tablets for the study were provided by Pfizer (Karlsruhe, Germany). All participants signed informed consent forms. The study was approved by the Ethics Committee of the Medical Faculty of Würzburg University and conducted in accordance with the principles outlined in the declaration of Helsinki. Figure 1 shows the CONSORT diagram for study patients screened providing details of exclusion and dropout criteria. Of 78 patients screened, 28 entered and 22 completed the study according to protocol. The diagnosis of HCM was derived from trans-thoracic two-dimensional echocardiography based on the typical characteristics of the left ventricle, and verified by CMR. All investigators were kept blinded until all measurements (including reproducibility analyses of CMR scans) had been completed.

Inclusion and exclusion criteria

Patients older than 18 years were eligible if they were on stable optimized therapy for at least 2 months, had no other causes for LV hypertrophy (e.g. arterial hypertension, aortic stenosis, athlete’s heart or Fabry disease), and gave written informed consent prior to study start. We excluded patients with absolute indications for cholesterol lowering therapy [i.e. low density lipoprotein (LDL) cholesterol above 5-70 mmol L⁻¹ (220 mg dL⁻¹) on two repeated measurements
patients at baseline and at the final visit. As an index for LV hypertrophy was measured for all occasions, signs of pulmonary congestion, known malignancy, previously known lack of compliance with treatment recommendations or alcohol abuse, and contraindications for CMR scanning.

Sample size considerations

To estimate the sample size, the following assumptions were made: a mean LV mass of 220 g in HCM patients [16], a standard deviation of 7% between pairs of CMR scans, and a dropout rate of 20%. Since animal studies had suggested a marked decrease in LV mass we applied a one-sided alpha of 2.5%. This resulted in 90% power to detect a 10% change in LV mass by CMR [17–19] using nine subjects per group in the final analysis. Hence, 13 patients per group had to be included.

CMR measurements and reproducibility

CMR was performed on a 1.5-T whole body scanner (Magnetom Vision, Siemens Medical Solutions, Erlangen, Germany) by using a four channel cardiac array coil wrapped around the chest. After localization of the heart, 10–12 short-axis cine movies of the LV were required to cover the entire heart from base to apex. Image parameters of the segmented FLASH cine sequence employed during acquisition were as follows: repetition time (TR) 80 ms, excitation time (TE) 2.1 ms, 224 × 256 image matrix 7/8 field of view (FOV) 28–32 cm, slice thickness 10 mm, no interslice gap, flip angle 30°. Images were acquired during multiple short breath-holding (12–15 s) at inspiration and ECG gating (Fig. 2). The time resolution achieved in the cine images was 40 ms. Quantitative cardiac functional analysis included: determination of end-diastolic diameter, end-systolic/end-diastolic volumes, ejection fraction and left ventricular mass. Endo- and epicardial borders at end-systole and end-diastole were manually traced using a commercially available software package (Argus, Siemens Medical Solutions, Erlangen, Germany). Data analysis was performed by two independent observers (CW, FF). To assess intraobserver reproducibility ten randomly selected scans were re-evaluated for a second time at a time interval of 14 days.

Electrocardiography

Electrocardiograms were routinely obtained according to the study protocol at baseline, at 4 months, and at the final visit. Electrocardiograms were interpreted by an observer blinded to other clinical data (MK). Besides standard time intervals the Sokolow-Lyon voltage criterion ($S_{V1/V2} + R_{V5/V6}$) as an index for LV hypertrophy was measured for all patients at baseline and at the final visit.

Echocardiographic image acquisition

Transthoracic echocardiography was performed at baseline and after 9 months using a Vingmed System 7 scanner (GE Ultrasound, Horten, Norway). All data were stored digitally for subsequent offline analysis. Three heart cycles of each apical 4- and 2-chamber view were captured by conventional 2-dimensional B-mode, and LV ejection fraction was calculated according to Simpson’s biplane method. LV wall thickness and diameters were measured from standard left parasternal long axis views. To measure transmural flow, the pulsed Doppler sample volume was positioned between the tips of the mitral valve leaflets and peak flow velocity in early diastole and during atrial contraction (E and A wave) were measured [20]. Using the 4-chamber view, a pulsed wave tissue Doppler trace of the lateral mitral annulus was extracted. From this trace, the early diastolic ring velocity ($E’$) was measured and the E/E’ ratio was calculated for the assessment of diastolic function. Further, real time 2-dimensional colour Doppler myocardial imaging data (CDMI) were recorded from all LV walls using standard apical views as described previously [21]. CDMI data derived from the most hypertrophic segments were post processed to strain rate curves using dedicated software (Echopac®, GE Ultrasound, Horten, Norway). The region of interest was manually adjusted frame by frame to comprise the same region of interest throughout the entire cardiac cycle. Strain rate profiles were averaged over three consecutive cardiac cycles and integrated over time to derive natural strain profiles using end-diastole as the reference point (Speqle®, University of Leuven, Belgium). From the resulting curves peak systolic strain rate and end-systolic strain were derived [21].

Collagen markers

Blood samples were centrifuged and plasma and serum stored at −70°C until assayed. Serum pro-collagen type I N-terminal pro-peptide (PINP), pro-collagen type III N-terminal pro-peptide (PIIINP), and collagen type I C-terminal telopeptide (ICTP) were measured by radioimmunoassay (Orion Diagnostica, Finland), and plasma matrix metalloproteinase-9 (MMP-9), and tissue inhibitor of MMP-1 (TIMP-1) by ELISA (Amersham, Braunschweig, Germany). All markers were measured in duplicate according to the manufacturer’s protocol. The remaining serum and plasma parameters were measured as part of the clinical routine in the Central Laboratory of the University Hospital Würzburg.

Data analysis

Continuous data were described with mean (SD) or median (25–75%ile) and categorical data with percent frequency. Comparisons between groups were made using the Mann–Whitney U-test or Fisher's exact test, as appropriate. Comparisons over time within groups were made by Wilcoxon's
test for paired observations. The primary endpoint, i.e. the comparison of the change in LV mass between atorvastatin and placebo, and all other change variables of interest were compared using a $t$-test after testing for equality of variances by Levene's test. All change variables listed above were re-analysed by ANOVA (difference of follow-up minus baseline as dependent variable, with adjustment for respective baseline levels) revealing very similar $P$-values in all instances.

**Results**

**Baseline characteristics, LDL cholesterol, C-reactive protein**

The characteristics of the patient cohort are listed in Table 1. According to guidelines, symptomatic patients were on beta-blockers or calcium antagonists, which are thought to allow increased ventricular filling, decrease myocardial oxygen demand and increase myocardial perfusion. Asymptomatic patients were not treated, as due to the lack of proven prognostic benefits, pharmacological therapy for these patients is not recommended. Although treatment with calcium channel blockers tended to be more common in the placebo than in the atorvastatin group, there were no significant differences between both groups at baseline. None of the participants showed clinical signs or symptoms of decompensated heart failure at baseline. LDL cholesterol levels were similar in both groups at baseline ($P = \text{NS}$) and decreased in the atorvastatin group from $3.24 \pm 1.14 \text{ mmol L}^{-1} (125 \pm 44 \text{ mg dL}^{-1})$ at baseline to $1.37 \pm 0.49 \text{ mmol L}^{-1} (53 \pm 19 \text{ mg dL}^{-1})$ at follow-up ($P < 0.001$), but were unchanged in the placebo group $[3.52 \pm 1.22 \text{ mmol L}^{-1} (136 \pm 47 \text{ mg dL}^{-1})$ and $3.41 \pm 0.80 \text{ mmol L}^{-1} (132 \pm 31 \text{ mg dL}^{-1})$, respectively; $P = \text{NS}$].
Figure 3 shows the respective changes during four measurement points in the course of the study ($P < 0.001$ for comparison of the change from baseline to final visit between groups). The median (25–75%ile) C-reactive protein levels showed a trend to decrease in the atorvastatin group from $0.16 (0.07–0.60) \text{mg dL}^{-1}$ at baseline to $0.07 (0.04–0.08) \text{mg dL}^{-1}$ at follow-up ($P = 0.11$), but remained unchanged in the placebo group [$0.14 (0.07–0.50)$ and $0.14 (0.08–0.28) \text{mg dL}^{-1}$, respectively; $P = 0.91$]. The comparison of the change in C-reactive protein levels between groups also showed a trend towards a decrease ($P = 0.090$).

Left ventricular mass (primary endpoint), morphology and function assessed by CMR

The intraobserver variability coefficient for ten randomly selected scans of LV mass measured by CMR was 3.2%. The respective Bland-Altman plot showed good agreement without any systematic measuring drift (Fig. 2). LV mass as assessed by CMR was $228 \pm 51 \text{g}$ in the placebo group and $232 \pm 67 \text{g}$ in the atorvastatin group at baseline. The primary endpoint of change in LV mass was $2 \pm 10\%$ in the atorvastatin group vs. $0 \pm 13\%$ in the placebo group ($P = 0.932$, Fig. 4). LV volume and diameters, as well as ejection fraction were not different at baseline, and there were no significant changes in either group during follow-up (Table 2).

Left ventricular morphology and function assessed by echocardiography

LV wall thickness, end-systolic and end-diastolic diameters, LV volumes, as well as ejection fraction and systolic strain rate and strain values were not different at baseline, and there was no significant change in either group during follow-up (Table 2). There was no difference in the indexes of diastolic function at baseline; however, there was a trend towards worsening of diastolic dysfunction during follow-up, which was similar in both groups (Table 2).

Left ventricular hypertrophy assessed by electrocardiography

The electrocardiographic Sokolow-Lyon index of LV hypertrophy was not different at baseline, and there was no significant change in either group during follow-up (Table 2).
Table 2: Baseline values and percent change at follow-up of cardiac magnetic resonance imaging, echocardiography, electrocardiography, and collagen markers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Atorvastatin</th>
<th>Placebo</th>
<th>Atorvastatin</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td></td>
<td>n = 11</td>
<td>n = 11</td>
<td>n = 11</td>
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<tr>
<td>Cardiac magnetic resonance imaging</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Left ventricular mass, g</td>
<td>228 ± 51</td>
<td>232 ± 67</td>
<td>0 ± 13</td>
<td>2 ± 10</td>
<td>0.932</td>
</tr>
<tr>
<td>End diastolic diameter, mm</td>
<td>44 ± 4</td>
<td>42 ± 6</td>
<td>3 ± 12</td>
<td>5 ± 13</td>
<td>0.589</td>
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<tr>
<td>End diastolic volume, ml</td>
<td>117 ± 22</td>
<td>112 ± 24</td>
<td>5 ± 21</td>
<td>-1 ± 21</td>
<td>0.570</td>
</tr>
<tr>
<td>End systolic volume, ml</td>
<td>38 ± 11</td>
<td>38 ± 14</td>
<td>5 ± 32</td>
<td>3 ± 27</td>
<td>0.940</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>67 ± 9</td>
<td>66 ± 10</td>
<td>1 ± 11</td>
<td>-1 ± 9</td>
<td>0.652</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
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<tr>
<td>Septal thickness, mm</td>
<td>15.8 ± 3.5</td>
<td>17.5 ± 5.0</td>
<td>2 ± 10</td>
<td>-5 ± 13</td>
<td>0.251</td>
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<td>Posterior wall thickness, mm</td>
<td>12.5 ± 1.9</td>
<td>13.2 ± 2.4</td>
<td>-4 ± 10</td>
<td>-3 ± 11</td>
<td>0.529</td>
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<tr>
<td>End diastolic diameter, mm</td>
<td>49.2 ± 6.9</td>
<td>46.6 ± 7.1</td>
<td>-1 ± 8</td>
<td>1 ± 9</td>
<td>0.282</td>
</tr>
<tr>
<td>End systolic diameter, mm</td>
<td>29.6 ± 6.1</td>
<td>28.8 ± 6.5</td>
<td>6 ± 13</td>
<td>6 ± 15</td>
<td>0.349</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>66.6 ± 6.1</td>
<td>63.7 ± 6.1</td>
<td>1 ± 10</td>
<td>0 ± 10</td>
<td>0.905</td>
</tr>
<tr>
<td>E/E'</td>
<td>6.8 ± 2.6</td>
<td>8.3 ± 5.4</td>
<td>21 ± 29</td>
<td>26 ± 32</td>
<td>0.356</td>
</tr>
<tr>
<td>Systolic strain rate, l/s</td>
<td>-0.8 ± 0.4</td>
<td>-0.9 ± 0.4</td>
<td>8 ± 36</td>
<td>-20 ± 35</td>
<td>0.142</td>
</tr>
<tr>
<td>Systolic strain, %</td>
<td>-11.9 ± 5.0</td>
<td>-11.3 ± 4.0</td>
<td>-7 ± 26%</td>
<td>-18 ± 32</td>
<td>0.496</td>
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<tr>
<td>Electrocardiography</td>
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<tr>
<td>Sokolow-Lyon index, mV</td>
<td>29.8 ± 9.8</td>
<td>35.0 ± 9.6</td>
<td>0 ± 33</td>
<td>-4 ± 29</td>
<td>0.882</td>
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<td>Collagen markers</td>
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<tr>
<td>TIMP-1, ng mL⁻¹</td>
<td>285 ± 49</td>
<td>314 ± 38</td>
<td>0 ± 13</td>
<td>-3 ± 19</td>
<td>0.905</td>
</tr>
<tr>
<td>MMP-9, ng mL⁻¹</td>
<td>865 ± 304</td>
<td>1046 ± 370</td>
<td>-13 ± 31</td>
<td>-24 ± 19</td>
<td>0.286</td>
</tr>
<tr>
<td>PINP, µg L⁻¹</td>
<td>37 ± 12</td>
<td>55 ± 23</td>
<td>5 ± 29</td>
<td>4 ± 27</td>
<td>0.519</td>
</tr>
<tr>
<td>PIIINP, µg L⁻¹</td>
<td>2.67 ± 0.46</td>
<td>2.79 ± 0.44</td>
<td>4 ± 36</td>
<td>5 ± 43</td>
<td>0.730</td>
</tr>
<tr>
<td>ICTP, µg L⁻¹</td>
<td>2.58 ± 0.89</td>
<td>3.47 ± 1.89</td>
<td>7 ± 34</td>
<td>8 ± 70</td>
<td>0.630</td>
</tr>
</tbody>
</table>

At baseline, no significant differences between groups were observed (Mann–Whitney U-test). 

P for comparison of the change from baseline to final visit between groups (Levene’s test followed by t-test). E/E’, index of diastolic performance from transmitral Doppler E wave and colour Doppler myocardial imaging E wave (for details see methods); TIMP-1, tissue inhibitor of matrix metalloproteinase-1; MMP-9, matrix metalloproteinase-9; PINP, pro-collagen type I N-terminal pro-peptide; PIIINP, pro-collagen type III N-terminal pro-peptide; ICTP, collagen type I C-terminal telopeptide.

Markers of collagen turnover

Collagen turnover was assessed by an array of serum markers of collagen metabolism as previously validated in patients with HCM [22]. However, none of the markers was significantly changed at follow-up (Table 2).

Discussion

In patients with HCM, this first randomized placebo-controlled double-blind pilot study did not detect an effect of a nine months treatment period with atorvastatin 80 mg on LV mass, dimensions, function, or collagen turnover.

Hypertrophy and fibrosis are the major clinical and pathological features of HCM, however, none of the existing pharmacological therapies for HCM is able to induce regression of hypertrophy or fibrosis, and no conclusive data are available about a reduction of mortality.

HMG-CoA reductase inhibition attenuated LV hypertrophy in several animal models, and improved LV remodelling and function [4–8]. In patients with hypertension and angina [10,11] statin treatment also reduced LV mass. In a rabbit model of HCM induced by cardiac-restricted expression of β-myosin heavy chain-glutamine 403, statins both prevented cellular signal-regulated kinase or mitogen-activated protein kinase. In addition, markers of oxidative stress were significantly attenuated by HMG-CoA reductase inhibition and diastolic dysfunction was improved [13]. Statins reduced the activation of ‘stress-responsive’ intracellular signalling molecules in HCM rabbits such as extracellular signal-regulated kinase or mitogen-activated protein kinase. In addition, markers of oxidative stress were significantly attenuated by HMG-CoA reductase inhibition [13,23].

Thus, there was a strong rationale for expecting a reduction of LV mass in patients with HCM by high-dose statin treatment. However, we neither observed an effect of atorvastatin on LV mass nor on other parameters of LV structure and function detected either by echocardiography, tissue Doppler imaging or CMR. Cine CMR is considered the reference standard for determination of LV mass as well as LV end-diastolic and -systolic volumes and ejection fraction.
and the present study showed good intraobserver variability in LV mass determination. According to our sample size calculation, our study had reasonable power to detect a 10% change in LV mass by CMR [17–19]. Post-hoc recalculation of the study power showed that under the given conditions a difference in change of LV mass of 10% could have been detected with a power of 79% at an alpha of 5%. Although the limited number of treated patients may have precluded the detection of a smaller beneficial effect of high-dose atorvastatin, the complete absence of any trend towards a reduction of LV mass or improvement in myocardial function suggests that a marked reduction of LV hypertrophy in HCM by statins is unlikely to be unmasked in larger studies with longer follow-up. With the percent change (SD) in LV mass found in the present study, a trial to detect differences between groups with a power of 90% at an alpha of 5% would need to include more than 600 participants per arm.

Beside the assessment of LV morphology (i.e. hypertrophy) this study also aimed at quantitative assessment of regional myocardial function by tissue CDMI. For the assessment of systolic function in the region of interest we extracted systolic strain rate and strain values, which are capable of detecting even subtle changes in myocardial function [25,26]. Values of strain and strain rate were clearly compromised if compared to healthy adults [27]. However, neither systolic strain rate, which is more related to regional contractility, nor systolic strain, which is related to stroke volume [27], disclosed an effect of atorvastatin treatment on myocardial function. With respect to the assessment of diastolic function using the index E/E′ a trend of worsening of diastolic function over time was observed, which was similar in both groups. Thus, using both the gold standard for the assessment of LV mass (= CMR) as well as sensitive methods for the quantitative assessment of myocardial systolic and diastolic function (= CDMI) [1] we demonstrated that there was no change in morphology and function during treatment.

The lack of effect on LV mass in our study is not the result of insufficient dosing of the statin or potential non-adherence to therapy in the verum group: We used a statin with well established effectiveness at the highest dose applicable in humans, and the marked drop in LDL cholesterol in the patients on active treatment during the complete follow-up is a clear indication of excellent adherence to therapy. Furthermore, high sensitivity C-reactive protein levels displayed a trend for reduction in the atorvastatin group; however, this did not reach statistical significance.

In the experimental rabbit model of HCM, statins were able to prevent the development of LV hypertrophy when started early [3,23]. As the penetrance of the mutations leading to hypertrophy in patients with HCM is age-dependent, it may be interesting to study the effect of HMG-CoA reductase inhibition started at an earlier time-point in patients with only mild hypertrophy. Our results do not exclude a role for statins in the prevention of hypertrophy in HCM. Also, HCM does not have a homogeneous aetiology and the genetic background is quite variable. Effects of statins may be present in some types of HCM but not in others and their detection may require larger or pre-selected samples.

In conclusion, in this first randomized placebo-controlled double-blind pilot study we did not detect an effect of a nine month high-dose statin treatment on LV mass in patients with HCM.

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Atorvastatin in hypertrophic cardiomyopathy