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The Effects of Candesartan on Left Ventricular Hypertrophy and Function in Nonobstructive Hypertrophic Cardiomyopathy

A Pilot, Randomized Study

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for the Candesartan use in Hypertrophic And Non-
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**Hypertrophic cardiomyopathy is caused by mutations
in the genes that encode sarcomeric proteins and is
primarily characterized by unexplained left ventricular
hypertrophy, impaired cardiac function, reduced exer-
cise tolerance, and a relatively high incidence of sudden
cardiac death, especially in the young. The extent of left
ventricular hypertrophy is one of the major determi-
nants of disease prognosis. Angiotensin II has trophic
effects on the heart and plays an important role in the
development of myocardial hypertrophy. Here in a dou-
ble-blind, placebo-controlled, randomized study, we
show that the long-term administration of the angioten-
sin II type 1 receptor antagonist candesartan in patients
with hypertrophic cardiomyopathy was associated with
the significant regression of left ventricular hypertro-
phy, improvement of left ventricular function, and ex-
ercise tolerance. The magnitude of the treatment effect
was dependent on specific sarcomeric protein gene mu-
tations that had the greatest responses on the carriers of
ß-myosin heavy chain and cardiac myosin binding pro-
tein C gene mutations. These data indicate that modu-
lating the role of angiotensin II in the development of
hypertrophy is specific with respect to both the affected
sarcomeric protein gene and the affected codon within
that gene. Thus, angiotensin II type 1 receptor blockade
has the potential to attenuate myocardial hypertrophy
and may, therefore, provide a new treatment option to
prevent sudden cardiac death in patients with hypertro-
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Hypertrophic cardiomyopathy (HCM) is a primary car-
diac disease characterized by unexplained cardiac hy-
pertrophy and a relatively high incidence of sudden car-
diac death, especially in young people.[1,2] The extent of
left ventricular hypertrophy is one of the major determi-
nants of symptoms and prognosis.[3,4]

Angiotensin II has trophic effects on the heart and plays
an important role in the development of myocardial hyper-
trophy.[5,6] Inhibition of angiotensin-converting enzyme
(ACE) or the angiotensin II type 1 receptor (AT1-R) induced
regression of myocardial hypertrophy in patients with hy-
pertension or after myocardial infarction.[7–9] In HCM, ACE
and AT1-R gene polymorphisms have been shown to be
associated with severity of hypertrophy, a high incidence of
atrial fibrillation and the risk of sudden cardiac death.[10–17]
Therefore, we designed a double-blind, placebo-controlled,
randomized, multicenter study to test the safety and effects
of AT1-R antagonist candesartan in patients with nonob-
structive HCM. We hypothesized that long-term use of can-
desartan would be associated with regression of left ven-
tricular (LV) hypertrophy and improvement of LV function.

Materials and Methods

Patients

This was a double-blind, placebo-controlled, randomized
multicenter study. The study population consisted of 24
consecutive, genetically independent, adult ($\geq$18 years)
patients (age 43 $\pm$ 13 yrs; 46% males) with nonobstruc-
tive HCM, and normal ejection fraction ($\geq$60%) and sinus
rhythm, who visited the participating institutions for rou-
tine follow-up. HCM had been diagnosed on the basis of
echocardiography showing a nondilated, hypertrophied

LV (any wall thickness >15 mm) in the absence of known causes of LV hypertrophy, hypertension, or valvular disease.[18,19] Exclusion criteria were as follows[1]: hypertrophic obstructive cardiomyopathy defined as presence of a resting gradient in LV outflow tract ≥30 mmHg or in right ventricular outflow tract ≥15 mm Hg at Doppler echocardiography[2]; atrial fibrillation[3]; treatment with ACE inhibitors or AT1-R antagonists at any time in the past[4]; contraindications to AT1-R antagonists[5]; coronary artery disease, renal failure, hepatic disorders or serious intercurrent illness limiting survival; and[6] poor echocardiographic image quality. The study protocol was approved by the Medical Ethics Committees of all participating institutions and informed consent was obtained from all patients. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institutions human research committee.

Protocol

At baseline, patients provided a blood sample for molecular genetic testing. The presence of a putative HCM-causing variant was determined by comprehensive mutational analysis of the ß-myosin heavy chain (ß-MHC), cardiac myosin binding protein C (cMYBPC), cardiac troponin T and cardiac troponin I genes that account for between 75% and 99% of all identified HCM-associated genotypes.[10,20–23] Patients were randomly assigned in a 1:1 ratio to candesartan ($n = 12$) or matching placebo ($n = 12$). The initial dose of the study drug was 8 mg once daily. Study drug dose was then doubled as tolerated every 2 weeks while aiming for a target dose of 32 mg once daily.[24] Blood pressure, serum creatinine, serum potassium, and pressure gradient in the LV outflow tract were monitored during dose titration. Patients were observed clinically at 3, 6, and 12 months after the maintenance dose was reached. Exercise tolerance by bicycle ergometry, the presence of malignant arrhythmias by Holter monitoring, the extent of LV hypertrophy by 2-dimensional echocardiography, and LV outflow tract pressure gradient by Doppler echocardiography were all assessed at baseline and 12-month follow-up.

Bicycle Ergometry

Patients cycled in the upright position starting with a workload of 25 W. The workload was increased in 25-W steps every 2 minutes until the patient was unable to continue because of dyspnea or fatigue. A 12-lead ECG and blood pressure were recorded during the last 10 seconds of each step of exercise and 1, 3, and 5 minutes after exercise testing. Total exercise time was measured to assess exercise tolerance.

Echocardiography

All studies were performed with a commercially available system equipped with tissue Doppler imaging (Hewlett-Packard Sonos 5500, Philips Medical Systems, Andover, MA). Transthoracic images were obtained in standard cross-sectional planes. M-mode echocardiograms were derived from two-dimensional images under direct anatomical visualization. LV diameters (end-diastolic and end-systolic) were assessed in parasternal long-axis view.[25] LV ejection fraction was calculated in apical 4-chamber and 2-chamber views using the biplane Simpson methods.[25] Peak LV outflow tract gradient at rest was estimated using the modified Bernoulli equation, $P = 4V^2$, where P is the pressure gradient and V is the velocity determined by Doppler echocardiography. LV filling pattern was assessed from the transmitral flow in apical views. Tissue Doppler was performed in pulsed wave mode. In apical 4-chamber view, peak mitral annular velocities during systole (Sa) and early diastole (Ea) were assessed as the average from two corners of the mitral annulus (septal and lateral). Gain and filters were adjusted to obtain an optimal tissue signal. Annular velocities were recorded during end-expiratory apnea at a sweep speed of 100 mm/s.

Analysis of LV Hypertrophy

End-diastolic LV wall thickness was assessed in all LV segments (16-segment model) in parasternal short-axis views.[25] Mean wall thickness was calculated in each patient. In addition, LV mass was determined according to the method described by Devereux[27]: LV mass = $0.8(1.04[(IVS+LVEDd + LVPW)^3 − LVEDd^3])+0.6$ g, where LVEDd is the LV end-diastolic diameter, and IVS and LVPW are the end-diastolic thickness of the interventricular septum and posterior wall, respectively. All studies were stored in digital format and on S-VHS videotape for off-line analysis. The mean from three consecutive beats was taken for each measurement. Digitized baseline and 12-month follow-up echocardiograms were analyzed side by side by two echocardiographers (M.P., J.K.) blinded to patient group assignment.

Statistical Analysis

All analyses were conducted according to the intention-to-treat principle. Continuous data are presented as mean ± SD Categorical data are presented as numbers and percentages. Two-sided paired and unpaired Student's *t*-test, Fisher's exact test and the Pearson test were used as appropriate. For all tests, $P < 0.05$ was considered significant.

The CHANCE investigators developed the study protocol with the sponsor. The sponsor had no access to the database. All data analyses were performed by investigators independently of the sponsor.

Results

Baseline Characteristics

Table 1 shows the baseline characteristics for patients assigned to candesartan and placebo. There were no differences between the two groups for any characteris-

Table 1.   Baseline Characteristics

	Candesartan group (*n* = 12)	Placebo group (*n* = 12)	*P*
Age, y	41 ± 15	45 ± 13	0.56
Male sex, *n* (%)	5 (42)	6 (50)	NS
Cardiac symptoms, *n* (%)	8 (67)	7 (58)	NS
Family history			
HCM, *n* (%)	7 (58)	8 (67)	NS
SCD, *n* (%)	3 (25)	3 (25)	NS
Myofilament genotype			
ß-MHC, *n* (%)	5 (42)	4 (33)	
cMYBPC, *n* (%)	3 (25)	3 (25)	
cTnT, *n* (%)	0	0	NS
cTnI, *n* (%)	2 (17)	1 (8)	
Myofilament genotype-negative, *n* (%)	2 (17)	2 (17)	
Medication			
ß-blockers, *n* (%)	4 (33)	4 (33)	
Verapamil, *n* (%)	4 (33)	4 (33)	NS
ß-blockers and verapamil, *n* (%)	1 (8)	1 (8)	

ß-MHC = ß-myosin heavy chain, cMYBPC = cardiac myosin binding protein C, cTnT = cardiac troponin T, cTnI = cardiac troponin I, HCM = hypertrophic cardiomyopathy, SCD = sudden cardiac death.

tic. None of the patients had isolated apical hypertrophy, an implantable cardioverter-defibrillator, pacemaker or a history of surgical septal myectomy or alcohol ablation.

In the placebo group, two individuals refused genetic screening. A putative HCM-causing myofilament variant was identified in 18 (82%) out of the 22 remaining patients who underwent genetic screening. The prevalence of specific HCM genotypes was similar between groups.

Effects of Candesartan on LV Hypertrophy and Function at 12-Month Follow-Up

Follow-up was completed by 23 patients (candesartan *n* = 12, placebo *n* = 11). One patient in the placebo group withdrew informed consent and was excluded from the analysis. Resting systolic blood pressure, heart rate, and LV outflow tract gradient did not differ between baseline and follow-up examination. At baseline, symptoms, exercise tolerance, LV systolic, and diastolic function and the magnitude of LV hypertrophy were similar between groups (Table 2). At 12-month follow up, patients in the candesartan group showed significant reductions of mean LV wall thickness and LV mass compared with patients receiving placebo, while LV end-diastolic diameter did not change (Figure 1). In the candesartan group, three patients showed a decrease in LV mass >100g and eight patients had a reduction >50g between baseline and follow-up. Of note, all patients with a marked decrease (>100g) had a mutation in ß-MHC. In contrast, no regression of hypertrophy was observed in patients with a cardiac troponin I gene mutation. Carriers of the cMYBPC genotype showed moderate responses (Table 3). In 10 study subjects, the inter- and intraobserver variability for assessment of LV mass was 6.4%

Table 2.   Symptoms, Exercise Tolerance, and Echocardiographic Indices of LV Hypertrophy and Function at Baseline and 12-Month Follow-Up

	Candesartan group (*n* = 12)*		Placebo group (*n* = 11)		*P* (follow-up) Candesartan versus Placebo
	Baseline	Follow-up	Baseline	Follow-up	
NYHA, *n*					
I	4	8	4	4	
II	4	4	4	5	0.07
III	4	0	3	2	
Systolic blood pressure, mmHg	113	114	119	119	NS
Heart rate, bpm	65	66	66	67	NS
Total exercise time at ergometry, s	574 ± 151	751 ± 161‡	629 ± 149	603 ± 162	0.049
Peak LV outflow tract gradient, mmHg	7.5 ± 3.1	8.2 ± 5.1	9.2 ± 6.3	8.6 ± 5.8	NS
LV end-diastolic diameter, mm	46 ± 4	46 ± 5	46 ± 7	46 ± 8	NS
LV ejection fraction, %	69 ± 5	68 ± 6	70 ± 6	69 ± 4	NS
Sa, cm/s	6.1 ± 1.5	8.2 ± 2.3†	6.6 ± 2.0	6.9 ± 2.2	0.04
Ea, cm/s	5.5 ± 1.8	8.0 ± 3.1†	5.3 ± 1.9	5.9 ± 3.2	0.01
E/Ea	13.5 ± 3.5	9.3 ± 1.3†	12.9 ± 3.9	12.3 ± 3.5	<0.01
Mean LV wall thickness, mm	20.0 ± 3.6	16.2 ± 3.0†	20.1 ± 2.5	20.2 ± 2.8	0.006
LV mass, g	407 ± 139	344 ± 102‡	451 ± 228	449 ± 232	0.04

*The 12-month follow-up data are reported in 23 patients who completed follow up.
†*P* < 0.01, ‡*P* < 0.001 baseline versus follow-up.
E = early transmitral filling peak velocity, Ea = mitral annular velocity during early diastole, LV = left ventricular, Sa = mitral annular velocity during systole.
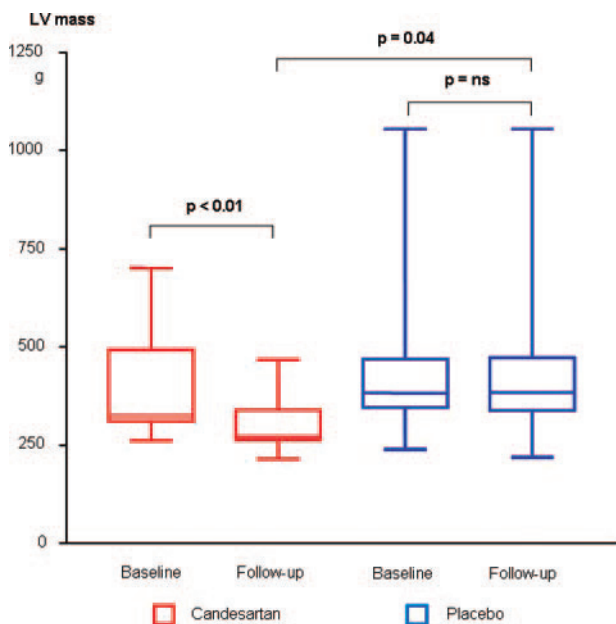
Figure 1. Left ventricular mass at baseline and 12-month follow-up in the candesartan (red) and placebo (blue) groups. The plots display the medians (horizontal bars), 25th and 75th percentiles (lower and upper limits of the boxes), and lowest and highest values (error bars).

(27 g) and 5.1% (22 g), respectively. Patients on candesartan showed significant increases in LV contractile (Sa) and diastolic function (Ea) and decreases in LV filling pressures (E/Ea) during follow-up (all $P < 0.01$). In contrast, no improvements in these parameters were observed in the placebo group. LV ejection fraction remained similar regardless of treatment assignment. Furthermore, six (50%) patients receiving candesartan showed ≥1 point decrease in New York Heart Association class compared with only one (9%) patient receiving

Table 3. Change in LV Mass in the Candesartan Group between Baseline and 12-Month Follow-Up According to Specific HCM-Causing Gene Mutation

	LV mass change, g (%)
ß-MHC (*n* = 5)	
Arg403Trp	[−]94 ([−]29)
Arg719Trp	[−]99 ([−]25)
Arg403Gln	[−]145 ([−]21)
Ile263Thr	[−]105 ([−]20)
Arg249Gln	[−]121 ([−]20)
Average	[−]113 ([−]23)
cMYBPC (*n* = 3)	
Arg502Gln	[−]51 ([−]16)
SDSint23	[−]50 ([−]13)
SASint20	[−]41 ([−]13)
Average	[−]47 ([−]14)
Other genotyped patients (*n* = 4)	
TnI: Arg141Gln	[−]10 ([−]4)
TnI: Ala157Val	+10 (+4)
Myofilament genotype-negative	[−]51 ([−]16)
Myofilament genotype-negative	[−]59 ([−]13)
Average	[−]28 ([−]7)
P (ANOVA)	< 0.001

Abbreviations: ß-MHC = ß-myosin heavy chain, cMYBPC = cardiac myosin binding protein C, cTnI = cardiac troponin I.
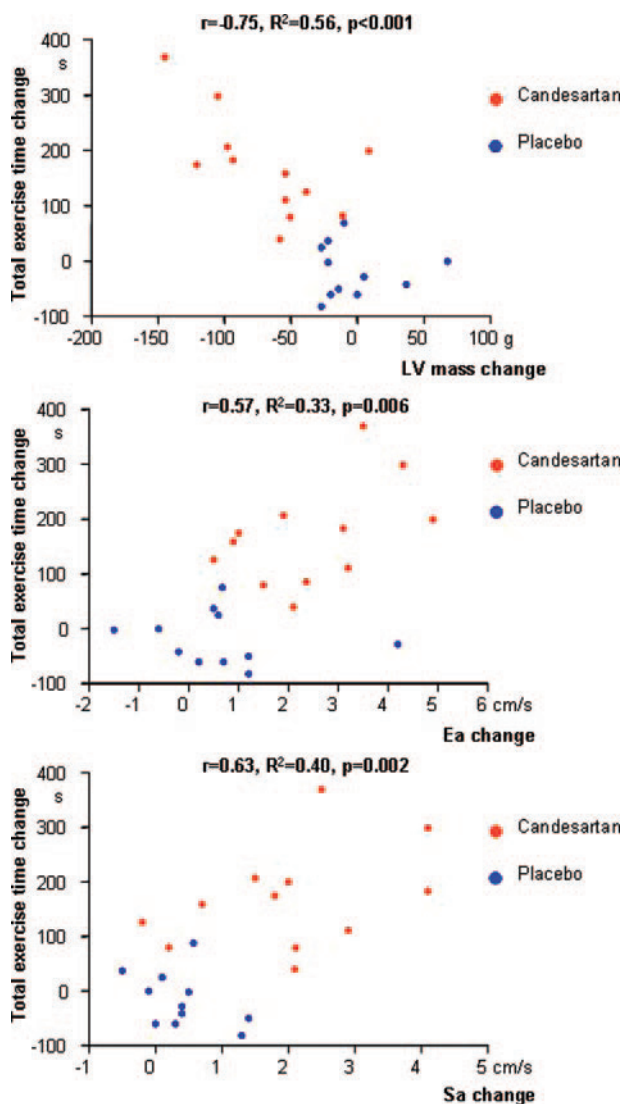

Figure 2. Relationship between change in LV mass (**upper panel**), change in peak mitral annular velocity at early diastole (Ea; **middle panel**) and systole (Sa; **lower panel**), and change in total exercise time by bicycle ergometry between baseline and 12-month follow-up. Red circles indicate the candesartan group, and blue circles indicate the placebo group.

placebo ($P = 0.07$). Finally, total exercise time increased only in patients on candesartan, and was associated with reduction of LV mass and improvements in LV diastolic and systolic function (Figure 2). The systolic blood pressure at peak exercise tended to be lower in the candesartan versus placebo group (166 ± 21 vs. 177 ± 18, $P = 0.08$).

Safety

Neither adverse events nor side effects were observed during the up-titration phase or the entire follow-up period. No patient developed LV outflow tract obstruction, malignant arrhythmias or showed an increase in serum creatinine and potassium levels. In the placebo group, one patient had an episode of atrial fibrillation that needed electrical cardioversion during follow up. The

target dose of study drug (32 mg daily) was reached by eight (67%) patients in the candesartan group and nine (75%) patients in the placebo group (NS). The remaining patients received 16 mg of study drug daily. The principal reason for stopping uptitration was a subjective feeling of lightheadedness. Once titration was completed, the maintenance dose remained unchanged throughout the follow-up period.

Discussion

The present study demonstrated that use of the AT1-R antagonist candesartan in patients with non obstructive HCM, is safe. Furthermore, candesartan use was associated with significant regression of LV hypertrophy, and improvement of LV function, symptoms and exercise tolerance. Finally, the magnitude of treatment effect was dependent on specific sarcomeric protein gene mutation with the greatest response in carriers of ß-MHC gene mutations.

Role of Angiotensin II in HCM

HCM is genetic disease, which is characterized by LV hypertrophy, impaired myocardial contractile and LV diastolic function, reduced exercise tolerance and risk of sudden death.[1,2] HCM is caused by mutations in genes encoding sarcomeric proteins. The phenotypic expression of HCM depends both on specific mutations and modifying factors. Angiotensin II is believed to be an important modulator of cardiac hypertrophy and even prognosis in HCM.[10–17] Several studies have demonstrated an association between the ACE insertion/deletion polymorphism and the AT1-R adenine/cytosine[1166] polymorphism and expression of LV hypertrophy.[10,12–16] Carriers of ACE D (increased myocardial angiotensin II level) and AT1-R C (increased angiotensin II effect) alleles showed higher penetrance and degree of LV hypertrophy compared with patients with the ACE I and AT1-R A alleles. Only three studies reported a HCM-causing genotype with controversial results.[13,14,16] Perkins et al[16] showed a significant pro-LV hypertrophic effect of ACE polymorphism only in patients with the cMYBPC gene mutation, but not in carriers of the ß-MHC mutation. In contrast, Tesson et al[14] observed a significant association between the ACE D allele and hypertrophy only in subjects carrying a mutation in the Arg403 codon of ß-MHC, but not for other ß-MHC or cMYBPC gene mutations. In the present study, patients in the candesartan group with either ß-MHC-HCM and cMYBPC-HCM mutations showed regression of hypertrophy, but the greatest effect was seen in the former group. The inconsistency in results may be accounted for by the heterogeneity of the underlying mutation. Several hundreds of HCM-causing mutations have been described,[28,29] and one may speculate that the modulating role of angiotensin II in the development of hypertrophy is specific both with respect to the affected sarcomeric protein gene and the affected codon within that gene. Yet, we observed a treatment effect of candesartan in the two most common genetic subtypes of HCM (ß-MHC and cMYBPC).

Angiotensin II Blockade in HCM

In a mouse model of human HCM, treatment with the AT1-R antagonist losartan decreased the extent of interstitial fibrosis and collagen synthesis compared with placebo.[30] In a hemodynamic study, intracoronary administration of the ACE inhibitor enalaprilat was associated with improvement of LV diastolic function and coronary blood flow as well as a decrease in LV filling pressures.[31] Three studies reported effects of AT1-R antagonists in patients with non obstructive HCM.[32–34] Kawano et al[32] randomized 23 patients to valsartan (maximal dose 80 mg/d) or conventional therapy. At 12-month follow-up, valsartan decreased collagen synthesis, while no favorable effects on LV diastolic function, filling pressures and LV hypertrophy were observed. In the study by Araujo,[33] losartan use was significantly associated with improvement of LV diastolic function, decrease in LV filling pressure and New York Heart Association functional class but not in LV hypertrophy at 6-month follow-up. Corroborating these results, we demonstrated significant increases in LV systolic and diastolic function and decreases in LV filling pressures, with concomitant improvements in symptoms and exercise tolerance in patients receiving candesartan. Since the Doppler-echocardiography was not performed immediately after exercise, the mechanisms of improvement in exercise tolerance by candesartan can be only speculative. Corroborating the previous results,[4,35] in the present study, increase in exercise tolerance correlated with improvement in myocardial systolic and diastolic function. Regression of LV mass appeared to be one of the major mechanisms underlying this improvement. Moreover, decrease in myocardial collagen synthesis associated with AT1-R antagonists[30,32] could also contribute to increased myocardial function. In the candesartan group, patients showed slightly lower systolic blood pressure at peak exercise compared with the placebo group. Blunted blood pressure response to exercise might have partly explained the positive effect of candesartan on exercise tolerance. In the study by Yamazaki et al,[34] nineteen patients with non obstructive HCM were randomized to 50 mg of losartan or conventional therapy. At 1-year follow up, patients on losartan showed a trend (p 0.07) toward regression of LV mass at magnetic resonance imaging. The mean reduction of LV mass by losartan was 6.4%. In the present study, we observed a larger regression of LV hypertrophy by 15.5% in the candesartan group. The explanations for conflicting effects of AT1-R blockade on LV hypertrophy between studies may be several. It appears that the magnitude of modulating effects of angiotensin II differ in various HCM-causing mutations.[14,16] It is likely that frequencies of putative mutations differ between continents. Corroborating this explanation, in the study by Yamazaki, the mean baseline LV mass was twofold lower (190 ± 55 cm^3 = 199.5 ± 58 g) compared with the present study (407 ± 139 g). This strongly suggests a heterogeneous

genetic substrate in patients included in these studies, which may account for differences in the extent of treatment effect on LV hypertrophy. The primary HCM-causing genetic substrate was not reported in either the Japanese[32,34] or the Brazilian[33] studies. Furthermore, in previous reports, the dose of study drug was lower[32,34] or the follow-up was shorter[33] than in the present study. This suggests that higher doses of AT1-R antagonist for a longer time may be required to decrease the magnitude of LV hypertrophy. Finally, in contrast to the present study, the open, non-placebo-controlled design of previous studies may hamper interpretation of results.[32,33] Nevertheless, these findings suggest that AT1-R blockade has the potential to attenuate myocardial fibrosis and hypertrophy, two major predictors of sudden cardiac death in patients with HCM.[3,36]

Safety of AT1-R Antagonists in HCM

ACE inhibitors and AT1-R blockers have been discouraged in HCM, because of their vasodilating properties.[1] In the present study, we did not observe any adverse events related to candesartan use and the predefined target dose was reached in the majority of patients, regardless of treatment arm assignment. These findings are consistent with the previous reports.[32,33]

Limitations

In the present study, the sample size both in general and for individual mutated genes was too small to draw a confident conclusion on the mutation-specific effects. The present study did not investigate specific molecular mechanisms underlying the effect of candesartan in HCM. The assessment of circulating angiotensin II, catecholamines or markers of oxidative stress could have provided more mechanistic insight since all these parameters affect both LV structure and function. Neither ACE nor AT1-R polymorphisms were assessed in the present study. Since the carriers of the ACE D or AT1-R C alleles may experience the greatest benefit from angiotensin II blockade, the information on these polymorphisms could help in selecting patients for AT1-R antagonist therapy. Thus, findings of the present study should be considered as preliminary and interpreted with caution.

The presented cohort showed higher prevalence of ß-MHC gene mutations than reported by other authors.[23] These discrepant findings might be explained by the selection bias. In the present study, only patients with LV wall thickness >15 mm were included. Of note, severe LV hypertrophy is the hallmark of ß -MHC hypertrophic cardiomyopathy, while carriers of other gene mutations (cMYBPC, cardiac troponin T, or cardiac troponin I) have milder hypertrophy.

Conclusions

In a double-blind, placebo-controlled, randomized study, candesartan induced regression of LV hypertrophy, and improved LV function and exercise tolerance with no side effects in patients with non obstructive HCM. The magnitude of treatment effects of AT1-R antagonists is likely to be dependent both on specific HCM-causing mutations and specific angiotensin II system polymorphisms. These findings call for a prospective trial to assess the effects of AT1-R antagonists on clinical outcome in a large cohort of patients with non obstructive HCM.

Acknowledgments

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