International Journal of Gerontology xxx (2015) 1–5

Contents lists available at ScienceDirect

International Journal of Gerontology

journal homepage: www.ijge-online.com

Original Article

Azilsartan, but not Candesartan Improves Left Ventricular Diastolic Function in Patients with Hypertension and Heart Failure☆

Mari Sakamoto [1], Masanori Asakura [1,2], Atsushi Nakano [2], Hideaki Kanzaki [1], Yasuo Sugano [1], Makoto Amaki [1], Takahiro Ohara [1], Takuya Hasegawa [1], Toshihisa Anzai [1], Masafumi Kitakaze [1,2]*

[1] Department of Cardiovascular Medicine, [2] Department of Clinical Medicine and Development, National Cerebral and Cardiovascular Center, Suita, Japan

ARTICLE INFO

Article history:
Received 1 June 2015
Received in revised form
4 June 2015
Accepted 8 June 2015
Available online xxx

Keywords:
angiotensin receptor blocker,
brain natriuretic peptide,
diastolic dysfunction,
echocardiography,
heart failure

SUMMARY

Background: Diastolic dysfunction is a major cause of heart failure (HF) with a preserved ejection fraction (HFpEF); however, there is no clear strategy for treating diastolic dysfunction. Myocardial and vascular abnormalities may cause HFpEF, which indicates that correcting both abnormalities may specifically improve the severity of diastolic dysfunction. Candesartan primarily affects the myocardium, but azilsartan affects the myocardium and the aortic vasculature. This study was undertaken to test the hypothesis that azilsartan, but not candesartan, improves left ventricular (LV) diastolic dysfunction in patients with hypertension and HFpEF.

Methods: Among patients with HF in our database, the patients who received azilsartan or candesartan were retrospectively screened. Fifteen patients treated with azilsartan were identified, and sex-matched patients who received candesartan were blindly selected.

Results: At baseline, there were no significant differences between the two groups in clinical findings, echocardiographic parameters, and plasma brain natriuretic peptide levels. At 3–6 months, blood pressure decreased to similar levels in both groups. However, the early LV filling velocity/early diastolic velocity (E/e′) ratio decreased in the azilsartan group (13.0 ± 4.2 vs. 10.9 ± 3.2, $p = 0.03$), but remained unchanged in the candesartan group (12.0 ± 3.6 vs. 12.5 ± 5.0, p = 0.58; for interaction, $p = 0.04$). Other echocardiographic parameters were unaltered by azilsartan or candesartan.

Conclusion: Azilsartan improves diastolic function in HF patients with hypertension, and it may be the preferred option over other angiotensin II receptor blockers in patients with HFpEF.

1. Introduction

The primary focus of research on cardiac diastolic dysfunction is to understand the pathophysiology of heart failure (HF) because HF with a preserved ejection fraction (HFpEF) is as aggressive as HF with a reduced ejection fraction (HFrEF). Despite current medical therapy of angiotensin-converting enzyme inhibitors or β-adrenergic receptor blockers for patients with HFrEF[1–3], no obvious evidence-based drugs or even potential therapeutic candidates have been identified for treating patients with HFpEF. Heart failure with a preserved ejection fraction is primarily attributable to left ventricular (LV) diastolic dysfunction[1–4]. Abnormalities in the LV myocardium such as myocardial hypertrophy, myocardial fibrosis, and LV geometrical changes are largely involved in both types of HF; in addition, endothelial dysfunction and abnormalities in aortic vessel properties such as aortic capacitance or resistance are involved in HFpEF[4,5]. In short, HFrEF is primarily caused by a myocardial abnormality, whereas HFpEF is primarily attributable to abnormalities in the myocardium and in the aortic vessels. Elzinga and Westerhof[6] showed that changes in aortic impedance or capacitance largely modulate the time of ejection onset: a low

☆ Conflicts of Interest: All authors of this manuscript have read and approved the submission of the manuscript. All authors have made important contributions to the study and are thoroughly familiar with the original data. We declare with regard to this paper that there are no financial or other relationships that could lead to a conflict of interest.

* Correspondence to: Dr Masafumi Kitakaze, Department of Clinical Medicine and Development, National Cardiovascular Center, 5-7-1 Fujishirodai, Suita City, Osaka Prefecture 565-8565, Japan.
E-mail address: kitakaze@zf6.so-net.ne.jp (M. Kitakaze).

http://dx.doi.org/10.1016/j.ijge.2015.06.003

compliance of aortic vasculature hastens the time of aortic opening and, consequently, the time of LV ejection onset. We previously reported that a delayed ejection fraction, characterized by an increase in aortic capacitance, increases the LV relaxation rate in canine models[7,8]. These considerations indicate that an improvement in cardiac dysfunction and vessel dysfunction is essential to improve LV diastolic dysfunction because cardiac improvement such as myocardial fibrosis may shift the LV diastolic pressure–volume relationship to the right, and an improvement in aortic arterial capacitance may increase the speed of the LV relaxation rate[9]. Azilsartan, a new type of angiotensin receptor blocker (ARB), was recently shown to largely affect the arterial vasculature and the myocardium[10]. This finding endorses the hypothesis that azilsartan improves LV diastolic dysfunction in patients with HFpEF.

The present study tested the hypothesis that azilsartan decreases the ratio of the early LV filling velocity (E) and the early diastolic velocity (e′) of the mitral valve annulus (LV E/e′), which is the diastolic property obtained on an echocardiogram of HFpEF patients with hypertension[9]. We also observed the early diastolic velocity of the mitral valve annulus (e′). We also compared the effects of azilsartan with the effects of candesartan, which has a chemical structure similar to azilsartan but fewer vascular effects.

2. Methods

2.1. Statement of ethics

This study was approved by the National Cerebral and Cardiovascular Center Research Ethics Committee (Suita, Japan). The Committee decided that acquisition of informed consent from the 30 selected patients was not required, based on the Japanese Clinical Research Guidelines, because it was a retrospective observational study. A public announcement was instead published in accordance with the request of the Ethics Committee and the Guidelines.

2.2. Study population and protocols

We enrolled HFpEF patients with hypertension who were treated with azilsartan and had undergone echocardiography before and after treatment. In our database of 3082 patients treated during 2011–2014, we found 15 patients who matched these criteria. We only found 15 patients in our database who were treated with azilsartan because it was recently launched in Japan and is only permitted to treat patients with hypertension. Using the same database, we also randomly selected 15 HFpEF patients with hypertension who were treated with candesartan and had undergone echocardiography before and after treatment. Clinical parameters and plasma brain natriuretic peptide (BNP) levels were recorded in addition to echocardiograms of all patients.

2.3. Echocardiography

We retrospectively reviewed the echocardiography data of the enrolled patients by using their medical records. The LV dimensions, left atrial volume, and wall thickness were measured in accordance with the American Society of Echocardiography Guidelines[11]. The LV ejection fraction (LVEF) was measured using the Simpson biplane method or the semiquantitative two-dimensional visual estimate method, as previously described[12]. The LV end-diastolic volume and mass were calculated using the Teichholz formula and Devereux formula[13,14], respectively. We obtained the early (E) and late (A) LV filling velocities of the mitral inflow and the E-wave deceleration time (DcT) from Doppler methods, and we recorded the ratio of the E-wave to A-wave (E/A ratio). We also recorded the LV E/e′ ratio, according to a previous report. The sample volume of pulsed-wave Doppler imaging was placed at the tip level of the mitral leaflets in the apical four-chamber view. On the Doppler tracing, the diastolic signal shows a negative deflection. Similar to conventional Doppler of mitral inflow, we defined the E-wave and an A-wave, measured the peak early and late LV filling velocities, and then used the average values of septal and lateral velocities as e′ and a′, respectively[12,15].

2.4. Statistical analysis

All statistical analyses were performed using JMP 11 software (SAS Institute Inc., Cary, NC, USA). The data are expressed as the mean ± the standard error. The Student *t* test was used to compare data between the two groups. Multiple comparisons were conducted by one-way analysis of variance (ANOVA) with Bonferroni's *post hoc* test. All values of $p < 0.05$ were considered statistically significant.

3. Results

As shown in Table 1, the background characteristics of patients such as age was similar in both groups. There were no significant differences between the two groups in baseline diseases and type of drugs used. As shown in Tables 2 and 3, blood pressure, plasma BNP levels, and echocardiographic parameters at baseline and 3–6 months after treatment were similar in the azilsartan and candesartan groups. The heart rate was slightly reduced after treatment with azilsartan but not with candesartan. This may be attributable to the effects of coadministered drugs such as calcium (Ca) channel blockers or to the direct effects of azilsartan. There were no differences between the two groups in echocardiographic parameters at baseline, and candesartan did not affect these parameters 3–6 months after treatment. However, azilsartan significantly decreased LV septal, lateral, and, consequently, average E/e′ values at 3–6 months. The changes in the average E/e′ value are shown in Figure 1.

Table 1
Patients' characteristics.

	Azilsartan (baseline)		Candesartan (baseline)		*p*
Number of patients	15		15		
Background					
Age, y	74	±11	68	±13	0.17
Male, *n* (%)	10	(67)	10	(67)	1.00
Height, cm	159	±9	165	±11	0.18
Body weight, kg	59	±16	69	±17	0.09
BMI	23	±4	25	±4	0.10
Systolic blood pressure, mmHg	140	±15	141	±13	0.86
Diastolic blood pressure, mmHg	81	±9	80	±10	0.76
Heart rate, bpm	76	±13	70	±9	0.21
Baseline disease, *n* (%)					
Hypertensive heart disease	10	(67)	5	(33)	0.07
Ischemic heart disease	1	(7)	3	(20)	0.28
Dilated cardiomyopathy	1	(7)	4	(27)	0.14
Hypertrophic cardiomyopathy	1	(7)	0	(0)	0.31
Valvular disease	2	(13)	3	(20)	0.62
Coadministrative drugs					
Ca channel blockers	3	(20)	1	(7)	0.28
ACE inhibitors	1	(7)	1	(7)	1.00
Alpha$_2$-agonists	1	(7)	0	(0)	0.31
Beta-blockers	0	(0)	3	(20)	0.07

Values are presented as the mean ± the standard deviation or *n* (%), as appropriate.
ACE = angiotensin converting enzyme; BMI = body-mass index; Ca = calcium.

Please cite this article in press as: Sakamoto M, et al., Azilsartan, but not Candesartan Improves Left Ventricular Diastolic Function in Patients with Hypertension and Heart Failure, International Journal of Gerontology (2015), http://dx.doi.org/10.1016/j.ijge.2015.06.003

Table 2
Changes from the baseline in the azilsartan group.

	Azilsartan at baseline		Azilsartan during treatment		p [a]
Background					
Systolic blood pressure, mmHg	140	±15	124	±15	<0.01*
Diastolic blood pressure, mmHg	81	±9	70	±9	<0.01*
Heart rate, bpm	76	±13	68	±6	0.04*
Echocardiographic parameters					
IVS, mm	9.8	±1	9.7	±3	0.92
PW, mm	9.9	±1	9.9	±3	0.93
LVDd, mm	51	±10	49	±9	0.11
LVDs, mm	35	±10	32	±9	0.13
LVEF, %	56	±15	57	±14	0.65
LAd, mm	39	±6	39	±6	0.90
LAVi, mL/m^2	64	±30	57	±32	0.19
TMF E, cm/s	71	±23	75	±35	0.49
TMF A, cm/s	86	±22	84	±22	0.58
TMF E/A	0.77	±0.3	0.78	±0.3	0.94
TMF DcT, ms	228	±53	219	±41	0.55
LV septal E/e′	15.2	±6.2	13.4	±4.7	0.03*
LV lateral E/e′	11.5	±4.1	9.3	±2.6	0.02*
Average LV E/e′	13.0	±4.2	10.9	±3.2	0.03*
Biomarker					
Plasma BNP levels, pg/mL	173	±32	113	±21	0.048*

A = the late (A) left ventricular filling velocity; BNP = brain natriuretic peptide; DcT = deceleration time; E = early left ventricular filling velocity; e′ = early diastolic velocity; IVS = interventricular septum; LAd = left atrium diameter; LAVi = left atrial volume index; LV = left ventricular; LVDd = left ventricular diameter at end diastole; LVDs = left ventricular diameter at end systole; LVEF = left ventricular ejection fraction; W = posterior wall; TMF = transmitral flow.
The values in the table are presented as the mean ± the standard deviation or *n* (%), as appropriate.
* Indicates a significant value, $p < 0.05$.
[a] The *p* values are based on analysis of variance (ANOVA), as appropriate.

Table 3
Changes from the baseline in the candesartan group.

	Candesartan baseline		Candesartan treatment		p [a]
Background					
Systolic blood pressure, mmHg	141	±13	130	±14	<0.01*
Diastolic blood pressure, mmHg	80	±10	75	±8	<0.01*
Heart rate, bpm	70	±9	69	±10	0.16
Echocardiographic parameter					
IVS, mm	9.7	±2	9.5	±3	0.75
PW, mm	9.6	±1	9.3	±2	0.63
LVDd, mm	55	±10	54	±11	0.59
LVDs, mm	38	±13	37	±13	0.43
LVEF, %	49	±16	50	±17	0.56
LAd, mm	42	±7	43	±10	0.48
LAVi, mL/m^2	52	±15	47	±23	0.41
TMF E, cm/s	62	±23	57	±23	0.51
TMF A, cm/s	67	±21	70	±26	0.18
TMF E/A	0.99	±0.4	0.94	±0.5	0.68
TMF DcT, ms	215	±78	197	±56.0	0.34
LV septal E/e′	12.6	±3.5	12.7	±3.9	0.90
LV lateral E/e′	12.2	±4.6	12.7	±6.4	0.68
Average LV E/e′	12.0	±3.6	12.5	±5.0	0.58
Biomarker					
Plasma BNP levels, pg/mL	171	±28	116	±19	0.10

BNP = brain natriuretic peptide; E = early left ventricular filling velocity; e′ = early diastolic velocity; IVS = interventricular septum; LAd = left atrium diameter; LAVi = left atrial volume index; LV = left ventricular; LVDd = left ventricular diameter at end diastole; LVDs = left ventricular diameter at end systole; LVEF = left ventricular ejection fraction; PW = posterior wall; TMF = transmitral flow; DcT = deceleration time.
The values in the table are presented as the mean ± the SD or *n* (%), as appropriate.
* Indicates a significant value, $p < 0.05$.
[a] The *p* values are based on analysis of variance (ANOVA), as appropriate.

4. Discussion

In the present study, we demonstrated that the LV E/e′ ratio substantially decreased in the azilsartan group, but not in the candesartan group. This finding demonstrated that azilsartan improves LV diastolic function in HF patients with systemic hypertension.

4.1. Angiotensin receptor blockers for patients with HF

Angiotensin receptor blockers are effective for treating patients with HF[16,17]. Candesartan improves clinical outcomes in patients with HFrEF[18], even with angiotensin-converting enzyme inhibitors[17]. This effect has also been demonstrated with valsartan[19]. However, there is no clear consensus on whether ARBs are effective for patients with HFpEF. The Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial showed that irbesartan did not improve the clinical outcomes of HFpEF patients[20], and the Candesartan in Heart Failure—Assessment of Mortality and Morbidity (CHARM)-Preserved trial showed the ineffectiveness of candesartan in HF patients with a moderately preserved ejection fraction, although the *p* value for improvement in the cardiac clinical outcome was 0.051[21]. The present study also had similar findings: there was no improvement in LV diastolic dysfunction in HF patients with hypertension and a decreased LV E/e′ ratio. Candesartan decreased plasma BNP levels to levels comparable with the levels in the azilsartan group, which suggests that the cardiac load was decreased with a consequent decrease in the extent of HF severity. This may be why candesartan is marginally effective in patients with a moderately preserved ejection fraction.

The most important finding in the present study is the effect of azilsartan on diastolic dysfunction: azilsartan decreased the LV E/e′ ratio. The E/e′ ratio seems to be the most reliable parameter to assess cardiac diastolic function[9]. The E/A ratio and the LV deceleration time are also parameters of cardiac dysfunction, although they are influenced by the LV loading conditions; therefore, we did not assess these parameters. The question arises as to what is the likely mechanism by which azilsartan, but not candesartan, improves LV diastolic dysfunction.

4.2. Azilsartan and candesartan in the improvement of LV diastolic dysfunction

Our hypothesis was that azilsartan improves cardiac diastolic function in patients with hypertension. We proved this hypothesis, but the mechanisms underlying this effect need to be considered. First, a decrease in the blood pressure may improve cardiac

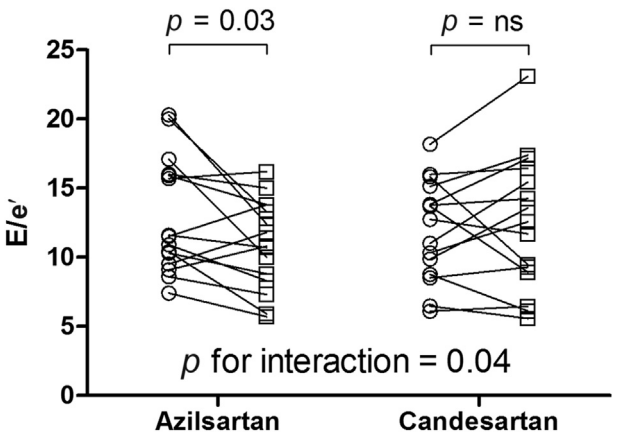

Figure 1. The E/e′ values of the patients before medication are plotted as circles, and the E/e′ values of 3–6 months after medication are plotted as squares. E = early left ventricular filling velocity; e′ = early diastolic velocity; ns = not significant.

Please cite this article in press as: Sakamoto M, et al., Azilsartan, but not Candesartan Improves Left Ventricular Diastolic Function in Patients with Hypertension and Heart Failure, International Journal of Gerontology (2015), http://dx.doi.org/10.1016/j.ijge.2015.06.003

diastolic function. However, this was not the circumstance because candesartan, which did not improve cardiac diastolic function, decreased the blood pressure to levels comparable to those in the azilsartan group. Second, a decrease in the heart rate may improve cardiac diastolic function. Azilsartan but not candesartan indeed significantly decreased the heart rate. The mechanisms may be attributable to the effects of coadministered drugs such as Ca channel blockers or to the direct effects of azilsartan; however, the mechanisms remain unclear. This possible mechanism cannot be denied because decreases in the heart rate may affect LV diastolic properties by increasing the LV relaxation rate. Third, pharmacological actions specific to azilsartan may affect the myocardium such as reversing remodeling; changes in the LV end-diastolic volume and end-systolic volume alter the LV relaxation rate[22]. However, the present study revealed that neither end-diastolic volume nor end-systolic volume had changed at 3–6 months. Myocardial fibrosis, which affects the LV diastolic pressure–volume relationship and, consequently, cardiac dysfunction, may be affected by azilsartan. The chemical structure of azilsartan is very similar to that of candesartan[10,20], which is difficult to believe considering it has specific effects on myocardial fibrosis. Fourth, the only difference between azilsartan and candesartan is the strength of their affinity to angiotensin II receptors and their affinity to the arterial vasculature[23,24]. Compared to candesartan, azilsartan has a higher affinity for angiotensin II receptors and a higher affinity for vasculature because of the difference of one residue in the molecular structure[24]. The effects on the arterial vasculature may affect the LV relaxation rate[22,25]; this effect increases the capacitance of the aorta and delays the onset of ejection, and thus increases the LV relaxation rate[22,25]. In the present study, we did not measure aortic capacitance, but differences in the aortic diastolic pressure may reflect changes in the aortic capacitance. We could not identify the exact hemodynamic mechanisms, although it would be plausible to say that azilsartan improves cardiac diastolic function, whereas other ARBs, including candesartan, do not.

4.3. Clinical importance

The number of patients with HFpEF is increasing progressively with a prognosis as poor as that of HFrEF[2,3]. The prognosis of patients with HFpEF has not improved, whereas the prognosis of patients with HFrEF has improved; there is consequently an urgent need to find suitable drugs for patients with HFpEF[2,3]. There are no effective drugs for HFpEF, including ordinary ARBs and aldosterone blockers. This study indicates that azilsartan is a potentially good candidate for patients with HFpEF. If azilsartan improves diastolic function and cardiovascular outcomes such as cardiovascular death or hospitalizations due to HF, it may be the first drug to treat patients with HFpEF. However, a large-scale clinical trial using azilsartan in patients with HFpEF is definitely required in the near future.

Another important clinical implication of the present study is that clinicians need to pay attention to vascular insufficiency in addition to myocardial stiffness in patients with HFpEF. If treating vascular insufficiency and improving myocardial remodeling can improve cardiac diastolic function, then such patients should be treated with ARBs, ACEs, and/or calcium channel blockers because calcium channel blockers improve vascular damage[26]. In addition to azilsartan, the combination of ARBs and Ca channel blockers may be a candidate for patients with HFpEF.

4.4. Study limitations

The present study has several limitations. First, it was an open-label trial with a small sample size. However, to decrease this limitation, we used the objective end-point of the LV E/e′ ratio.

Second, the severity of HF pathophysiology may differ between retrospective and prospective studies. Therefore, we enrolled all HF patients with hypertension who received azilsartan in our department, which resulted in the absence of selection bias.

Third, because azilsartan can also be used to treat hypertension, an improvement in LV E/e′ may be attributable to a decrease in high blood pressure. However, this does not seem to be the circumstance because lowering the blood pressure using candesartan did not improve cardiac diastolic function. This suggests that the decrease in the LV E/e′ ratio is attributable to azilsartan-specific pharmacological actions, and not the secondary effects of decreased blood pressure.

In summary, despite these limitations, we propose the hypothesis that azilsartan improves cardiac diastolic function in HF patients with hypertension. Further large-scale trials are required to verify the beneficial effects of azilsartan in HF patients.

Acknowledgments

This study was supported by Grants-in-aid for Human Genome, Tissue Engineering and Food Biotechnology (H13-Genome-011), Health and Labour Sciences Research grants; Comprehensive Research on Aging and Health [H13-21seiki (seikatsu)-23], Health and Labour Sciences Research grants, Japan (Tokyo, Japan); and a grant from the Japan Cardiovascular Research Foundation (H16-H22) (Tokyo, Japan). The funding sources had no involvement in the current study.

References

1. Braunwald E, Bristow MR. Congestive heart failure: fifty years of progress. *Circulation*. 2000;102(20 Suppl 4):14–23.
2. Torre-Amione G. The syndrome of heart failure: emerging concepts in the understanding of its pathogenesis and treatment. *Curr Opin Cardiol*. 1999;14:193–195.
3. Packer M. Neurohormonal interactions and adaptations in congestive heart failure. *Circulation*. 1988;77:721–730.
4. Wachter R, Edelmann F. Diagnosis of heart failure with preserved ejection fraction. *Heart Fail Clin*. 2014;10:399–406.
5. Komajda M, Lam CS. Heart failure with preserved ejection fraction: a clinical dilemma. *Eur Heart J*. 2014;35:1022–1032.
6. Elzinga G, Westerhof N. Pressure and flow generated by the left ventricle against different impedances. *Circ Res*. 1973;32:178–186.
7. Hori M, Inoue M, Kitakaze M, et al. Ejection timing as a major determinant of left ventricular relaxation rate in isolated perfused canine heart. *Circ Res*. 1984;55:31–38.
8. Hori M, Inoue M, Kitakaze M, et al. Loading sequence is a major determinant of afterload-dependent relaxation in intact canine heart. *Am J Physiol*. 1985;249:H747–H754.
9. Shapiro BP, Lam CS, Patel JB, et al. Acute and chronic ventricular-arterial coupling in systole and diastole: insights from an elderly hypertensive model. *Hypertension*. 2007;50:503–511.
10. White WB, Weber MA, Sica D, et al. Effects of the angiotensin receptor blocker azilsartan medoxomil versus olmesartan and valsartan on ambulatory and clinic blood pressure in patients with stages 1 and 2 hypertension. *Hypertension*. 2011;57:413–420.
11. Lang RM, Bierig M, Devereux RB, et al, Chamber Quantification Writing Group; American Society of Echocardiograshy's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.
12. Redfield MM, Jacobsen SJ, Burnett Jr JC, et al. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA*. 2003;289:194–202.
13. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol*. 1986;57:450–458.
14. Teichholz LE, Kreulen T, Herman MV, et al. Problems in echocardiographic volume determinations: echocardiographic–angiographic correlations in the presence of absence of asynergy. *Am J Cardiol*. 1976;37:7–11.
15. Dokainish H, Zoghbi WA, Lakkis NM, et al. Optimal noninvasive assessment of left ventricular filling pressures: a comparison of tissue Doppler

echocardiography and B-type natriuretic peptide in patients with pulmonary artery catheters. *Circulation*. 2004;109:2432–2439.
16. Chrysant SG. Angiotensin II receptor blockers in the treatment of the cardiovascular disease continuum. *Clin Ther*. 2009;30(Pt 2):2181–2190.
17. Angiotensin. II receptor antagonists and heart failure: angiotensin-converting-enzyme inhibitors remain the first-line option. *Prescrire Int*. 2005;14:180–186.
18. Khawaja Z, Wilcox CS. An overview of candesartan in clinical practice. *Expert Rev Cardiovasc Ther*. 2011;9(8):975–982.
19. Skvortsov AA, Nasonova SN, Sychev AV, et al. Effects of long term therapy with angiotensin-converting enzyme inhibitor quinapril, antagonists of receptors to angiotensin II valsartan, and combination of quinapril and valsartan in patients with moderate chronic heart failure. Main results of the SADKO-CHF study [in Russian]. *Kardiologiia*. 2006;46:33–51.
20. Massie BM, Carson PE, McMurray JJ, et al, I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359:2456–2467.
21. Yusuf S, Preffer MA, Swedberg K, et al, CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet*. 2003;362:777–781.
22. Goebel B, Hauqaa KH, Meyer K, et al. Early diastolic strain rate predicts response to heart failure therapy in patients with dilated cardiomyopathy. *Int J Cardiovasc Imaging*. 2014;30:505–513.
23. Baker WL, White WB. Azilsartan medoxomil: a new angiotensin II receptor antagonist for treatment of hypertension. *Ann Pharmacother*. 2011;45:1506–1515.
24. Ishii T, Yasuda M, Saito Y, et al. Examination of the effect of changing to azilsartan from candesartan in renal transplant patients. *Transplant Proc*. 2014;46:492–495.
25. Chung CS, Strunc A, Oliver R, et al. Diastolic ventricular-vascular stiffness and relaxation relation: elucidation of coupling via pressure phase plane-derived indexes. *Am J Physiol Heart Circ Physiol*. 2006;291:H2415–H2423.
26. Andreadis EA, Sfakianakis ME, Tsourous GI, et al. Differential impact of angiotensin receptor blockers and calcium channel blockers on arterial stiffness. *Int Angiol*. 2010;29:266–272.

Please cite this article in press as: Sakamoto M, et al., Azilsartan, but not Candesartan Improves Left Ventricular Diastolic Function in Patients with Hypertension and Heart Failure, International Journal of Gerontology (2015), http://dx.doi.org/10.1016/j.ijge.2015.06.003