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Original Article

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Candesartan, an angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients on chronic haemodialysis—a randomized study

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Abstract

Background. Cardiovascular events are the major determinants of the prognosis of patients on chronic haemodialysis. The present study was designed to investigate whether candesartan, an angiotensin II type-1 receptor blocker, reduces the incidence of cardiovascular events in these patients.

Methods. A total of 80 chronic haemodialysis patients (male/female, 47/33; mean age ± SEM, 61 ± 1 years) in stable condition and with no clinical evidence of cardiac disorders were enrolled. Patients were randomly assigned candesartan 4–8 mg/day (candesartan group; $n = 43$) or nothing (control group; $n = 37$), and followed for 19.4 ± 1.2 months with as endpoint cardiovascular events such as fatal/nonfatal myocardial infarction, unstable angina pectoris, congestive heart failure, severe arrhythmia and sudden death.

Results. Both groups exhibited similar clinical characteristics at baseline. During follow-up, cardiovascular events occurred in seven patients in the candesartan group and 17 in the control group. Kaplan–Meier analysis revealed that cardiovascular events and mortality rates were significantly ($P < 0.01$) higher in the control group than in the candesartan group (45.9 *vs* 16.3% and 18.9 *vs* 0.0%, respectively).

Conclusions. Candesartan therapy significantly reduces cardiovascular events and mortality in patients on chronic maintenance haemodialysis and therefore improves the prognosis of these patients.

Keywords: angiotensin receptor antagonists; brain natriuretic peptide; cardiovascular disease; cardiovascular mortality; congestive heart failure; randomized trail

Introduction

The number of patients with end-stage chronic renal failure is increasing [1]. Although induction of haemodialysis dramatically improves prognosis, subsequent occurrence of cardiovascular events is a common problem and new strategies that reduce the incidence of cardiovascular events in these patients are required.

Atherosclerosis is a frequently observed clinical feature of haemodialysis patients. Accumulating evidence suggests that the renin–angiotensin system (RAS) plays a crucial role in the pathogenesis of atherosclerotic lesions [2–5]. Activation of angiotensin II type-1 receptors increases oxidative stress resulting in the initiation of an inflammatory cascade in the vascular wall; treatment with angiotensin II type-1 receptor blockers (ARBs) reduces oxidative stress, inflammation [6] and cardiovascular events in patients with hypertension [7]. On the other hand, heart failure (left ventricular systolic and/or diastolic dysfunction), which is associated with active cardiac RAS, also contributes to the frequent incidence of cardiovascular events in patients on chronic haemodialysis [8]. Suppression of RAS by ARBs has been shown to elicit beneficial effects in patients with heart failure [9–11]. These results suggest that blockade of angiotensin II type-1 receptors might reduce the high prevalence of cardiovascular events observed in haemodialysis patients. Indeed, a recent retrospective study demonstrated that angiotensin-converting enzyme inhibitors reduce mortality among patients on chronic haemodialysis [12]. Thus, the present study was designed to investigate whether angiotensin II type-1 receptor blockade using candesartan inhibits progression of atherosclerosis and cardiac dysfunction and thereby prevents cardiovascular events in patients on chronic maintenance haemodialysis.

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Subjects and methods

Study design

This study was a prospective, randomized, open blinded-endpoint trial to assess the effect of candesartan on clinical outcome in patients on chronic maintenance haemodialysis. We undertook the study in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Enshu General Hospital. All patients gave written informed consent to participate prior to the start of the study. The core centre was the Nagoya City University responsible for data collection, safety and event monitoring, and statistical analysis. Recruitment and follow-up of patients were performed by investigators in the Enshu General Hospital.

Subjects

The three categories of patients aged ≥35 years eligible for the study were: (i) those who were in stable condition and asymptomatic for at least the previous 6 months; (ii) those with interdialytic increase of body weight <5% and with stable dry weight, defined as regularly reached end-dialysis weight without the signs of dehydration or overhydration, for at least 3 months; (iii) those with post-haemodialytic cardiothoracic ratio on chest X-ray <50% in males and <55% in females. The exclusion criteria were: a history of myocardial infarction, angina pectoris and cardiac revascularization, valvular heart disease, congestive heart failure, severe arrhythmia and pulmonary, hepatic, renal, active inflammatory and malignant diseases. We screened patients on chronic maintenance haemodialysis in the Enshu General Hospital between October 1999 and December 2001 (Figure 1).

Procedures

Between April 2000 and February 2002, a total of 80 maintenance haemodialysis patients (male/female, 47/33; mean age ± SEM, 61 ± 1 years) were randomly assigned to receive candesartan 4–8 mg q.d. after breakfast (candesartan group; $n = 43$) or nothing (control group; $n = 37$) for 3 years (Figure 1). Their haemodialysis had commenced between January 1990 and December 2000. Patients were dialysed three times a week and were receiving adequate dialysis treatment. A computer-generated random number sequence was obtained in the core centre and the sealed envelop method was used for randomization. Randomization was not blocked or stratified (simple randomization). Baseline assessment included blood sampling for the measurement of brain natriuretic peptide (BNP), chest X-rays and ultrasound cardiograms (UCG) examined after haemodialysis. Left ventricular mass was calculated using the method described by Devereux and Reichek [13]. The study endpoint was the overall incidence of cardiovascular events defined as: (i) sudden death; (ii) fatal and non-fatal myocardial infarction detected by clinical symptoms combined with Q waves, ST-segment elevation or both on electrocardiogram and elevated levels of cardiac enzymes; (iii) unstable angina pectoris requiring hospitalization; (iv) congestive heart failure requiring hospitalization (New York Heart Association class III or IV) and (v) severe arrhythmia (ventricular tachycardia, ventricular fibrillation). Assessment of the endpoint was done by the core centre in a blinded manner. All the events were assessed without any knowledge of the treatment group to which the patients had been assigned.

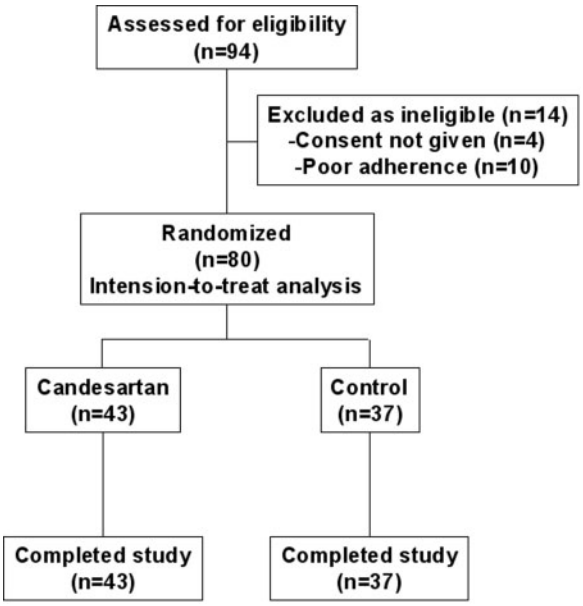

Fig. 1. Flow of patients through the study.

BNP measurement

For the measurement of BNP, 3 ml of blood was transferred to plastic tubes containing 2Na-ethylenediamine-tetraacetic acid 4.5 mg and aprotinin 1500 IU. Plasma samples were prepared within 30 min by pre-cooled centrifuge, immediately frozen and stored at −70°C until analysis. The BNP level was measured by radioimmunoassay (Shionoria BNP kit, Shionogi, Osaka, Japan) [14]. Analytical range, intra- and inter-assay coefficients of variation and normal reference range (99th percentile of the control population) of BNP assay were 4.0–2000 ng/l, 10.9%, 10.6% and <18.4 ng/l, respectively.

Statistical analysis

Based on our previous data, the assumed rate of cardiovascular events in patients on chronic maintenance haemodialysis with stable condition was 26.7 per 100 patient-years [15]. The present study was designed to investigate whether candesartan would reduce the risk of cardiovascular events based on the assumption that the odds ratio (OR) was 0.5 for candesartan *vs* control. To achieve a power of 80% with a two-sided test of significance at an α-level of 0.05, 40 patients per arm were required for this study. With the added expectation of subjects withdrawing from the study, 45 subjects were planned for each group.

The core centre independently monitored the progress of all aspects of this study. To protect the patients' safety a yearly interim analysis was scheduled. Although the study was originally designed to follow the patients for a mean of

3 years, the core centre recommended termination of the study after the second interim analysis because of clear evidence of the beneficial effect of candesartan. All the analyses were done by intention-to-treat.

Except where otherwise stated, all data are expressed as mean ± SEM. Differences between the two means that had normal distribution were compared by paired or unpaired Student's *t*-test. Because the distribution of BNP levels was skewed rightward, BNP concentrations are expressed as median ± median absolute deviation values. Significance of any difference in medians was assessed by Mann–Whitney U-test and Wilcoxon signed-rank test. Yates' corrected χ^2 test was used for comparisons between categorical data. To determine the factors that predict patient prognoses, several variables were subjected to Cox proportional-hazards analysis. Intra-group changes of blood pressure were analysed by analysis of variance (ANOVA) with repeated measures. To evaluate candesartan's effects, cumulative event-free curves were determined by Kaplan–Meier analysis; differences between these were analysed by the log-rank test. *P*-values <0.05 were considered statistically significant.

Results

The number of patients screened and randomized are reported in Figure 1. The follow-up was 100% complete and the mean follow-up period was 19.4 months.

Table 1 presents baseline characteristics. No difference was observed in the patients' characteristics and parameters obtained from UCG between the two groups at baseline. Furthermore, risk factors and concomitant medications were similar in the two groups except for the usage of α-blockers (Table 2). As shown in Figure 2, blood pressure was not different between the two groups and no changes were noted in the either group during follow-up. Mean blood pressure during follow-up was 153 ± 2/83 ± 1 mmHg in the candesartan and 149 ± 3/80 ± 2 mmHg in the control group ($P = 0.21/P = 0.18$).

A total of seven (16.3%) and 17 (45.9%) patients experienced cardiovascular events, and no patient and seven patients died in the candesartan and control groups, respectively, during the follow-up period (Table 3). Kaplan–Meier analysis demonstrated that the incidence of cardiovascular events was significantly higher in the control than the candesartan group (Figure 3). Univariate Cox proportional-hazards analysis revealed that candesartan therapy was the only significant predictor of event-free survival [χ^2, 7.57; OR, 0.29 (95% confidence interval (CI), 0.12–0.70); $P < 0.01$]. Candesartan therapy remained a significant predictor of event-free survival after adjustment for concomitant use of β-blockers [χ^2, 7.41; OR, 0.29 (95% CI, 0.12–0.71); $P < 0.01$] and of α-blockers [χ^2, 6.03; OR, 0.32 (95% CI, 0.13–0.80); $P < 0.01$] and follow-up blood pressure [χ^2, 7.30; OR, 0.23 (95% CI, 0.08–0.67); $P < 0.01$]. Furthermore, mortality was significantly higher in the control than the candesartan group (18.9 *vs* 0.0%) (Figure 4). The median plasma BNP level did not differ between the two groups at enrolment, whereas in patients who did not experience cardiovascular events at 12 months the levels were significantly increased in the control group ($n = 21$, $P < 0.01$) but not in the candesartan group ($n = 36$, $P = 0.92$) (Figure 5).

No severe adverse events and side effects thought to be related with candesartan usage were observed throughout the study period. Treatment with candesartan did not alter haemoglobin levels (candesartan, 9.9 ± 0.2 g/dl, $P = 0.31$; control, 10.3 ± 1.0 g/dl,

Table 1. Baseline characteristics of patients and UCG findings

	Control ($n = 37$)	Candesartan ($n = 43$)	*P*
Male (%)	21 (56.8)	26 (60.5)	0.75
Age (years)	62 ± 2	60 ± 2	0.31
Body mass index (kg/m^2)	20.4 ± 0.7	20.2 ± 0.6	0.81
Systolic blood pressure (mmHg)	152 ± 4	153 ± 3	0.92
Diastolic blood pressure (mmHg)	85 ± 3	82 ± 2	0.46
Heart rate (beats/minute)	81 ± 3	81 ± 2	0.90
Cardiothoracic ratio (%)	49.5 ± 0.7	48.3 ± 0.8	0.28
Haemoglobin (g/dl)	8.8 ± 0.3	9.2 ± 0.3	0.31
Haematocrit (%)	28.5 ± 0.6	30.9 ± 0.7	0.02
Brain natriuretic peptide (ng/l)	182 ± 93	168 ± 94	0.99
Haemodialysis duration (months)	33.2 ± 8.1	32.9 ± 5.2	0.97
UCG findings			
LVDd (mm)	51.3 ± 1.5	51.7 ± 0.8	0.79
LVDs (mm)	34.3 ± 1.7	32.9 ± 0.8	0.39
IVST (mm)	10.3 ± 0.5	10.1 ± 0.5	0.81
LVPWT (mm)	10.3 ± 0.3	10.5 ± 0.4	0.86
LVMI (g/m^2)	152.4 ± 14.9	143.3 ± 10.3	0.60
LVEF (%)	61.0 ± 2.8	66.3 ± 1.5	0.07
LVFS (%)	33.4 ± 1.9	37.0 ± 1.1	0.09

Data are expressed as mean ± SEM (median ± median absolute deviation for brain natriuretic peptide). UCG, ultrasound cardiogram; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; IVST, intraventricular septal thickness; LVPWT, left ventricular posterior wall thickness; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening.

Table 2. Medications during follow-up period and risk factors of patients

	Control ($n = 37$)	Candesartan ($n = 43$)	*P*
Medication			
Angiotensin-converting enzyme inhibitor	4 (11%)	7 (16%)	0.70
α-Blocker	1 (3%)	9 (21%)	0.03
β-Blocker	3 (8%)	10 (23%)	0.13
Calcium antagonist	22 (59%)	33 (77%)	0.16
Aspirin	3 (8%)	7 (16%)	0.45
Diuretics	6 (16%)	14 (33%)	0.15
Isosorbide dinitrate	5 (14%)	14 (33%)	0.08
Anti-diabetic agents	9 (24%)	10 (23%)	0.99
Risk factor			
Hypertension	29 (78%)	36 (84%)	0.75
Hyperlipidaemia	2 (5%)	1 (2%)	0.89
Diabetes mellitus	11 (30%)	15 (35%)	0.80
Body mass index >25 kg/m^2	3 (8%)	3 (7%)	0.99

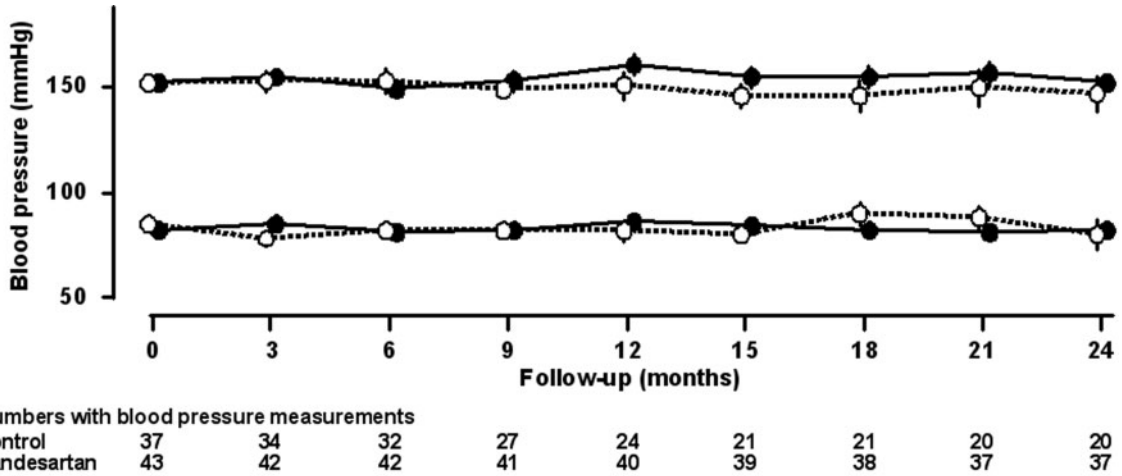

Fig. 2. Mean blood pressure readings at baseline and during follow-up.

Table 3. Cardiovascular events

	Control group ($n=37$)	Candesartan group ($n=43$)
Heart failure	11 (3)*	5 (0)
Unstable angina pectoris	2 (1)	2 (0)
Sudden death	3 (3)	0
Severe arrhythmia	1 (0)	0

*Numbers in parentheses indicate fatal cases.

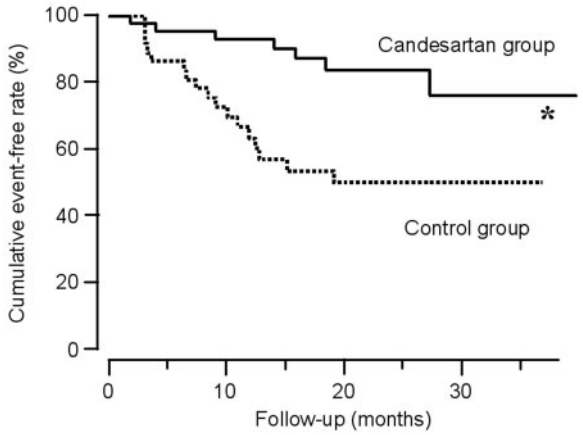

Fig. 3. Kaplan–Meier analysis of cumulative cardiovascular event-free rate in patients on chronic haemodialysis. *$P=0.0066$.

$P=0.49$; *vs* baseline) and haematocrit (candesartan, $30.7\pm0.5\%$, $P=0.15$; control, $31.4\pm1.5\%$, $P=0.26$; *vs* baseline). The number of patients on erythropoietin therapy was 40 out of 43 in the candesartan and 31 out of 37 in the control group ($P=0.34$). Serum potassium level measured before haemodialysis was not different in the candesartan and control group both at baseline (4.75 ± 0.14 and 4.36 ± 0.22 mEq/l, respectively, $P=0.12$) and during follow-up (5.11 ± 0.17 and 5.34 ± 0.43 mEq/l, respectively, $P=0.56$).

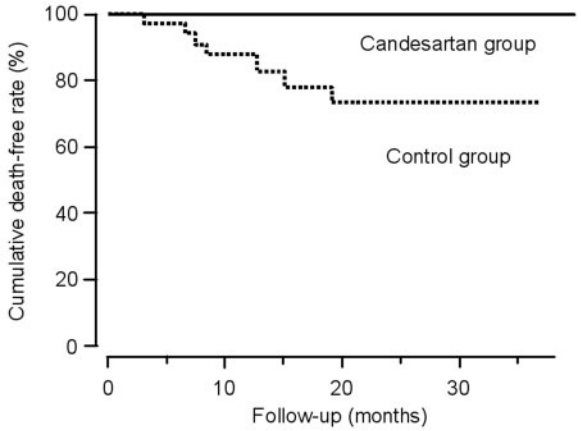

Fig. 4. Kaplan–Meier analysis of cumulative cardiovascular death-free rate in patients on chronic haemodialysis.

Discussion

The present study suggests that treatment with candesartan reduces cardiovascular events in patients on chronic maintenance haemodialysis. Since cardiovascular disease is the major determinant of prognosis in the dialysis patients, these findings may help provide a new strategy to improve long-term well-being in this population.

The beneficial effect of candesartan on the primary outcome was mainly attributed to lower incidence of heart failure, sudden death and severe arrhythmia in the candesartan arm as compared with the control group. Although none of the patients in the present study had symptomatic heart failure or cardiac dysfunction as assessed by UCG at baseline, patients on haemodialysis are generally considered at an elevated risk of heart failure. Treatment with candesartan may have prevented latent cardiac dysfunction from becoming symptomatic. In line with the speculation, baseline BNP levels were above the normal

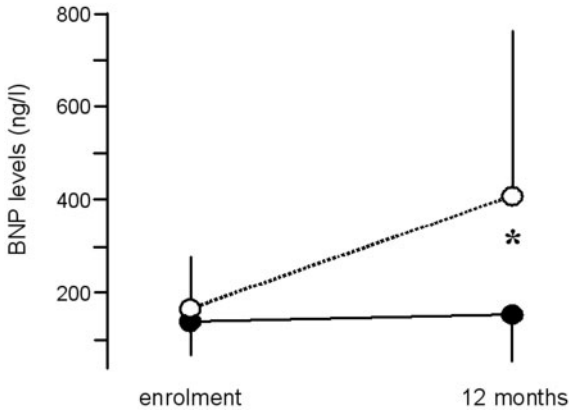

Fig. 5. Circulating brain natriuretic peptide (BNP) levels measured at enrolment and at 12 months thereafter [closed circle, candesartan group ($n=36$); open circle, control group ($n=21$)] in patients who did not experience adverse events. Values are median ± median absolute deviation. $*P<0.01$ *vs* enrollment in the control group (Wilcoxon signed-rank test).

reference range and candesartan prevented further progressive elevation of this parameter. The findings that the ARB exerted beneficial effects on cardiovascular outcomes are compatible with the recent reports that RAS plays pathophysiological roles in the process of heart failure [16,17]. Protective effects of candesartan against progressive increase of BNP levels in dialysed patients are quite important because elevated levels of BNP indicate an increased risk of cardiovascular events in patients on chronic haemodialysis [15]. Elevated BNP levels may also be associated with myocardial hypertrophy [18,19] leading to diastolic dysfunction. Candesartan may have prevented progression of cardiac hypertrophy in dialysed patients, since RAS has untoward effects on myocardial hypertrophy. Indeed, ARBs have been shown to retard cardiac hypertrophy in non-dialysed populations [7,20]. Furthermore, blockade of RAS by angiotensin-converting enzyme inhibitors given at doses not affecting blood pressure are able to reverse cardiac hypertrophy in patients on chronic haemodialysis [18]. The effective prevention of sudden death and arrhythmia observed in the present study is consistent with the effect of ARBs in non-dialysed patients [21,22]. Causal relationship between potassium levels and the anti-arrhythmic effect of candesartan is not clear, because the present data could not detect differences of serum potassium levels between the two groups.

In contrast to these beneficial effects of candesartan on the prevention of heart failure, sudden death and arrhythmia, the present study did not reveal anti-atherogenic effects of ARBs in patients on chronic haemodialysis. This seems consistent with reports that ARBs, unlike angiotensin-converting enzyme inhibitors, do not have protective effects against myocardial infarction in non-dialysed patients [23]. ARBs are either neutral or increase the rates of myocardial infarction despite their beneficial effects on reducing blood pressure [7,10,24]. However, protective effects of ARBs against myocardial infarction are controversial because beneficial protective effects of candesartan against myocardial infarction have recently been reported in non-dialysed patients with heart failure [25]. The failure of candesartan to prevent ischaemic cardiovascular events in the present study may be related to differences in the mechanisms underlying atherogenic processes between dialysed and non-dialysed subjects. Indeed, cardiovascular alterations in patients on chronic haemodialysis are characterized by high prevalence rates of cardiovascular calcification, which is related to hyperphosphataemia and increased calcium–phosphate ion product and may exert an important contribution to excess cardiovascular mortality and morbidity [26,27]. Traditional risk factors that are common in patients on chronic haemodialysis may not be sufficient to account for the high prevalence of atherosclerosis in this condition and contribution of RAS to pathological changes in the vasculature may be smaller in such patients as compared with these in non-dialysed subjects.

In the present study, candesartan's anti-hypertensive action may not have significantly contributed to the beneficial results observed, because changes of blood pressure during follow-up did not differ between the two groups. This concept is consistent with a recent report that angiotensin-converting enzyme inhibitors reduced mortality in chronic haemodialysis patients independently of their anti-hypertensive effect [12].

Interpretation of the present data is limited by the small number of patients studied and the relatively short follow-up period. This results in a reduced power of the analysis and might contribute at least in part to the failure to detect any effect of candesartan on ischaemic events. On the other hand, this study may be considered hypothesis generating. It provides some preliminary data suggesting that candesartan therapy reduces cardiovascular events and inhibits elevation of BNP level in patients on chronic haemodialysis. Further studies with larger numbers of patients are necessary to confirm the beneficial effects of ARBs in this setting. BNP levels at 12 months were measured only in patients who did not experience cardiovascular events at that time, because patients with cardiovascular events had already dropped out. Thus, the data indicate that in patients without cardiovascular events BNP levels were elevated in the control as compared with that in the candesartan group. This should be noted when interpreting the data. At baseline, patients on candesartan appeared to have severer hypertension since not only blood pressure but also the number of anti-hypertensive medications tended to be higher in this than in the control group. This imbalance was a consequence of simple randomization performed in the present study, and although the difference was not statistically significant, this may have affected the results.

In conclusion, this study suggests that candesartan improves prognosis of patients on chronic maintenance haemodialysis.

Conflict of interest statement. None declared.

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