Original Article

Effects of Candesartan for Middle-Aged and Elderly Women with Hypertension and Menopausal-Like Symptoms

Hideo IKEDA[1], Teruo INOUE[2], Shumpo UEMURA[1], Ryota KAIBARA[1], Hiroyuki TANAKA[1], and Koichi NODE[2]

Hypertension in middle-aged or elderly women is often accompanied with various symptoms, which may be related to climacteric. The symptoms of post-menopausal women are suggested to be derived in part from instability of the sympathetic nerve system due to a low estrogen state. An angiotensin-receptor blocker, candesartan cilexetil (candesartan), is known to suppress sympathetic nerve activity by inhibiting the renin-angiotensin system in the brain, suggesting that it may be effective for ameliorating these symptoms. The aim of this study was to elucidate whether candesartan improves menopausal symptoms in hypertensive women. A total of 69 female patients, aged 40 years or older, who had hypertension and various menopausal-like symptoms, were recruited from 39 centers to participate in this study. Patients were prescribed candesartan 4 to 8 mg/day (average dose 7.2 mg/day), alone or in addition to current antihypertensive medications. We interviewed patients in regard to their menopausal symptoms and scored them using the Simplified Menopausal Index (SMI). During the 12-month observation period, significant decreases were seen in both blood pressure (157±21/85±11 to 141±18/77±12 mmHg, $p<0.001$) and SMI (29±18 to 18±17, $p<0.001$), although the heart rate did not change. The percentage of decrease in SMI was correlated with that in systolic blood pressure ($r=0.43$, $p<0.001$). Candesartan may be an effective antihypertensive agent to relieve menopausal-like symptoms in middle-aged or elderly hypertensive women. (*Hypertens Res* 2006; 29: 1007–1012)

***Key Words*: candesartan, hypertension, menopausal-like symptom, simplified menopausal index, middle-aged or elderly women**

Introduction

Hypertension in middle-aged and elderly women is often accompanied with various symptoms, which may be related to climacteric. The symptoms of these patients often cannot be improved even if effective blood pressure lowering is achieved by medical therapies. In addition, it is difficult to assess the types and degree of symptoms, because patients with well-controlled blood pressure tend to bear their symptoms with little complaint. Nonetheless, these symptoms clearly limit the quality of life (QOL) of patients. The symptoms of post-menopausal women are suggested to be derived in part from instability of the sympathetic nerve system accompanied by a low estrogen state (*1*). The angiotensin-receptor blocker, candesartan cilexetil (candesartan), is known to suppress sympathetic nerve activity by inhibiting the renin-angiotensin system in the brain, suggesting that it may also be effective for ameliorating menopausal symptoms (*2*). The aim of this study was to elucidate whether or not can-

From the [1]Saga Medical Association, Saga, Japan; and [2]Department of Cardiovascular and Renal Medicine, Saga University Faculty of Medicine, Saga, Japan.

This work was supported in part by a Grant from the Takeda Science Foundation.

Address for Reprints: Teruo Inoue, M.D., Department of Cardiovascular and Renal Medicine, Saga University Faculty of Medicine, 5–1–1 Nabeshima, Saga 849–8501, Japan. E-mail: inouete@med.saga-u.ac.jp

Received April 7, 2006; Accepted in revised form September 4, 2006.

Table 1. Simplified Menopausal Index (SMI)

Symptoms	Severe	Moderate	Mild	Absent
Hot flushes	10	6	3	0
Sweats	10	6	3	0
Cold constitution	14	9	5	0
Shortness of breath or palpitation	12	8	4	0
Insomnia	14	9	5	0
Easy excitability or irritability	12	8	4	0
Worry about self depression	7	5	3	0
Headache, vertigo or nausea	7	5	3	0
Easy fatigability	7	4	2	0
Shoulder stiffness, lumbago or joint pain	7	5	3	0

Table 2. Patient Characteristics

Patient number	69
Age (years)	66.8±9.4
Body weight (kg)	54.7±9.2
Systolic blood pressure (mmHg)	156.8±20.7
Diastolic blood pressure (mmHg)	84.8±10.5
Heart rate (beats/min)	73.5±12.3
Newly administration (*n* (%))	28 (40.6)
Additional administration to calcium antagonists (*n* (%))	30 (43.5)
Exchanged administration from calcium antagonists (*n* (%))	11 (15.9)
Combining drugs	
β-Blockers (*n* (%))	3 (4.3)
Others (*n* (%))	2 (2.9)
Dose of candesartan (mg/day)	7.2±1.6

desartan improves menopausal-like symptoms in female patients with hypertension.

Methods

Study Design

We conducted a single-arm prospective longitudinal study, recruiting 69 middle-aged or elderly female outpatients (≥40 years) with hypertension who had various menopausal-like symptoms, independent of blood pressure control status. All of them were followed by local general practitioners or physicians in 9 hospitals and 30 clinics. Patients who had already received angiotensin-receptor blockers or angiotensin converting enzyme inhibitors were excluded. Other exclusion criteria were the presence of serious cardiac, cerebrovascular or renal complications or the current or prior use of hormone replacement therapy or tranquilizers to treat the symptoms.

In all of the recruited patients, administration of candesartan was started at a dose of 4 mg/day or 8 mg/day independently of patients' blood pressure control status and continued for 12 weeks. The following considerations were applied to the prescription of candesartan. 1) Candesartan was begun as a sole treatment for patients with high blood pressure who were currently under no medications. 2) Candesartan was added to the other currently prescribed antihypertensive drugs for patients whose blood pressure was poorly controlled under their present regimen. 3) Candesartan was used to replace other antihypertensive drugs in patients whose blood pressure was well controlled or poorly controlled under their present regimen. If blood pressure control was still poor in patients whose starting dose of candesartan was 4 mg/day, the dose was increased to 8 mg/day. The study protocol was approved by the ethics committees of all participating institutions and written informed consent was obtained from each patient.

Measurement of Blood Pressure and Heart Rate

Measurement of blood pressure and heart rate were made at each clinic visit, 24±4 h after the previous intake of study medication, in duplicate, with an interval of at least 5 min, after the patients had rested in a seated position for 5 min. Office blood pressures were measured to the nearest 2 mmHg in the same arm at each visit, using a mercury sphygmomanometer with an appropriately sized cuff. Heart rate was measured by pulse palpation for 30 s immediately after the blood pressure measurements.

Assessment of Patients' Symptoms

Patients' menopausal-like symptoms were assessed using the simplified menopausal index (SMI), which is performed using simple, 2–3 min interviews and considered to be representative of the depression of estrogen levels in menopausal women (*3*). Briefly, patients were asked a total of 10 questions regarding typical menopausal symptoms. First, the answer to each question was given on a 4-scale (absent, mild, moderate, or severe). Next, scores of 0 to 14 points were assigned as shown in Table 1. Finally, the SMI score was calculated as the sum of these points. The SMI was assessed by

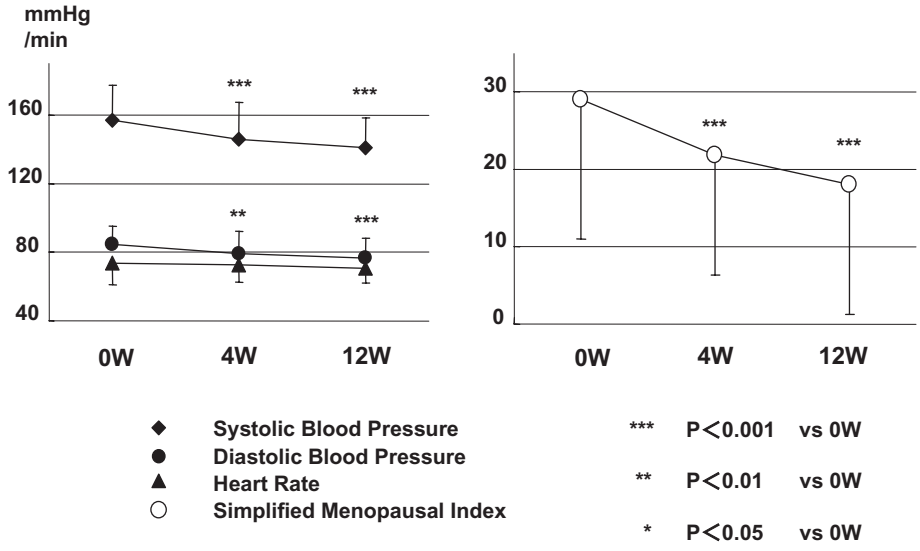

Fig. 1. *Changes in blood pressure, heart rate (left), and the simplified menopausal symptoms (SMI) (right) in overall patients. Blood pressure significantly decreased after candesartan administration. Although heart rate did not change, the SMI also decreased significantly.*

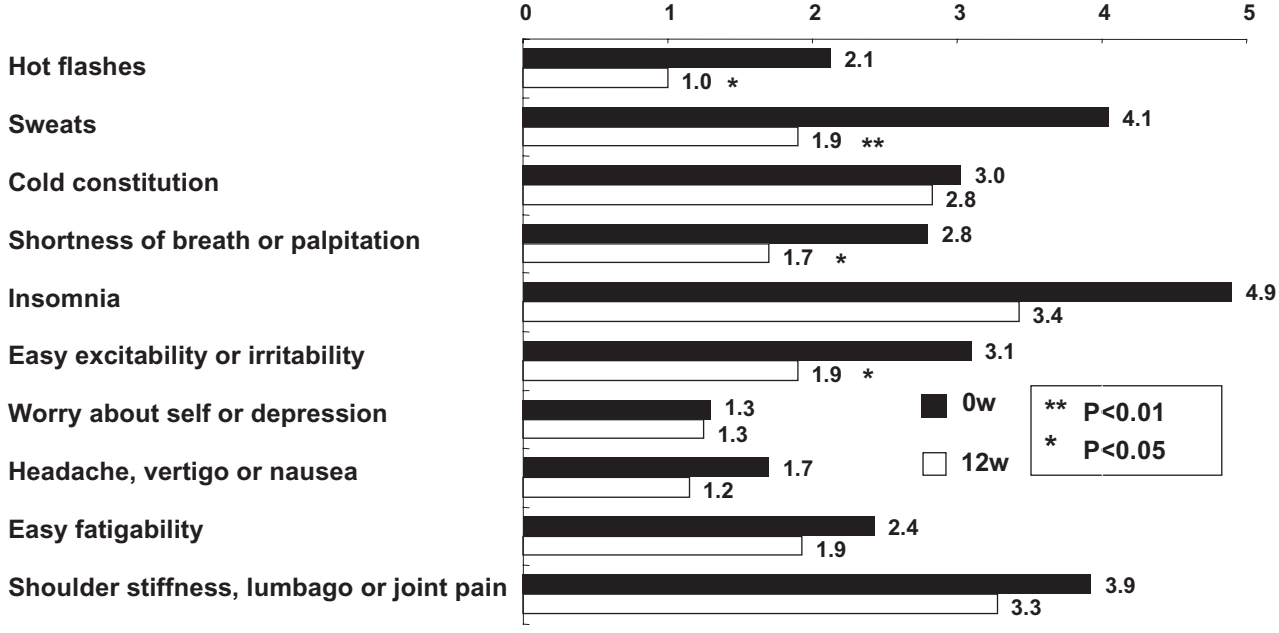

Fig. 2. *Changes in the scores of each of the 10 symptoms based on the interview results. Sympathetic symptoms such as hot flashes, sweats or palpitation tended to be well improved after candesartan administration.*

interviewers in each institute who were not aware of the study design.

Data Analysis

Data were collected at 3 points: before (baseline value), 4 weeks after, and 12 weeks after the initiation of candesartan administration. Changes in blood pressure and heart rate were analyzed using the repeated measures analysis of variance, and the analysis of change in SMI was performed using the Wilcoxon test. Correlations between two parameters were assessed using simple linear regression. Data were expressed as the mean±SD. Values of $p<0.05$ were considered to indicate statistically significant differences.

Results

The patients' characteristics are shown in Table 2. Candesartan was administrated as a new prescription in 28 patients (40.6%), as an adjunct to calcium antagonists in 30 patients (43.5%) and in place of discontinued calcium antagonists in the remaining 11 patients (15.9%). Candesartan was used in combination with β-blockers in 3 patients (4.3%) and in combination with other drugs in 2 patients (2.9%). In overall patients, systolic and diastolic blood pressure (SBP and DBP) decreased at 4 weeks (157±21 to 146±22 mmHg, $p<0.001$ and 85±11 to 79±13 mmHg, $p<0.01$, respectively) and still more at 12 weeks (to 141±18 mmHg, $p<0.001$ and to 77±12 mmHg, $p<0.001$, respectively), while heart rate did not change significantly (Fig. 1, left). The SMI also decreased significantly at 4 weeks (29±18 to 22±16, $p<0.001$) and still more at 12 weeks (to 18±17, $p<0.001$) (Fig. 1, right). Figure 2 shows the changes in the scores of each of the 10 symptoms based on the interview results. Sympathetic symptoms such as hot flashes, sweats or palpitation tended to be well improved after candesartan administration. Changes in SBP and those in SMI at 12 weeks were correlated in overall patients ($r=0.43$, $p<0.001$) (Fig. 3). Next, we separately analyzed 31 patients whose SBP either increased or did not decrease by more than 5 mmHg at 12 weeks. The changes in the blood pressure and heart rate of these patients are shown in Fig. 4 (left). The SMI decreased significantly (22±16 to 16±15, $p<0.05$) at 12 weeks even in these 31 patients (Fig. 4, right).

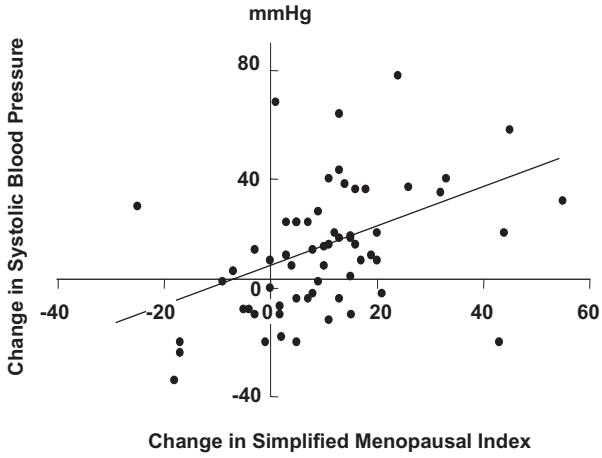

Fig. 3. *Relationship between changes in systolic blood pressure (SBP) and those in SMI at 12 weeks. The percentage decrease in the SMI was correlated with that in SBP in overall patients.*

Discussion

In this study, we demonstrated that candesartan administration, whether given singly, added to an existing regimen, or used as a replacement for discontinued calcium antagonists, was effective for not only blood pressure reduction but also relief from menopausal-like symptoms as assessed by the SMI in middle-aged and elderly women with hypertension.

After menopause the incidence of hypertension increases progressively in women, eventually leading to an incidence equivalent to that in men (*4*). Cardiovascular morbidity and mortality are higher in post-menopausal than in pre-menopausal women with hypertension (*5*, *6*). In addition, hypertension in middle-aged or elderly women has been shown to be complicated with various symptoms that are related to climacteric and adversely affect QOL. QOL is one of the important targets to be improved in the treatment of hypertension, and the QOL-guided treatment may improve the patients' psychological status and improve compliance to antihypertensive agents. Numerous studies have demonstrated that antihypertensive treatments improve patient's QOL (*7–10*), and beneficial effects of candesartan are also evident (*11–14*). Basically the improvement of patients' QOL seems to depend on blood pressure–lowering effects (*10*). Our results also showed that the improvement of patients' symptoms, as demonstrated by a change in SMI after candesartan administration, was associated with a decrease in blood pressure. Interestingly, however, these symptoms improved even in patients whose blood pressure did not decrease. Malmqvist *et al*. (*12*) showed that candesartan had a better effect on QOL and better tolerability than enalapril or hydrochlorothiazide under an equivalent decrease in blood pressure in women, suggesting that candesartan has beneficial effects beyond its blood pressure–lowering effects.

The climacteric-related symptoms are suggested to be derived in part from instability of the sympathetic nerve system accompanied by a low estrogen state. Based on an observation of ambulatory blood pressure profiles, Mercuro *et al*. (*15*) showed that estrogen treatment lowered blood pressure throughout a 24-h period in post-menopausal women with mild-to-moderate hypertension, and that the blood pressure–lowering effect was associated with a decrease in circulating norepinephrine levels. It may therefore be hypothesized that the increase in blood pressure observed after menopause is linked, at least partially, to an increase in sympathetic nerve activity. Among the various angiotensin receptor blockers, candesartan is the only one that is considered to suppress sympathetic nerve activity by inhibiting the renin-angiotensin system in brain (*2*). Owada (*16*) reported that candesartan had prophylactic efficacy for migraine in hypertensive patients, a property that may derive, at least in part, from its effects on the autonomic nerve system. Thus, the ability of candesartan to reduce sympathetic nerve activity may contribute to the amelioration of patients' symptoms, although heart rate did not change after candesartan administration in the present work. In addition, estrogen can down-regulate angiotensin type 1 receptor expression, providing another possible mechanism for the association between post-menopausal decrease

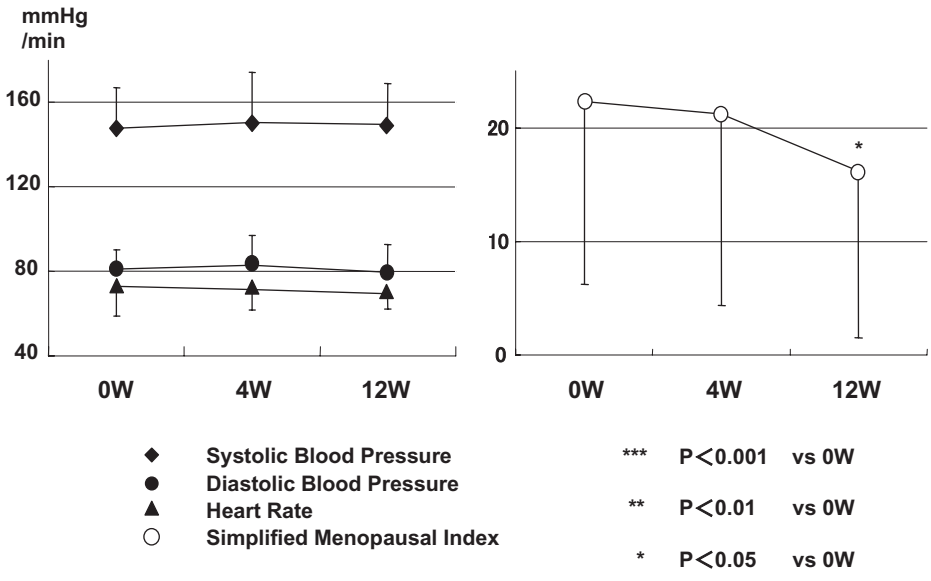

Fig. 4. *Analysis in 31 patients whose SBP either increased or did not decrease by more than 5 mmHg at 12 weeks. The SMI decreased significantly at 12 weeks even in these 31 patients.*

in estrogen levels and hypertension and providing further evidence that candesartan may be effective for the treatment of hypertension in post-menopausal women (*17*).

Candesartan has already been established as an effective agent for conferring protection against further cardiovascular events based on studies in Japan (*18*) and Western countries (*19–22*). This protection may be the result of various cardiovascular protective effects (pleiotropic effects) of candesartan, including anti-inflammatory or anti-oxidative actions, (*23*) in addition to blood pressure–lowering effects. The significant feature of our study is the fact that it was mainly performed by local medical practitioners, almost none of whom were specialists for cardiovascular diseases or hypertension. In addition to providing cardiovascular protection or preventing cardiovascular events, it is also very important for antihypertensive therapies to relieve patients' symptoms and to improve their QOL. In light of these concerns, candesartan would be a rational choice of antihypertensive drug for middle-aged and elderly women with various menopausal-like symptoms.

Study Limitations

This study was a non-comparative single-arm study including a small number of patients. Thus, the relief from patients' symptoms by candesartan may have been a mere placebo effect. To elucidate whether or not the effects were attributable to candesartan, randomized comparisons should be designed in future trials. Since we assessed neither sympathetic nerve activity nor estrogen levels, our discussions regarding the mechanisms by which candesartan improves menopausal-like symptoms are quite speculative. Future trials should evaluate sympathetic nerve functions by plasma catecholamine levels or heart rate variability and should also measure the plasma estrogen levels. It is very difficult for the practitioners to precisely assess patient symptoms by interview. In this study we used the SMI to assist with this process. Although the SMI is not established worldwide, it is widely used by Japanese gynecologists because it is easy to perform, its results are well representative of the depression of estrogen levels in menopausal women, and its reproducibility has been established (*3*, *24*). Given the limited number of office hours in most practices, the SMI should be considered as a convenient index for a wide range of practitioners.

Conclusions

It is very important for antihypertensive therapies to relieve patients' symptoms as well as to prevent cardiovascular events. Candesartan may be an effective antihypertensive agent to relieve menopausal-like symptoms in middle-aged or elderly hypertensive women.

Appendix

The following physicians in Saga Medical Association, Japan, participated in this study: Hiromichi Fukuda, Hideo Ikeda, Ryota Kaibara, Hirokuki Tanaka, Hitoshi Ohteki, Naoki Kojima, Naoaki Higuchi, Akira Takahashi, Masanori Shida, Ryutaro Yamaguchi, Masazumi Mitsuoka, Shinji Eguchi, and Yoshitaka Muto.

References

1. Takamatsu K, Ohta H, Makita K, *et al*: Effects of counsel-

ing on climacteric symptoms in Japanese postmenopausal women. *J Obstet Gynecolol* 2001; **27**: 133–140.
2. Saavedra JM, Ando H, Armando I, *et al*: Anti-stress and anti-anxiety effects of centrally acting angiotensin II AT1 receptor antagonists. *Regul Pept* 2005; **128**: 227–238.
3. Koyama T: Climacteric disorders. *Obstet Gynecol Ther* 1994; **69**: 506–509 (in Japanese).
4. Bradshaw K: Hormone replacement therapy in hypertensive postmenopausal women. Role of the gynecologist. in Safer M, Stimpel M, Zanchetti A (eds): Hypertension in Postmenopausal Women. Berlin and Heidelberg, Springer-Verlag, 1994, pp 45–51.
5. Stacssen J, Bulpitt CJ, Fagard R, *et al*: The influence of menopause on blood pressure. *J Hum Hypertens* 1989; **3**: 427–433.
6. Anastos R, Charney P, Charon RA, *et al*, The Women's Caucus, Working Group on Women's Health of the Society of Geneal Internal Medicine: Hypetension in women: what is really known? *Ann Intern Med* 1991; **115**: 287–293.
7. Hjemdahl P, Wiklund I: Quality of life on antihypertensive drug therapy: end point or marketing exercise? *Hypertension* 1992; **10**: 1437–1446.
8. Barnet DB: Assessment of quality of life: a medical imperative. *Am J Cardiol* 1991; **67**: 41C–44C.
9. Wenger NK: Assessment of quality of life: a medical imperative. *Cardiovasc Drug Ther* 1988; **1**: 553–558.
10. Dahlöf B, Innocenti AD, Elmfeldt D, *et al*: Felodipine-metoprolol combination tablet: maintained health-related quality of life in the presence of substantial blood pressure reduction. *Am J Hypertens* 2005; **18**: 1313–1319.
11. Schulte KL, Fischer M, Lenz T, *et al*: Efficacy and tolerability of candesartan cilexetil monotherapy or in combination with other antihypertensive drugs: results of the AURA study. *Clin Drug Invest* 1999; **18**: 453–460.
12. Malmqvist K, Kahan T, Dahl M: Angiotensin II type 1 (AT1) receptor blockade in hypertensive women: benefits of candesartan cilexetil *versus* enalapril or hydrochlorothiazide. *Am J Hypertens* 2000; **13**: 504–511.
13. Kloner RA, Weinberger M, Pool JL, *et al*: Comparative effects of candesartan cilexetil and amlodipine in patients with mild systemic hypertension. *Am J Cardiol* 2001; **87**: 727–731.
14. Kirpizidis H, Stavrati A, Geleris P: Assessment of quality of life in a randomized clinical trial of candesartan only or in combination with DASH diet for hypertensive patients. *J Cardiol* 2005; **46**: 177–182.
15. Mercuro G, Zonc S, Pilia I, *et al*: Effects of acute administration of transdermal estrogen on postmenpausal women with systemic hypertension. *Am J Cardiol* 1997; **80**: 652–655.
16. Owada K: Efficacy of candesartan in the treatment of migraine in hypertensive patients. *Hypertens Res* 2004; **27**: 441–446.
17. Nickenig G, Bäumer AT, Grohe C, *et al*: Estrogen modulates AT1 receptor gene expression *in vitro* and *in vivo*. *Circulation* 1998; **97**: 2197–2201.
18. Suzuki H, Kanno Y, for the Efficacy of Candesartan on Outcome in Saitama Trial (E-COST) Group: Effects of candesartan on cardiovascular outcomes in Japanese hypertensive patients. *Hypertens Res* 2005; **28**: 307–314.
19. Pfeffer MA, Swedberg K, Granger CB, *et al*: Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003; **362**: 759–766.
20. McMurray JJ, Ostergren J, Swedberg K, *et al*: Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; **362**: 767–771.
21. Yusuf S, Pfeffer MA, Swedberg K, *et al*: 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. Lithell H, Hanson L, Skoog I, *et al*: The Study on Cognition and Prognosis in Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* 2003; **21**: 875–886.
23. Dohi Y, Ohashi M, Sugiyama M, *et al*: Candesartan reduces oxidative stress and inflammation in patients with essential hypertension. *Hypertens Res* 2003; **26**: 691–697.
24. Kubota T, Sagara Y, Nakazawa N, *et al*: The influence of pregnancy and delivery on the climacteric symptom. *Acta Obstet Gynaecol Jpn* 1996; **48**: 1–8 (in Japanese).