

# Effects of Losartan on Left Ventricular Hypertrophy and Fibrosis in Patients With Nonobstructive Hypertrophic Cardiomyopathy

Yuichi J. Shimada, MD,\* Jonathan J. Passeri, MD,† Aaron L. Baggish, MD,† Caitlin O'Callaghan, NP,† Patricia A. Lowry, MS, RN, APRN-BC,† Gia Yannekis, BA,† Suhny Abbara, MD,‡ Brian B. Ghoshhajra, MD,‡ Richard D. Rothman, MD,† Carolyn Y. Ho, MD,\* James L. Januzzi, MD,† Christine E. Seidman, MD,\*§|| Michael A. Fifer, MD†  
*Boston, Massachusetts*

- Objectives** The aim of this study was to evaluate the effects of losartan on left ventricular (LV) hypertrophy and fibrosis in patients with nonobstructive hypertrophic cardiomyopathy (HCM).
- Background** Despite evidence that myocardial hypertrophy and fibrosis are mediated by angiotensin II and are important determinants of morbidity and mortality in patients with HCM, no prior studies have evaluated the effects of angiotensin receptor blockers on LV hypertrophy and fibrosis with cardiac magnetic resonance imaging.
- Methods** In double-blind fashion, 20 patients (3 women, 17 men; age:  $51 \pm 13$  years) with HCM were randomly assigned to receive placebo (n = 9) or losartan 50 mg twice a day (n = 11) for 1 year. Cardiac magnetic resonance imaging was performed at baseline and 1 year to measure LV mass and extent of fibrosis as assessed by late gadolinium enhancement.
- Results** There was a trend toward a significant difference in the percent change in LV mass (median [interquartile range]: +5% [-4% to +21%] with placebo vs. -5% [-11% to -0.9%] with losartan; p = 0.06). There was a significant difference in the percent change in extent of late gadolinium enhancement, with the placebo group experiencing a larger increase (+31% ± 26% with placebo vs. -23% ± 45% with losartan; p = 0.03).
- Conclusions** This pilot study suggests attenuation of progression of myocardial hypertrophy and fibrosis with losartan in patients with nonobstructive HCM. Confirmation of these results in a larger trial is required to confirm a place for angiotensin receptor blockers in the management of patients with HCM. (Effect of Losartan in Patients With Nonobstructive Hypertrophic Cardiomyopathy; [NCT01150461](https://doi.org/10.1016/j.jchf.2013.09.001)) (J Am Coll Cardiol HF 2013;1:480-7) © 2013 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is characterized by left ventricular (LV) hypertrophy in the absence of pressure overload. Manifestations of the disease include heart failure

associated with diastolic dysfunction and atrial and ventricular tachyarrhythmias. HCM is the most common cause of sudden death in the young population (1). Pathological features of HCM include myocyte hypertrophy, interstitial fibrosis, and myocyte disarray (2). Observational studies have shown that LV hypertrophy and fibrosis are important determinants of morbidity and mortality in patients with HCM (3-5) and that both LV hypertrophy and extent of fibrosis may increase appreciably in a 2-year interval in patients with HCM (6). Our group reported that profibrotic molecules have increased expression in mouse HCM models and their expression precedes the onset of myocardial fibrosis (7). It has also been suggested that hypertrophy and interstitial fibrosis occur in response to trophic and fibrotic factors such as angiotensin II (8).

Animal and human studies have suggested that angiotensin II receptor blockers (ARBs) attenuate progression of

From the \*Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; †Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; ‡Cardiac MR PET CT Program, Department of Radiology and Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; §Howard Hughes Medical Institute, Boston, Massachusetts; and the ||Department of Genetics, Harvard Medical School, Boston, Massachusetts. Dr. Ho has received financial support from the National Institutes of Health. Dr. Januzzi has received grants from Roche, Critical Diagnostics, BG Medicine, Siemens, Singulex, Novartis, Amgen, Zensun, and Thermo Fisher Scientific. Dr. Seidman is a founder and owns shares of Myokardia Inc., a startup company that is developing therapeutics that target the sarcomere, and has received financial support from the National Institutes of Health and the Howard Hughes Medical Institute. Dr. Fifer has received financial support from Merck & Co., Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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LV hypertrophy and fibrosis in HCM. We have shown that transforming growth factor (TGF)- $\beta$  is an important mediator of profibrotic signals and that early inhibition of TGF- $\beta$  (by administration of TGF- $\beta$  neutralizing antibodies or losartan) diminishes the development of fibrosis independently of blood pressure (9). In a mouse model of HCM, losartan reversed cardiac interstitial fibrosis and decreased expression of collagen 1- $\alpha$  and TGF- $\beta$  (10). In humans, valsartan decreased the serum concentration of procollagen type 1 (11). Yamazaki *et al.* (12) and Penicka *et al.* (13) observed that LV mass decreased during 1 year of treatment with losartan or candesartan, respectively. Furthermore, improvement in symptoms and parameters of diastolic function and decreases in left atrial size and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations were observed in association with administration of losartan in a non-randomized trial (14).

To date, no studies have assessed the effect of an ARB on the progression of both myocardial hypertrophy and LV fibrosis by cardiac magnetic resonance imaging (CMR) in patients with HCM. We therefore designed the present study to test the hypothesis that treatment with the ARB losartan would attenuate the progression of both myocardial hypertrophy and myocardial fibrosis in patients with non-obstructive HCM.

## Methods

**Study participants.** We assessed all patients followed up in the Hypertrophic Cardiomyopathy Program at Massachusetts General Hospital between April 1, 2007, and March 31, 2010, for study eligibility. HCM was diagnosed in the presence of LV hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient (15). Inclusion criteria included age  $\geq 18$  years, resting blood pressure  $\leq 140/90$  mm Hg, LV ejection fraction  $\geq 0.55$ , and absence of LV intracavitary or outflow tract obstruction (gradient  $< 30$  mm Hg at rest and with Valsalva maneuver). Patients with a contraindication to losartan such as pregnancy or lactation, with a contraindication to CMR such as a pacemaker or an implantable cardioverter-defibrillator, with a contraindication to gadolinium administration such as renal insufficiency with an estimated glomerular filtration rate  $< 60$  ml/min, with hemodynamic instability, or already taking an angiotensin-converting enzyme inhibitor or ARB were excluded from the study. The Partners Institutional Review Board approved the study protocol, and all participants provided written informed consent.

**Study design and protocol.** This was a prospective, randomized, placebo-controlled, double-blind study. The primary endpoint was the percent change in the extent of LV myocardial fibrosis assessed by late gadolinium enhancement (LGE) on CMR between baseline and 1 year. The secondary endpoint was the percent change in LV mass at 1 year as measured by CMR. Participants were randomly

assigned to one of the 2 treatment arms. Initial treatment was losartan 50 mg once daily or matching placebo tablet once daily. The dosage of losartan and matching placebo tablet was increased to twice daily (a total of 100 mg/day in the losartan group) if the lower dosage was well tolerated after 1 week. It was advised that all participants continue their other medications and maintain pre-study exercise regimens. At enrollment and at 1 year, participants underwent CMR with gadolinium enhancement to assess the primary and secondary study endpoints by investigators blinded to group allocation. Participants also underwent a comprehensive medical history and physical examination, New York Heart Association class assessment, Minnesota Living with Heart Failure Questionnaire assessment, peripheral venous blood sampling, electrocardiography, 6-min walk test, and 2-dimensional and Doppler echocardiography at both study visits. Interim follow-up evaluations at 3 and 6 months were conducted to determine symptom status, medication compliance, and vital signs. The data from the follow-up visits were reviewed to detect potential adverse effects with the plan to discontinue the study drug if any adverse effects possibly attributable to losartan were observed.

Because there were no published data using serial CMR to assess the reduction in myocardial fibrosis in patients with HCM after a therapeutic intervention, the sample size calculation was based on a study of hypertensive patients that showed a  $30 \pm 8\%$  relative reduction ( $20 \pm 7\%$  reduction in patients without severe baseline fibrosis) in the degree of fibrosis estimated by carboxy-terminal propeptide of type I procollagen after 1 year of treatment with losartan (16). We assumed that a 20% change in fibrosis would be of scientific and clinical interest and estimated that the SD would be 15% based on more heterogeneous involvement of the myocardium in patients with HCM compared with patients with hypertension. On the basis of these assumptions, we calculated that enrollment of 20 patients would yield a power of 80% to detect an effect of losartan on the extent of fibrosis.

**Biochemical analysis.** A 10-ml sample of blood was obtained from the peripheral vein and immediately separated by centrifugation, with aliquots stored at  $-80^{\circ}\text{C}$ . Concentrations of NT-proBNP were measured using a commercially available immunoassay (Elecys proBNP; Roche Diagnostics, Indianapolis, Indiana). Additional samples were obtained simultaneously for analysis of collagen turnover markers as well as soluble ST2 and galectin-3. Concentrations of carboxy-terminal telopeptide of collagen type I were determined using a quantitative enzyme immunoassay (Orion Diagnostica, Espoo, Finland), and concentrations

### Abbreviations and Acronyms

**ARB** = angiotensin II receptor blocker

**CMR** = cardiac magnetic resonance imaging

**HCM** = hypertrophic cardiomyopathy

**LGE** = late gadolinium enhancement

**LV** = left ventricular

**NT-proBNP** = N-terminal pro-B-type natriuretic peptide

**TGF** = transforming growth factor

of carboxy-terminal propeptide of type I procollagen were measured by sandwich enzyme-linked immunosorbent assay using the METRA EIA kit (Quidel Corp., San Diego, California). For the measurement of ST2 levels, Presage ST2 sandwich immunoassay (Critical Diagnostics, San Diego, California) was used as described previously (17). Concentrations of galectin-3 were analyzed using an enzyme-linked immunosorbent assay kit (BG Medicine, Inc., Waltham, Massachusetts) as previously described (18).

**Cardiac imaging.** Two-dimensional and Doppler echocardiographic studies were performed with iE33 (Philips Medical Systems, Andover, Massachusetts) to obtain the parameters displayed in Table 1 using standard definitions (19,20). Tissue Doppler velocity measurements were obtained

using pulsed-wave Doppler with imaging frame rates in excess of 100 Hz by placing the sample volume on the lateral and septal regions of the mitral valve annulus. Peak LV outflow tract gradient was measured with continuous-wave Doppler.

CMR scans were performed on a 1.5-T field strength scanner (HDxt platform, General Electric Healthcare, Milwaukee, Wisconsin) with a dedicated 8-channel cardiac-coil. The scan protocol included localizer images with cine-balanced steady-state free precession imaging in the short axis, paraseptal long axis, horizontal long axis, and 3-chamber views. Myocardial late enhancement images were performed in LV short axis and radial long axis images 8 to 15 min after intravenous injection of 0.2 mmol/kg gadopentetate dimeglumine (Magnevist, Bayer HealthCare Pharmaceuticals

**Table 1 Baseline Clinical Characteristics of the Study Participants**

Baseline Characteristics	Placebo (n = 9)	Losartan (n = 11)	p Value
<b>Demographics</b>			
Age (yrs)	54 ± 11	49 ± 14	0.47
Women/men	0/9	3/8	0.22
<b>Functional status and quality of life</b>			
New York Heart Association functional class (I/II)	9/0	9/2	0.48
Minnesota living with Heart Failure Questionnaire score	6 (1-45)	9 (5-84)	0.42
6-min walk distance (m)	1,160 ± 188	1,165 ± 277	0.96
<b>Concurrent cardiac medications</b>			
Beta-blocker	3	4	0.24
Verapamil	0	4	
Both beta-blocker and verapamil	0	1	
<b>Vital signs</b>			
Heart rate (beats/min)	63 ± 9	63 ± 10	0.95
Systolic blood pressure (mm Hg)	118 ± 13	123 ± 8	0.26
<b>Echocardiographic parameters</b>			
Interventricular septum thickness (mm)	16 ± 4	15 ± 3	0.41
Posterior wall thickness (mm)	11 ± 0.6	13 ± 3	0.14
Left ventricular diastolic diameter (mm)	47 ± 5	44 ± 4	0.11
Left ventricular ejection fraction (%)	73 ± 7	71 ± 8	0.73
E/A	0.9 (0.8-1.1)	1.0 (0.9-1.4)	0.31
E/E' (lateral)	7.6 (6.9-9.9)	9.4 (7.9-11.9)	0.38
E/E' (septal)	10.9 (10.0-15.7)	10.8 (9.9-14.9)	0.75
Diastolic dysfunction grade	2 (1-2)	2 (1-2)	0.66
Deceleration time (ms)	217 ± 62	226 ± 69	0.75
Left atrial volume (ml)	84 ± 20	71 ± 17	0.14
Right ventricular systolic pressure (mm Hg)	35 ± 9	36 ± 5	0.90
<b>Cardiac magnetic resonance imaging</b>			
Left ventricular mass (g)	155 (135-222)	139 (112-205)	0.39
Left ventricular fibrosis (ml)	0.6 (0-5.5)	1.9 (0-3.5)	0.87
<b>Laboratory data</b>			
Potassium (mEq/l)	4.1 ± 0.4	4.0 ± 0.5	0.64
Blood urea nitrogen (g/dl)	18 ± 8	15 ± 4	0.39
Creatinine (mg/dl)	1.1 ± 0.10	1.0 ± 0.2	0.40
CITP (μg/l)	0.29 (0.27-0.47)	0.30 (0.17-0.40)	0.72
PICP (ng/ml)	87 (81-130)	92 (63-112)	0.82
NT-proBNP (pg/ml)	547 (106-688)	309 (12-465)	0.69
Galectin-3 (ng/ml)	5.5 ± 2.0	6.8 ± 2.0	0.21
ST2 (U/ml)	38 (29-43)	30 (26-38)	0.42

Values are mean ± SD or median (interquartile range). Nominal and categorical variables are shown in frequencies.

A = atrial filling peak velocity of the mitral valve inflow; CITP = carboxy-terminal telopeptide of collagen type I; E = early filling peak velocity of the mitral valve inflow; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PICP = C-terminal propeptide of type I procollagen.

Inc., Wayne, New Jersey). Short axis late enhancement views were obtained with both 3-dimensional volumetric ventricular imaging and 2-dimensional single slice per breath-hold imaging. Inversion times were determined for each subject to null the signal arising from normal myocardium.

Images were reviewed independently by 2 expert readers (S.A., B.B.G.) on a remote offline workstation using dedicated magnetic resonance imaging analysis software (cmr<sup>42</sup>, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada). Readers were blinded to clinical history and scan dates and independently analyzed the steady-state free precession datasets in random order. For the LV mass analysis, each reader traced the end-diastolic endocardial and epicardial borders, excluding the papillary muscles, in all short axis views showing LV myocardium. Coregistration with long axis cine views was used to aid definition of myocardial borders at the basal segments. LV myocardial mass was determined using Simpson's method by calculating the sum of all areas between epicardial and endocardial myocardial borders multiplied by the sum of slice thickness plus slice spacing. Intraclass correlation coefficients for intraobserver and interobserver measurements of LV mass were 0.996 ( $p < 0.001$ ; 95% confidence interval: 0.961 to 1.000) and 0.975 ( $p < 0.001$ ; 95% confidence interval: 0.876 to 0.991), respectively. Myocardial late enhancement images were analyzed using 2-dimensional acquisitions, with use of coregistered 3-dimensional and long axis views for correlation when indicated. Volumetric late enhancement size was determined via manual area tracing of regions of interest of increased myocardial signal with adjustment for slice spacing and thickness. Voxels within the myocardium were considered enhanced if the signal intensity was higher than the mean + 6 SDs at the region of interest (21), and the extent was described in milliliters. The number and location of lesions were recorded and adjudicated by consensus readings in cases of discrepancy between the readers. Figure 1 shows representative CMR images.

**Statistical analysis.** Variables were assessed for normality by the Shapiro-Wilk test. Values for continuous variables are presented as mean  $\pm$  SD or median (interquartile range) as appropriate for data distribution. Nominal and categorical variables are shown in frequencies. We calculated the differences between the values at baseline and 1 year for continuous normal variables. The percent change was calculated for continuous variables that did not follow normal distribution. For comparisons between the placebo and losartan groups, independent 2-sample Student *t* tests were performed if the differences were normally distributed. The Mann-Whitney-Wilcoxon test was performed when the differences were skewed. To assess the effect of change in blood pressure on the change in extent of fibrosis, changes in extent of LGE and systolic blood pressure were displayed on a scatter plot and the Pearson correlation coefficient was calculated. Reliability testing using intraclass correlation coefficients was performed to determine the intraobserver and interobserver variability of LV mass analysis. Statistical

analyses were performed with Stata statistical software release 12 (StataCorp LP, College Station, Texas).

## Results

**Baseline characteristics.** We enrolled 20 participants (3 women and 17 men; age  $51 \pm 13$  years). Eleven participants were randomly assigned to receive losartan and 9 to receive placebo. Table 1 summarizes the baseline characteristics of the study population by treatment group. No significant baseline differences were observed between the 2 treatment groups. With the exception of 2 participants in New York Heart Association class II, participants were asymptomatic. All participants were in normal sinus rhythm. Five participants had a history of hypertension, but all were normotensive on enrollment in the trial without anti-hypertensive agents other than verapamil and/or beta-blockers; of these 5 participants, 4 had a family history of HCM (including 1 with a *MYH7* mutation), and the fifth had asymmetrical septal hypertrophy and a family history of sudden cardiac death. One participant had chronic stable angina and a normal coronary arteriogram. No participants had a history of syncope. Seven participants had no LGE at baseline, and 1 patient declined CMR. The Online Table shows left ventricular mass and extent of late gadolinium enhancement for each participant.

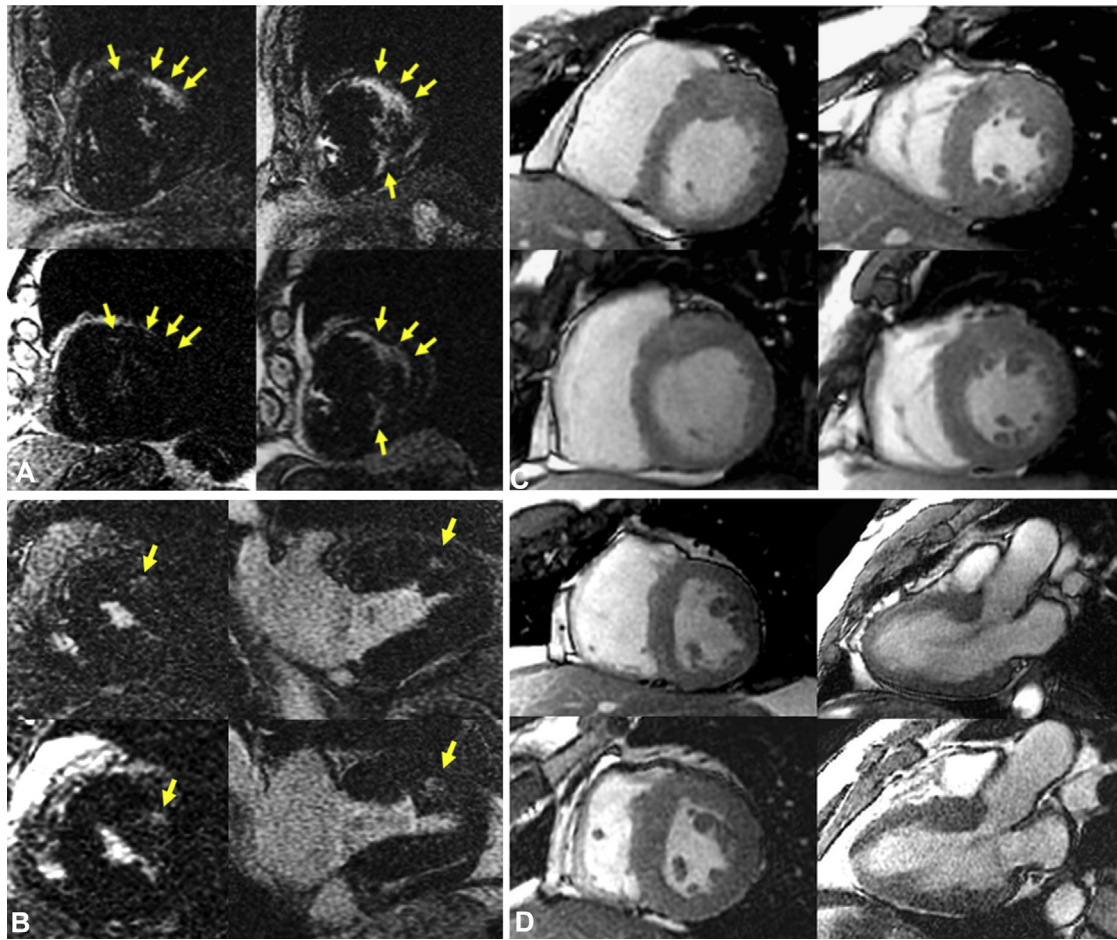
**Comparison of changes at 1 year.** All participants in the losartan arm were able to increase the dosage to 100 mg/day at 1 week and continue this dosage for 1 year. No participants experienced hypotension, hyperkalemia, renal insufficiency, development of LV outflow tract obstruction, or other adverse effects attributable to the study drug.

There was a significant difference in the percent change in amount of fibrotic myocardium as assessed by LGE between the placebo group (mean increase:  $+31 \pm 26\%$ ) and the losartan group (mean decrease:  $-23 \pm 45\%$ ;  $p = 0.03$ ) (Fig. 2). None of the participants without LGE at baseline had LGE at 1 year. There was a trend toward a significant difference in the change in LV mass measured by CMR between the placebo group (median increase:  $+5\%$  [ $-4\%$  to  $+21\%$ ]) and the losartan group (median decrease:  $-5\%$  [ $-11\%$  to  $-0.9\%$ ];  $p = 0.06$ ) (Fig. 3). There was no significant difference between the groups in the other parameters (Table 2).

There was no correlation between the change in systolic blood pressure and the change in fibrosis or between the change in systolic blood pressure and the change in LV mass at 1 year (correlation coefficient: 0.36;  $p = 0.15$ ).

## Discussion

This is the first study to evaluate the effects of angiotensin receptor blockade on the progression of both LV hypertrophy and LGE by CMR in patients with HCM. Using a prospective, randomized, placebo-controlled, double-blind design, we observed that the percent change in the extent of LGE at 1 year was larger in the placebo group than in



**Figure 1** Representative Cardiac Magnetic Resonance Images

(A) Regression of areas with late gadolinium enhancement (arrows) in a patient in the losartan group (top row = baseline; bottom row = follow-up at 1 year). (B) Progression of areas with late gadolinium enhancement (arrows) in a patient in the placebo group (top row = baseline; bottom row = follow-up at 1 year). (C) Decrease in left ventricular mass in a patient in the losartan group (top row = baseline; bottom row = follow-up at 1 year). (D) Increase in left ventricular mass in a patient in the placebo group (top row = baseline; bottom row = follow-up at 1 year).

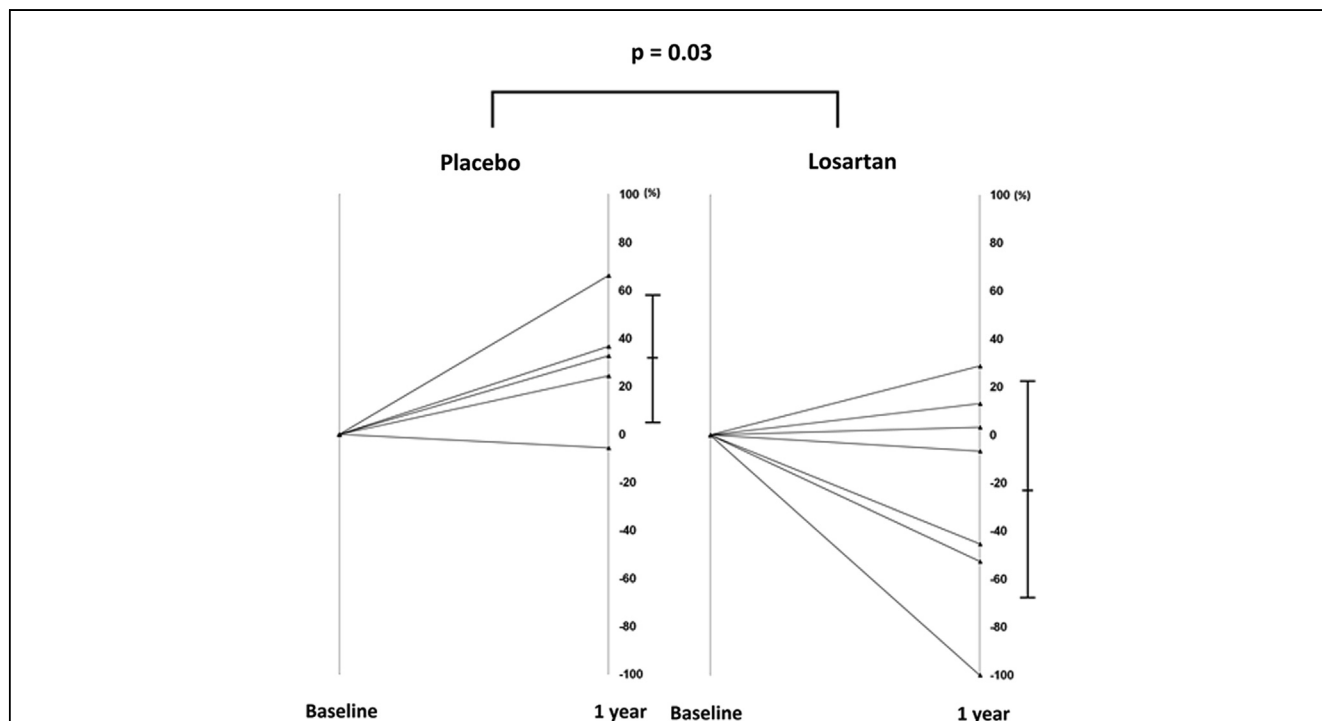
the losartan group. There was also a trend toward a larger increase in LV mass at 1 year in the placebo group as compared with the losartan group. These results suggest that treatment with angiotensin receptor blockade may attenuate the progression of LV hypertrophy and fibrosis in patients with nonobstructive HCM.

**Effect of losartan on LV hypertrophy.** LV hypertrophy in patients with HCM is an important determinant of morbidity and mortality, in particular the risk of sudden death (3,4). The rate of progression of LV hypertrophy in patients with HCM was investigated by Todiere *et al.* (6). Between 2 CMR examinations 2 years apart, LV mass increased in 30 of 55 patients (55%), with LV mass index increasing from  $109 \pm 23 \text{ g/m}^2$  to  $113 \pm 27 \text{ g/m}^2$  ( $p = 0.04$ ).

Yamazaki *et al.* (12) randomized 19 men with non-obstructive HCM to treatment with 50 mg/day losartan or no losartan. By CMR, the ratio of LV mass at 1 year to that at baseline was  $0.93 \pm 0.10$  in the losartan group and  $1.02$

$\pm 0.07$  in the control group ( $p = 0.03$ ). Penicka *et al.* (13) randomized 24 patients to candesartan at a dosage of up to 32 mg/day or placebo and found that echocardiographically assessed LV mass decreased in the candesartan group but not in the placebo group. Our study confirms the favorable effect of an ARB on progression of myocardial hypertrophy in patients with nonobstructive HCM and shows, for the first time, a parallel effect on progression of myocardial fibrosis.

**Effect of losartan on myocardial fibrosis.** LGE after gadolinium contrast injection correlates well with areas of fibrosis and increased collagen content in HCM (22). Focal myocardial fibrosis demonstrated by LGE on CMR is associated with an adverse prognosis in patients with HCM. It was shown that LGE in patients with HCM predicts the composite endpoint of cardiovascular death, unplanned cardiovascular admission, sustained ventricular tachycardia, ventricular fibrillation, or delivery of appropriate implantable



**Figure 2** Percent Change in Late Gadolinium Enhancement Between Baseline and 1 Year by Treatment Group

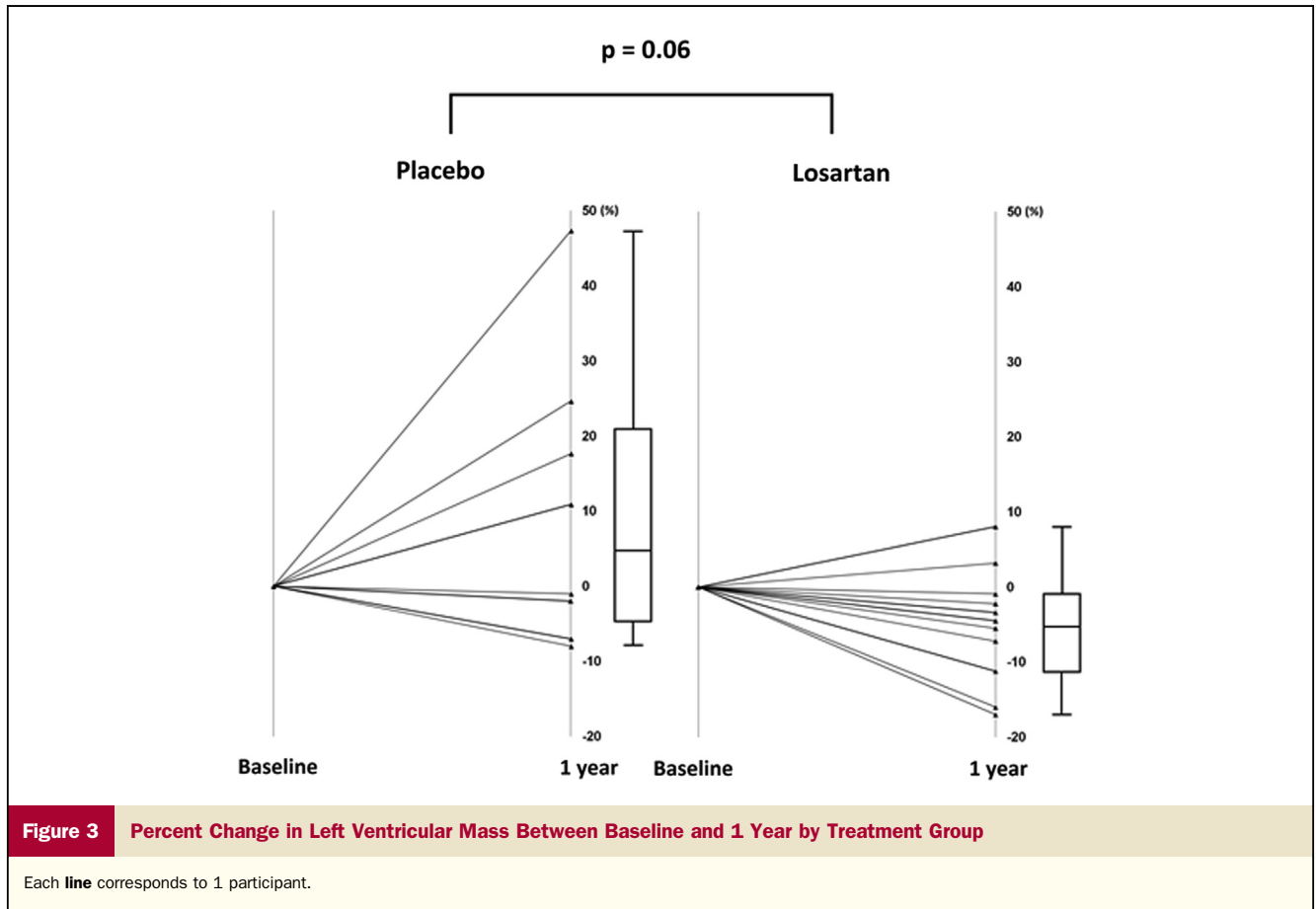
Each line corresponds to 1 participant.

cardioverter-defibrillator shocks (23). Another study suggested that LGE is a predictor of cardiovascular death (24). Progression of LV fibrosis in patients with HCM may be observed during a relatively short interval. When 55 patients with HCM underwent 2 cardiac MRI evaluations for LGE, the amount of fibrotic tissue increased from  $13 \pm 15$  g to  $25 \pm 28$  g ( $p < 0.001$ ) in 2 years, increasing in 44 (80%) of the patients (6).

It has been proposed that interstitial fibrosis in patients with HCM is mediated by activation of cardiac trophic factors such as angiotensin II and TGF- $\beta$  (8). In a mouse model of HCM, turning off expression of the mutant gene resulted in normalization of the phenotype, with regression of myocardial fibrosis, underscoring the possible reversibility of even those histologic abnormalities associated with genetic mutations (25). In this model, administration of losartan was associated with decreases in collagen volume fraction and expression of collagen 1- $\alpha$  and TGF- $\beta$  (10). Díez *et al.* (16) reported that, in patients with hypertensive heart disease, 1 year of treatment with losartan was associated with regression of myocardial fibrosis on endomyocardial biopsy specimens. Kawano *et al.* (11) randomized 23 patients with HCM to valsartan up to 80 mg daily or placebo for 1 year. The serum level of procollagen type I decreased in the valsartan group but not in the placebo group; there was no assessment of the extent of fibrotic tissue with cardiac imaging. Thus, our study is the first to show that treatment with an ARB is associated with

attenuation of myocardial fibrosis demonstrated by LGE in patients with HCM.

**Effect of losartan on diastolic dysfunction.** Both LV hypertrophy and fibrosis contribute to impaired LV compliance and diastolic function. Araujo *et al.* (14) found that patients with nonobstructive HCM treated with losartan at a dosage of 50 mg twice daily for 6 months had amelioration of symptoms, decrease in left atrial size, improvement in Doppler echocardiography-derived parameters of diastolic function, and reduction in serum NT-proBNP levels, whereas there were no such changes in a group of 10 nonrandomized, nonconcurrent control patients. Penicka *et al.* (13) showed that exercise tolerance and tissue Doppler measures of diastolic function improved in the candesartan group but not in the placebo group, corresponding to the improvement in LV hypertrophy. Among patients with hypertensive LV hypertrophy and fibrosis, Díez *et al.* (16) reported that losartan decreased LV chamber stiffness measured by Doppler echocardiography. In the present study, none of the echocardiographic parameters of diastolic function showed significant improvement after treatment with losartan for 1 year. A possible explanation for this difference is that the mean age of the participants in the present study (51 years) was significantly higher than that in the other studies (predominantly in the fourth decade of life), suggesting that diastolic properties may be more difficult to alter in older patients.



**Study limitations.** First, it is a small pilot study. A study of this size cannot be used to assess the effects of angiotensin receptor blockade on clinical endpoints. Second, only participants with LGE at baseline could be included in the intergroup comparison of change in extent of LGE, because we could not calculate the percent change in extent of LGE

in participants with no LGE at baseline. None of the participants without LGE at baseline developed LGE over 1 year of follow-up. Third, the CMR protocol used in this study detects focal fibrosis but not diffuse interstitial fibrosis. A recently published method of LGE analysis showed enhanced ability to detect both interstitial and focal

**Table 2** Comparison of Changes Between the Treatment Groups

Parameter	Placebo (n = 9)	Losartan (n = 11)	p Value
New York Heart Association functional class	Unchanged in all participants		—
Minnesota Living with Heart Failure Questionnaire score (% change)	-16 (-67 to +58)	-17 (-91 to +47)	0.69
6-minute walk distance (m)	+32 ± 182	+79 ± 416	0.76
Systolic blood pressure (mm Hg)	-0.4 ± 21	-8 ± 11	0.31
E/E' (lateral) (%)	+1.6 (-17 to +24)	-6.7 (-19 to +19)	0.91
E/E' (septal) (%)	-8.2 (-22 to +11)	-7.5 (-13 to +14)	0.79
Left atrial volume (ml)	+5 ± 12	-9 ± 11	0.41
Right ventricular systolic pressure (mm Hg)	-5.5 ± 9.3	+0.7 ± 6.8	0.26
Left ventricular mass (% change)	+5 (-4 to +21)	-5 (-11 to -0.9)	0.06
Left ventricular fibrosis (% change)	+31 ± 26	-23 ± 45	0.03
CITP (% change)	-8 (-37 to +19)	-23 (-43 to +7)	0.66
PICP (% change)	+13 (+4 to 20)	+8 (-22 to +32)	0.86
NT-proBNP (% change)	-3 (-45 to +47)	-7 (-38 to +8)	0.59
Galectin-3 (ng/ml)	+1.8 ± 1.6	+0.9 ± 2.4	0.38
ST2 (% change)	+6 (-11 to +18)	0 (-7 to +12)	0.86

Values are median (interquartile range) or mean ± SD.  
Abbreviations as in Table 1.

replacement fibrosis, although it was in a small cohort and limited to the site of surgical myectomy (26). Fourth, there was a discrepancy between the difference in change in extent of LGE and lack of difference in changes in markers of collagen turnover despite our previous findings (27). Finally, ARBs with more potent TGF- $\beta$  inhibition are now available and might be worthy of further study.

## Conclusions

The results of this study indicate that angiotensin receptor blockade may attenuate the progressive myocardial hypertrophy and fibrosis observed in some patients with HCM. Given the lack of established treatment to modify the natural history of HCM, our results support the design of a larger, multicenter study with a longer follow-up period to determine whether angiotensin receptor blockade should be widely applied to the management of HCM.

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**Reprint requests and correspondence:** Dr. Michael A. Fifer, Massachusetts General Hospital, Cardiology Division, 55 Fruit Street, Gray/Bigelow 800, Mailstop 843, Boston, Massachusetts 02114. E-mail: [mfifer@partners.org](mailto:mfifer@partners.org).

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**Key Words:** angiotensin II receptor blocker ■ cardiac magnetic resonance imaging ■ hypertrophic cardiomyopathy ■ late gadolinium enhancement ■ left ventricular fibrosis.

## APPENDIX

For the supplemental table, please see the online version of this article.