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ORIGINAL ARTICLE

Association between blood pressure and target organ damage in patients with chronic kidney disease and hypertension: results of the APrODiTe study

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Blood pressure control is the most established practice for preventing the progression of chronic kidney disease. Evidence addressing blood pressure control status or nocturnal blood pressure dipping in Korean hypertensive patients with chronic kidney disease is scarce. We recruited 1317 hypertensive patients (chronic kidney disease stages 2–4, median age 58) from 21 centers in Korea. These patients underwent office and ambulatory blood pressure monitoring. High office and ambulatory blood pressure were defined as $>140/90$ mm Hg and $>135/85$ mm Hg (daytime)/ $>120/70$ mm Hg (nighttime), respectively. The blood pressure control status was as follows: true controlled (19%), white-coat (4.3%), masked (33.9%) and sustained uncontrolled (42.3%) hypertension. The dipping status was as follows: extreme-dipping (14.9%), dipping (33.3%), non-dipping (34.5%) and reverse-dipping (17.3%). Masked and sustained hypertension as well as non-dipping/reverse-dipping was more apparent in proportion to renal dysfunction and the extent of proteinuria. Ageing ($\geqslant 58$ years), male gender, obesity, diabetic nephropathy and proteinuria (>300 mg g^{-1} Cr or dipstick proteinuria $\geqslant 1+$) were independently associated with sustained uncontrolled hypertension. Diabetic nephropathy, old age, a history of stable angina/heart failure, advanced renal dysfunction and higher proteinuria levels were also significantly associated with non-dipping and reverse-dipping. Half of Korean chronic kidney disease patients had uncontrolled blood pressure and a non-dipping nocturnal blood pressure pattern. Future studies are warranted to assess the predictive values of ambulatory blood pressure for cardiorenal events in Korean chronic kidney disease patients.
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INTRODUCTION

Uncontrolled hypertension causes target organ damage (TOD) in the heart, brain, eyes, arteries and kidneys, and the coexistence of TOD and hypertension increases the overall cardiovascular risk.[1] Chronic kidney disease (CKD), which is either a consequence or cause of hypertension, is frequently observed in patients with hypertension, and substantially accelerates the hypertension-related risk of cardiovascular events.[1–4] In addition, hypertension is the second most common cause of end-stage renal disease, and it aggravates the age-related decline of renal function if blood pressure (BP) is not adequately controlled.[5]

Current guidelines recommend a strict BP control ($<130/80$ mm Hg) in patients with CKD, although the target of BP remains a matter of debate.[1,2] Despite the need for strict BP control in patients with CKD, past evidence shows that a mere 27% of CKD patients achieve a BP of $<140/90$ mm Hg and even fewer (11%) reach a BP of $<130/85$ mm Hg.[6] In Korea, nationwide studies suggested office BP control ($<130/80$ mm Hg) in the general population and Type 2 diabetes was inadequate (58.5% and 39.9%, respectively).[7,8] We can predict that the BP of a large amount of patients with CKD or at an increased risks for CKD is not adequately controlled in Korea, although there was no direct information regarding the control status of BP in Korean CKD patients.

CKD is associated with not only elevated office BP but also high ambulatory BP (ABP) (for example, masked hypertension) and a lack of diurnal BP variation.[9,10] Several studies reported that high ABP and/or an abnormal circadian BP variation (that is, non-dipper or reverse-dipper) could predict combined cardiovascular disease and

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renal outcomes better than office BP values in patients with CKD.[11–15] In Korea, Song *et al.*[16] reported that nocturnal declines in the BP do not occur in patients with renal failure and that the impairment of circadian rhythm occurred in the early stage of renal dysfunction even though BP was well-controlled. However, these data were driven by a small number and are not representative of the Korean population.

In this nationwide survey, using office BP and ABP monitoring (ABPM), we examined the BP control status and nocturnal BP dipping pattern in hypertensive patients with CKD. We also examined the clinical factors associated with such BP pattern.

METHODS

Study design

The Assessment of Blood Pressure Control and Target Organ Damage in Patients with Chronic Kidney Disease and Hypertension (APrODiTe) study was a nationwide, cross-sectional study conducted at 21 centers between October 2009 and May 2011. The primary objective was to identify the distribution of BP control categories, such as 'true controlled,' 'white-coat,' 'masked' and 'sustained uncontrolled hypertension,' and dipping statuses, such as 'extreme-dipper,' 'dipper,' 'non-dipper' and 'reverse-dipper.' Secondary objectives were to evaluate (1) TOD, according to BP control status (estimated glomerular filtration rate (eGFR), proteinuria (spot urine protein-to-creatinine ratio $>300\,mg\,g^{-1}$ Cr or alb $\geqslant 1+$ at urinalysis, left ventricular hypertrophy (LVH) and heart failure)) and (2) factors related to each BP control pattern.

The study included patients who (1) provided informed consent, (2) were aged 20–75 years, (3) were diagnosed with hypertension for >6 months (or $\geqslant 3$ clinic visits) prior to participation and had taken antihypertensive drugs for >3 months, (4) had an eGFR (calculated using the MDRD study equation) between 15 and $89\,ml\,min^{-1}$ per $1.73\,m^2$ and (5) had good compliance to medication and no change in prescription 2 weeks prior to participation. Diabetic nephropathy was defined according to the clinical or pathological diagnosis by clinicians. We clinically diagnosed diabetic nephropathy if patients had a prolonged duration of diabetes, impaired renal function or proteinuria, and if there was no evidence of other diseases. We did not include patients who had an eGFR over 60 and no proteinuria. All participants had abnormalities in renal function, urinalysis, pathology or imaging studies. The study excluded patients who (1) changed prescription according to ABPM regularly, (2) had acute kidney injury/hospitalization, (3) had a proteinuria of $>6\,g\,day^{-1}$ (spot urine protein-to-creatinine ratio of $>6.0\,g$ per g Cr), (4) had end-stage renal disease with dialysis and/or were a kidney recipient, (5) had diseases, such as uncontrolled arrhythmia, uncontrolled bronchial asthma/chronic obstructive pulmonary disease or primary endocrinologic diseases except diabetes mellitus, (6) were pregnant/lactating women or (7) were night-shift workers.

We estimated the sample size using the following equation (95% confidence interval and 2.5% confidence interval length).

$$n = \left(\frac{(Z_\alpha \times p(1-p)}{d}\right)^2$$

The estimate is the largest under a prevalence of 0.5. Therefore, the sample size for this study was calculated to be 1537.

The protocol was approved by the institutional review boards of the participating centers. Data collected included clinic BP, ABP, anthropometric measures, prescribed drugs, past medical history (including the incidence of coronary artery disease and heart failure) and laboratory data including serum creatinine, eGFR and morning urine protein-to-creatinine ratio. LVH was defined using the Romhilt–Estes point score system ('definite' $\geqslant 5$ points; 'probable' 4 points), because only 31 participants (2.35%) performed echocardiography in this study. Previous studies reported that the Romhilt–Estes scoring system generated the most favorable predictive values for LVH.[17,18]

Clinic BP measurement

All clinic BP measurements were performed by trained staff using an oscillometric OMRON IA-2 automatic BP device (IntelliSense, Omron, Kyoto, Japan). Three consecutive seated BP readings were recorded at intervals of 1–2 min, and the clinic BP reading was the mean of the last two readings.

ABP measurement

Twenty-four-hour ABPM was performed using an oscillometric TM-2430 monitor (A&D, Seoul, Korea). The monitor was programmed to record BP every 30 min. The ABP readings were considered adequate if the monitor had been worn for 24 h and if there were $\geqslant 16$ acceptable readings between 0800 hours and 2200 hours (daytime) and $\geqslant 12$ acceptable readings between 2200 hours and 0800 hours (nighttime). We used the ABP definitions proposed by Fagard *et al.*[19]

Definitions

Controlled clinical BP was defined as a level $<140/90$ mm Hg. ABP was considered normal if the daytime value was $<135/85$ mm Hg and the nighttime value was $<120/70$ mm Hg.

True controlled hypertension was defined as a controlled clinic and ambulatory (daytime and nighttime) BP. Masked hypertension was defined as controlled clinic BP and elevated daytime/nighttime ABP. Sustained uncontrolled BP was defined as uncontrolled clinic and ABP. The nocturnal dipping pattern was defined as a ratio of the mean nighttime systolic BP (SBP) to the mean daytime SBP. The patients were classified as extreme-dippers, if the ratio was less than 0.8; dippers, if the ratio was between 0.8 and 0.9; non-dippers, if the ratio was between 0.9 and 1.0; and reverse-dippers, if the ratio was greater than 1.0.

Statistical analysis

The baseline characteristics were compared between the patients of different BP categories using an ANOVA/Kruskal–Wallis test or the χ^2-test, as appropriate. Multiple logistic regression models were used to relate the BP category status to demographic factors, anthropometric data and laboratory findings. Continuous variables were expressed as the mean ± s.d. (parametric)/median (non-parametric), and categorical variables were expressed as n (%). All P-values were two-sided and were considered significant if $P<0.05$.

RESULTS

A total of 1545 patients were enrolled and 1317 patients were evaluated (Figure 1).

Baseline characteristics

The median age of the analyzed patients was 58 years and 62.9% of the patients were men. Diabetic nephropathy was reported in 298 (25.0%) patients. Hypertensive nephropathy, chronic glomerulonephritis and polycystic kidney disease were reported in 510 (38.7%),

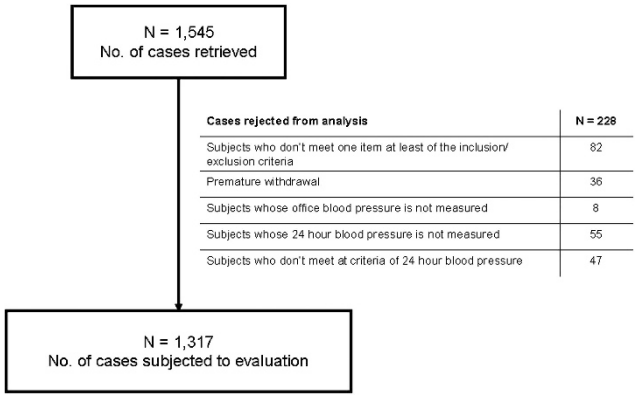

Figure 1 Diagram of participant enrollment and analysis. A total of 1545 patients were enrolled, and 228 patients were excluded ($n=1,317$). Of the 228 patients excluded from the analysis, 102 (44.7%) patients could not complete the ambulatory BP monitoring.

289 (21.9%) and 27 (2.1%) patients, respectively. A total of 345 (26.2%) patients were given a single antihypertensive drug, whereas 461 (35.0%) and 294 (22.3%) patients received two and three antihypertensive drugs, respectively. As many as 1171 (88.9%) patients took angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ARBs). Beta-blockers were used in 33.9% of all patients, calcium channel blockers in 56.3% and diuretics in 37.5%. The median serum creatinine was 1.45 mg dl^{-1}, and the median eGFR was 48 ml min^{-1} per 1.73 m^2 (CKD stages 2, 3 and 4: 416 (31.6%), 640 (48.6%) and 261 (19.8%), respectively).

Hypertension control categories

Among participants, the mean clinic BP was 137.4/81.6 mm Hg. As assessed via ABPM, the mean daytime BP was 135.7/80.9 mm Hg, and the mean nighttime BP was 122.9/73.4 mm Hg. According to the definitions of clinic and ABP, 703 (53.4%) patients had controlled clinic BP, whereas 504 (38.3%) patients had controlled ambulatory daytime or nighttime BP. Sustained uncontrolled hypertension was encountered most frequently ($n=557$, 42.3%), followed by masked hypertension ($n=447$, 33.9%), true controlled hypertension ($n=256$, 19.4%) and white-coat hypertension ($n=57$, 4.3%). Twenty-four-hour SBP was the highest in patients with sustained uncontrolled hypertension, followed by those with masked hypertension, white-coat hypertension and true controlled hypertension (Table 1 and Figure 2).

The prevalence of dippers and non-/reverse-dippers on the hypertension control categories were as follows: true controlled, 119 (46.5%) *vs.* 99 (38.7%); white-coat, 29 (50.9%) *vs.* 8 (14.1%); masked, 120 (26.8%) *vs.* 267 (59.7%); and sustained uncontrolled, 171 (30.7%) *vs.* 308 (55.3%) ($P<0.001$). When we compared the night SBP/day SBP ratio according to the hypertension control categories, the values in the true controlled, white-coat, masked and sustained uncontrolled hypertension were 0.88 ± 0.078, 0.82 ± 0.067, 0.92 ± 0.111 and 0.92 ± 0.111, respectively ($P<0.001$). In conclusion, masked and sustained uncontrolled hypertension was associated with a loss of dipping (non-/reverse-dipper).

The percentage of men was the highest among patients with sustained uncontrolled hypertension and the lowest among those with true controlled hypertension. The highest number of current smokers was among patients with sustained uncontrolled hypertension.

Diabetic nephropathy and an LVH score $\geqslant 4$ were the most prevalent factors in patients with sustained uncontrolled hypertension. A medical history of stable angina, acute coronary syndrome and heart failure was similar among the four hypertension control categories. The eGFR was highest among patients with true controlled hypertension (51.85 ml min^{-1} per 1.73 m^2 *vs.* 48.20, 45.80 and 43.00 ml min^{-1} per 1.73 m^2 in masked, sustained uncontrolled and white-coat hypertension, respectively), and the magnitude of proteinuria was the highest among patients with sustained uncontrolled hypertension (620.0 mg g^{-1} Cr *vs.* 376.0, 230.9 and 180.0 mg g^{-1} Cr in masked, true controlled and white-coat hypertension, respectively). Patients with sustained uncontrolled hypertension were prescribed more antihypertensive drugs than other patients.

True controlled hypertension was the most frequently encountered pattern among patients with CKD stage 2 (23.1%, $P=0.03$), whereas sustained uncontrolled hypertension was most frequently encountered among those with CKD stage 4 (48.3%, $P=0.05$) (Table 2).

Dipping patterns

The prevalence of non-dippers was the highest ($n=454$, 34.5%), followed by dippers ($n=439$, 33.3%), reverse-dippers ($n=228$, 17.3%) and extreme-dippers ($n=196$, 14.9%). The prevalence of dippers among patients with CKD stages 2, 3 and 4 were 158 (38.0%), 203 (31.7%) and 78 (29.9%), respectively ($P<0.05$) (Table 2). Although there were no significant differences in clinic SBP or daytime SBP (except among extreme-dippers) between the four groups, nighttime SBP was highest in reverse-dippers (141.4 mm Hg) (Table 1 and Figure 2).

Age, gender and duration of hypertension were not different between the four groups. The prevalence of diabetic nephropathy, stable angina and heart failure were higher in reverse-dippers than in patients of the other groups. The eGFR was highest in extreme-dippers (53.0 ml min^{-1} per 1.73 m^2) and the prevalence of CKD stage 4 was highest in reverse-dippers ($n=59$, 25.9%). Proteinuria differed according to the dipping status. The proteinuria amount of extreme-dippers, dippers, non-dippers and reverse-dippers were 662 ± 948.4, 744 ± 1001.5, 1096 ± 1362.1 and 1163 ± 1446.3 mg g^{-1} Cr, respectively ($P<0.001$). Reverse-dippers were prescribed more antihypertensive drugs than other patients. Non-dippers and reverse-dippers were taking more beta-blockers and calcium channel blockers than dippers and extreme-dippers. The use of diuretics was similar among all groups.

Association between BP burden and TOD

Young age (<58 years), female gender and the presence of non-diabetic CKD were independently related to true controlled hypertension. The use of angiotensin-converting enzyme inhibitor or ARB was also associated with true controlled hypertension, even though this association was not statistically significant (Table 3). Old age ($\geqslant$58 years), male gender, high body mass index (BMI) and diabetic CKD were independently related to sustained uncontrolled hypertension. The use of beta-blocker and calcium channel blocker was also significantly associated with sustained uncontrolled hypertension. When we analyzed BP patterns according to renal function, sustained uncontrolled hypertension was found to be significantly related to CKD stage 4, female gender, lower BMI and diabetic CKD (Table 4).

Table 3 also presents data on factors associated with the categories of dipping patterns. A high BMI, non-diabetic CKD and current smoking were independently associated with extreme-dippers. Extreme-dippers showed low levels of proteinuria. Diabetic nephropathy and the use of beta-blockers were significantly associated with being a reverse-dipper. A high BP burden (non-dippers and reverse-dippers), old age, low BMI and diabetic nephropathy were independently associated with CKD stages 3 and 4 (Table 4).

DISCUSSION

This study demonstrated a high prevalence of masked/sustained uncontrolled hypertension and non-/reverse-dippers in Korean patients with CKD. Uncontrolled BP and less nocturnal BP dipping in CKD patients were associated with low eGFR, higher levels of proteinuria and pre-existing heart disease.

Several studies from Japan, China and the USA also reported the associations of BP control status or ABP values with TOD.[20–22] The results of these studies were concordant with those of this study regarding a significantly large proportion of higher BP load (masked, sustained uncontrolled hypertension/non-, reverse-dipper) in CKD patients and a meaningful association between a higher BP load and severe TOD, including renal dysfunction and cardiovascular disease. However, there was a small difference between the studies in the proportion of hypertension categories and dipping status. These differences may arise from the difference in baseline characteristics such as ethnicity, diabetes, distribution of CKD stages and diuretic use.

Table 1 Characteristics by hypertension control categories and dipping patterns

	True controlled	*White coat*	*Masked*	*Sustained uncontrolled*		*Extreme-dipper*	*Dipper*	*Non-dipper*	*Reverse-dipper*	
N	*256*	*57*	*447*	*557*	*P-value*	*196*	*439*	*454*	*228*	*P-value*
Demographics										
Age (years)	54 ± 12.4[a]	59 ± 11.1[b]	57 ± 11.8[a,b]	58 ± 11.8[a,b]	<0.001	57 ± 11.4	56 ± 11.8	56 ± 12.6	58 ± 11.4	>0.05
Males	133 (52.0)	35 (61.4)	274 (61.3)	386 (69.3)	<0.001	132 (67.3)	290 (66.1)	270 (59.5)	136 (59.6)	>0.05
BMI ($kg\,m^{-2}$)	25.1 ± 3.5	25.0 ± 3.0	25.1 ± 3.4	25.6 ± 3.4	0.067	25.9 ± 3.4	25.3 ± 3.4	25.2 ± 3.4	25.2 ± 3.6	0.049
Current smoking	28 (10.9)	1 (1.8)	71 (15.9)	96 (17.2)	<0.001	41 (20.9)	65 (14.8)	59 (13.0)	31 (13.6)	>0.05
Past medical history										
HTN duration (months)	83 ± 80.5[a]	120 ± 117.3[b]	96 ± 80.8[a,b]	107 ± 93.9[a,b]	<0.001	98 ± 99.9	98 ± 87.5	98 ± 86.5	105 ± 86.6	0.761
DM nephropathy	28 (10.9)	9 (15.8)	108 (24.2)	152 (27.3)	< 0.001	27 (13.8)	100 (22.8)	93 (20.5)	77 (33.8)	<0.001
LVH score ⩾4	23 (10.0)	8 (14.5)	50 (12.9)	100 (18.9)	0.006	28 (15.6)	59 (14.6)	54 (13.1)	40 (19.4)	0.224
Stable angina	6 (2.3)	1 (1.8)	16 (3.6)	32 (5.7)	0.292	10 (5.1)	9 (2.1)	18 (4.0)	18 (7.9)	0.003
ACS	8 (3.1)	2 (3.5)	16 (3.6)	17 (3.1)	0.923	5 (2.6)	16 (3.6)	12 (2.6)	10 (4.4)	0.257
Heart failure	3 (1.2)	1 (1.8)	10 (2.2)	12 (2.2)	0.588	1 (0.5)	6 (1.4)	7 (1.5)	12 (5.3)	0.003
Laboratory parameters										
SCr ($mg\,dl^{-1}$)	1.5 ± 0.6	1.7 ± 0.6	1.6 ± 0.7	1.7 ± 0.7	0.002	1.5 ± 0.6[a]	1.6 ± 0.7[a]	1.7 ± 0.7[a,b]	1.8 ± 0.7[b]	<0.001
eGFR ($ml\,min^{-1}$ per $1.73\,m^2$)	52.0 ± 19.5	45.8 ± 19.3	49.2 ± 19.4	47.4 ± 19.3	<0.01	52.9 ± 18.9[c]	50.8 ± 19.6[b,c]	47.8 ± 19.3[a,b]	43.7 ± 18.8[a]	<0.001
Spot urine PCR ($mg\,g^{-1}$ Cr)	591 ± 865.4[a]	562 ± 753.3[a]	882 ± 1192.3[a,b]	1150 ± 1381.4[b]	<0.001	662 ± 948.4[a]	744 ± 1001.5[a]	1096 ± 1362.1[b]	1163 ± 1446.3[b]	<0.001
PCR <25th percentile	78 (31.1)	19 (33.9)	118 (27.6)	103 (18.9)	<0.001	69 (35.9)	102 (23.9)	98 (22.3)	49 (22.0)	0.002
BP measurements (mean ± s.d.)										
24-h SBP (mm Hg)	113 ± 8.1[a]	117 ± 6.8[b]	131 ± 12.5[c]	142 ± 14.5[d]	<0.001	127 ± 12.3[a]	129 ± 14.4[a,b]	132 ± 17.4[b]	138 ± 19.0[c]	<0.001
24-h DBP (mm Hg)	69 ± 4.6[a]	71 ± 4.5[b]	78 ± 6.4[c]	83 ± 8.8[d]	<0.001	76 ± 7.3[a,b]	78 ± 8.2[b,c]	79 ± 9.2[c,d]	80 ± 10.4[d]	<0.001
Night SBP (mm Hg)	103 ± 8.4[a]	103 ± 8.2[a]	124 ± 16.0[b]	133 ± 19.0[c]	<0.001	138 ± 19.1	136 ± 17.8	137 ± 19.7	139 ± 20.8	0.432
Night DBP (mm Hg)	63 ± 4.7[a]	63 ± 4.8[a]	74 ± 8.1[b]	78 ± 10.4[c]	<0.001	65 ± 7.3[a]	71 ± 8.2[b]	76 ± 9.4[c]	82 ± 11.3[d]	<0.001
Day SBP (mm Hg)	118 ± 9.9[a]	125 ± 6.9[b]	135 ± 13.2[c]	146 ± 14.7[d]	<0.001	140 ± 13.8[a]	136 ± 15.4[b]	134 ± 18.0[b]	133 ± 18.3[b]	<0.001
Day DBP (mm Hg)	72 ± 5.8[a]	75 ± 5.3[b]	80 ± 7.8[c]	86 ± 9.6[d]	<0.001	83 ± 8.6[a]	82 ± 9.1[a,b]	80 ± 9.9[b,c]	79 ± 10.7[c]	<0.001
Office SBP (mm Hg)	121 ± 11.0[a]	148 ± 11.3[b]	125 ± 9.6[c]	154 ± 13.9[d]	<0.001	105 ± 11.3[a]	116 ± 13.5[b]	127 ± 17.1[c]	143 ± 21.0[d]	<0.001
Office DBP (mm Hg)	74 ± 8.8[a]	88 ± 9.3[b]	76 ± 8.4[a]	89 ± 11.1[b]	<0.001	82 ± 11.6	82 ± 11.8	81 ± 12.3	81 ± 12.8	0.402
Prescribed drugs										
No. of drugs	2.1 ± 1.0[a]	2.3 ± 1.3[a]	2.2 ± 1.1[a]	2.5 ± 1.2[b]	<0.001	2.2 ± 1.0[a]	2.2 ± 1.1[a]	2.3 ± 1.1[a]	2.6 ± 1.2[b]	<0.001
ACEI or ARB	240 (93.8)	53 (93.0)	389 (87.0)	489 (87.8)	0.020	179 (91.3)	390 (88.8)	406 (89.4)	179 (86.0)	0.359
Beta-blocker	67 (26.2)	15 (26.3)	136 (30.4)	229 (41.1)	<0.001	138 (29.6)	137 (31.2)	144 (31.7)	120 (47.4)	<0.001
CCB	112 (43.8)	32 (56.1)	246 (55.0)	352 (63.2)	<0.001	101 (51.5)	231 (52.6)	255 (56.2)	155 (68.0)	<0.001
Diuretics	94 (36.7)	19 (33.3)	165 (36.9)	216 (38.8)	0.826	74 (37.8)	151 (34.4)	174 (38.3)	95 (41.7)	0.302

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HTN, hypertension; LVH, left ventricular hypertrophy; PCR, protein-to-creatinine ratio; SCr, serum creatinine

Categorical variables were expressed as *n* (%).

Mann–Whitney *U*-test: the same letters (a, b, c or d) indicate non-significant differences between groups.

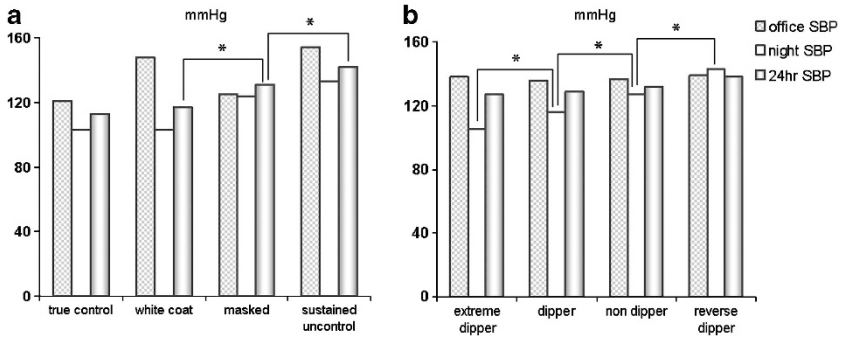

Figure 2 Comparison of clinic and ambulatory BP in each BP control and dipping category. (**a**) The 24-hour SBP was the highest among patients with sustained uncontrolled hypertension followed by those with masked, white-coat and true controlled hypertension. (**b**) Although there were no significant differences in clinic SBP and daytime SBP (except among extreme-dippers) among the four groups, nighttime SBP was highest in reverse-dippers (136.4 mm Hg). The nighttime SBP of non-dippers, dippers and extreme-dippers followed that of the reverse-dippers (130.2, 127.4 and 126.9 mm Hg, respectively). *$P<0.05$.

Table 2 Hypertension control patterns according to renal function

	Hypertension control categories					*Dipping patterns*		
	True controlled	*White coat*	*Masked*	*Sustained uncontrolled*	*Extreme-dipper*	*Dipper*	*Non-dipper*	*Reverse-dipper*
N	*256*	*57*	*447*	*557*	*196*	*439*	*454*	*228*
CKD stage 2	96 (23.1)	17 (4.1)	142 (34.1)	161 (38.7)	79 (19.0)	158 (38.0)	128 (30.8)	51 (12.3)
CKD stage 3	121 (18.9)	28 (4.4)	221 (34.5)	270 (42.2)	95 (14.8)	203 (31.7)	224 (35.0)	118 (18.4)
CKD stage 4	39 (14.9)	12 (4.6)	84 (32.2)	126 (48.3)	22 (8.4)	78 (29.9)	102 (39.1)	59 (22.6)
P-value	0.030	0.936	0.796	0.050	0.001	0.047	0.080	0.001

Abbreviation: CKD, chronic kidney disease.
Categorical variables were expressed as *n* (%).

Table 3 Factors related with each BP control and dipping category

Variables	*Hypertension control categories*					*Dipping patterns*		
	True controlled	*White coat*	*Masked*	*Sustained uncontrolled*	*Extreme-dipper*	*Dipper*	*Non-dipper*	*Reverse-dipper*
N	*256*	*57*	*447*	*557*	*196*	*439*	*454*	*228*
Age (⩾58 years)	0.694 (0.016)	1.015 (0.960)	0.921 (0.508)	1.367 (0.010)	1.233 (0.210)	0.957 (0.724)	0.904 (0.416)	1.071 (0.664)
Gender (female)	1.788 (<0.001)	0.922 (0.778)	1.111 (0.418)	0.615 (<0.001)	0.938 (0.719)	0.797 (0.083)	1.125 (0.357)	1.233 (0.198)
BMI	0.979 (0.334)	0.973 (0.526)	0.976 (0.183)	1.043 (0.016)	1.060 (0.014)	0.999 (0.952)	0.987 (0. 452)	0.971 (0.202)
DM nephropathy	0.427 (<0.001)	0.681 (0.316)	1.220 (0.178)	1.354 (0.036)	0.558 (0.010)	1.135 (0.396)	0.745 (0.052)	1.864 (<0.001)
CKD stage 4	0.802 (0.293)	1.371 (0.387)	0.958 (0.792)	1.131 (0.424)	0.634 (0.070)	0.908 (0.551)	1.223 (0.198)	1.096 (0.626)
Current smoking	0.681 (0.103)	0.097 (0.022)	1.191 (0.311)	1.292 (0.130)	1.583 (0.031)	0.896 (0.529)	0.845 (0.343)	0.985 (0.946)
PCR <25th percentile	1.503 (0.015)	1.697 (0.087)	1.270 (0.091)	0.546 (<0.001)	1.602 (0.007)	0.894 (0.437)	0.849 (0.259)	0.950 (0.782)
ACEI or ARB	1.707 (0.066)	1.725 (0.319)	0.796 (0.246)	0.855 (0.419)	1.335 (0.324)	0.952 (0.808)	1.042 (0.840)	0.832 (0.427)
Beta-blocker	0.814 (0.226)	0.789 (0.464)	0.779 (0.064)	1.483 (0.002)	0.844 (0.351)	0.845 (0.210)	0.848 (0.217)	1.870 (<0.001)
CCB	0.691 (0.015)	1.030 (0.919)	0.992 (0.952)	1.279 (0.048)	0.925 (0.640)	0.823 (0.125)	1.047 (0.715)	1.387 (0.050)
Diuretics	1.131 (0.436)	0.955 (0.879)	1.017 (0.898)	0.909 (0.453)	1.025 (0.885)	0.819 (0.128)	1.128 (0.349)	1.086 (0.611)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CKD, chronic kidney disease; DM, diabetes mellitus; PCR, protein-to-creatinine ratio
Each number means odds ratio (*P*-value).
Adjusted variables are age, gender, BMI, DM nephropathy, CKD stage 4, current smoking, protein-to-creatinine ratio <25%, and the use of ACEI or ARB, beta-blocker, CCB and diuretics.

Ethnicity has an impact on BP control and dipping status. Ethnicity can also be related to genetic variation, environmental factors such as diet, smoking and alcohol, or an interaction between these components. Several reports found various allele frequencies of BP-related genes such as ACE/angiotensinogen genes and their association with responsible proteins.[23,24] These variations can lead to varied effects in ARB/-ACE inhibitor treatment in various ethnicities. Furthermore, polymorphisms were related with hypertension itself and TODs such as LVH. Sacks *et al.* reported that SBP was associated with salt intake and that the DASH diet had an increased positive effect especially in

Table 4 Effect of each BP control and dipping category on renal dysfunction

	CKD stage 4 (n = 261)		*CKD stage 3–4 (n = 901)*	
	Odds ratio	*P-value*	*Odds ratio*	*P-value*
BP control categories				
Age (⩾58 years)	1.080	0.601	1.517	0.001
Gender (female)	2.272	<0.001	1.166	0.246
BMI	0.933	0.002	0.941	0.001
DM nephropathy	2.306	<0.001	3.219	<0.001
Current smoking	0.945	0.804	1.251	0.219
True controlled	1		1	
White coat	1.557	0.248	1.304	0.416
Masked	1.247	0.320	1.125	0.492
Sustained uncontrolled	1.757	0.008	1.272	0.150
Dipping categories				
Age (⩾58 years)	1.123	0.431	1.542	0.001
Gender (female)	2.095	<0.001	1.112	0.424
BMI	0.941	0.004	0.946	0.002
DM nephropathy	2.304	<0.001	3.231	<0.001
Current smoking	0.640	0.999	1.292	0.161
Dipper	1		1	
Non-dipper	1.307	0.125	1.499	0.007
Reverse-dipper	1.440	0.073	1.764	0.004
Extreme-dipper	0.665	0.123	0.916	0.632

Abbreviations: BMI, body mass index; DM, diabetes mellitus.
Adjusted variables are age, gender, BMI, DM nephropathy, current smoking and each BP control or dipping category.

the high-salt group. Both genetics and environmental factors, therefore, are associated with differences in BP control and dipping status between various ethnicities.[25]

The prevalence of diabetes was approximately 35, 5.4 and >22.6% in the Japanese, Chinese and our study, respectively. Participants in the Japanese, American and our study used diuretics in 27, 82.4 and 37.5%, respectively. In addition, analyses using variables such as the presence of nocturia and smoking status as measured via a simple questionnaire may affect the results.

In patients with CKD, more strict BP control is recommended to reduce TOD. However, it is difficult to follow this recommendation because of several mechanisms including extracellular fluid volume expansion, the activation of the rennin angiotensin system and increased sympathetic nervous system activity, among others, leading to the loss of BP circadian rhythm.[26–31] Thus, clinic BP provides an incomplete and potentially misleading assessment of the severity of hypertension. An assessment of the actual BP with ABPM may be useful in the pharmacological management of hypertension in patients with CKD to slow the progression of renal impairment and reduce the development of cardiovascular disease.[32] As shown in the present study, the use of ABPM reveals a high prevalence of masked hypertension and a high number of non-/reverse-dippers among the Korean population, which is in turn associated with TOD.

Several mechanisms have been proposed for elevated nighttime BP and a high BP burden in patients with CKD. These mechanisms include an expanded extracellular fluid volume caused by a decreased renal excretion of sodium and water with a linked elevation of oxidative stress as well as increased sympathetic nervous system activity.[27–31] The activation of the renin angiotensin system in CKD patients is also a critical factor leading to the loss of dipping.[30,31]

The capacity to excrete sodium during the day is a significant determinant of nocturnal BP and dipping.[22] Non-dipping is a compensatory phenomenon to produce pressure natriuresis in volume-overloaded patients. Diuretic treatment has been shown to have a beneficial role in modulating the circadian rhythm of BP.[29,33,34] Furthermore, dietary potassium supplementation and sodium restriction can restore normal dipping and enhance the effect of nighttime BP drug therapy.[35] Only 37.5% of patients used diuretics as an antihypertensive drug in this study. The pattern of antihypertensive drug choice can be related to a higher prevalence of patients with masked and sustained uncontrolled hypertension and increased numbers of non-/reverse-dippers in this study.

Previous studies have suggested that the alteration of the timing of antihypertensive drug therapy may reduce nighttime BP.[36] A simple modification such as switching the dosing of an ARB from morning to evening may be all that is needed.[37] Several studies have reported a decrease in the night/day ratio as a result of changing the time of dosing of one of the antihypertensive agents from the morning to the evening.[31,38] Studies have also shown that urinary albumin excretion is also significantly reduced after bedtime treatment with ARB[39] and that the progression of nephropathy was delayed.[40] Given that non-dipping is a potential independent risk factor for CKD progression and the development of cardio-renal syndrome, optimizing antihypertensive therapy (pharmacological or dietary) may be relevant. Unfortunately, we could not deduce an association between the timing of anti-hypertensive drug therapy and the dipping pattern.

In this study, beta-blockers and calcium channel blockers were used in patients with a high BP burden (sustained uncontrolled hypertension, reverse-dipper). This may be due to the practice pattern of physicians prescribing angiotensin-converting enzyme inhibitors or ARBs first, especially in cases of diabetic nephropathy. However, further studies are required to evaluate the effects of specific classes of antihypertensive drugs on BP burden and dipping.

Home-measured BP is superior to clinic-measured BP in reducing the misclassification of hypertension caused by white-coat and masked hypertension[41] as well as in predicting CKD-associated complications.[10] Several experts have recommended increasing the use of home BP monitoring for routine care and suggested that this should be supported by health-care systems. In this study, 44.7% of the excluded patients from the analysis failed to properly carry out ABPM. Although ABPM may provide more detailed information, home BP monitoring, which is easier and more accessible, may be better for assessing BP patterns in high-risk patients such as those with CKD.

To the best of our knowledge, this is the largest study of ABPM in patients with CKD, and in which the clinic BP measurements were carefully standardized and performed by a trained staff using frequently calibrated equipment. However, our study has some limitations. First, we obtained data concerning heart problems such as stable angina, acute coronary syndrome and heart failure through the patients' medical history based on patients' recall and medical records; therefore, there may be a significant lack of data. Second, we did not fully evaluate the LVH or LV mass index because only a small proportion of patients underwent echocardiography ($n = 31$ (2.3%)). We therefore may have underestimated the relationship between each BP category or dipping pattern and heart problems. Third, ABPM was evaluated once; thus, the variability may result in some degree of misclassification. Fourth, our study did not assess sleep quality, which influences nocturnal BP. We were unable to draw a longitudinal relationship between any BP category and TOD because of the cross-sectional nature of the analyses.

In conclusion, clinic BP potentially mischaracterized patients' BP burden because of increased nighttime BP. ABPM revealed a significantly high prevalence of masked/sustained uncontrolled hypertension and a large number of non-/reverse-dippers, which may be associated with hypertension-related TOD. Korean physicians should attempt to acquire more data regarding patients' BP through frequent home BP or ABPM. Korean physicians should also be more careful in drug choice and chronotherapy to reverse their patients' dipping pattern to normal. Future studies are warranted to assess the predictive values of ABP for cardiorenal events in Korean CKD patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1 Mancia G, Backer GD, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM. 2007 guidelines for the management of arterial hypertensionThe task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart* 2007; **28**: 1462–1536.
2 Lenfant C, Chobanian AV, Jones DW, Roccella EJ. Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–2572.
3 Hansoon L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, Ménard J, Rahn KH, Wedel H, Westerling S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the hypertension optimal treatment (HOT) randomized trial. HOT Study Group. *Lancet* 1998; **35**: 1755–1762.
4 Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting = enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; **342**: 145–153.
5 Bakris GL, Wiliams M, Dworkin L, Elliott WJ, Epstein M, Toto R, Tuttle K, Douglas J, Hsueh W, Sowers J. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis* 2000; **36**: 646–661.
6 Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2003; **41**: 1–12.
7 Lee SW, Kim YC, Oh SW, Koo HS, Na KY, Chad DW, Kim S, Chin HJ. Trends in the prevalence of chronic kidney disease, other chronic diseases and health-related behaviors in an adult Korean population: data from the Korea National Health and Nutrition Examination Survey (KNHANES). *Nephrol Dial Transplant* 2011; **26**: 3975–3980.
8 Seo MH, Lee WJ, Park CY, Kim SR, Park JY, Yoon KH, Lee MK, Park SW. Management of blood pressure in patients with type 2 diabetes mellitus: a nationwide survey in Korean. *Diabetes Metab J* 2011; **35**: 348–353.
9 Terawaki H, Metoki H, Nakayama M, Ohukubo T, Kikuya M, Asayama K, Inoue R, Hoshi H, Ito S, Imai Y. Masked hypertension determined by self-measured blood pressure at home and chronic kidney disease in the Japanese general population: the Ohasama study. *Hypertens Res* 2008; **31**: 2129–2135.
10 Portaluppi F, Montanari L, Massari M, Chiara VD, Capanna M. Loss of nocturnal decline of blood pressure in hypertension due to chronic renal failure. *Am J Hypertens* 1991; **4**: 20–26.
11 Lurbe E, Redon J, Kesani A, Pascual JM, Tacons J, Alvarez V, Batlle D. Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. *N Engl J Med* 2002; **347**: 797–805.
12 Timio M, Venanzi S, Lolli S, Lippi G, Verdura C, Monarca C, Guerrini E. 'Non-dipper' hypertensive patients and progressive renal insufficiency: a 3-year longitudinal study. *Clin Nephrol* 1995; **43**: 382–387.
13 Thomson AM, Pickering TG. The role of ambulatory blood pressure monitoring in chronic and end-stage renal disease. *Kidney Int* 2006; **70**: 1000–1007.
14 Agarwal R, Andersen MJ. Correlates of systolic hypertension in patients with chronic kidney disease. *Hypertension* 2005; **46**: 514–520.
15 Liu M, Takahashi H, Morita Y, Maruyama S, Mizuno M, Yuzawa Y, Watanabe M, Toriyama T, Kawahara H, Matsuo S. Non-dipping is a potent predictor of cardiovascular mortality and is associated with autonomic dysfunction in haemodialysis patients. *Nephrol Dial Transplant* 2003; **18**: 563–569.
16 Song HC, Choi EJ, Park IS, Ahn SJ, Jin DC, Kin SY, Koo WS, Chang YS, Bang BK. Impaired circadian rhythm of blood pressure in various stage of renal failure. *Korean J Nephrol* 1995; **4**: 310–316.
17 Buchner S, Debl K, Haimerl J, Djavidani B, Poschenrieder F, Feuerbach S, Riegger GA, Luchner A. Electrocardiographic diagnosis of left ventricular hypertrophy in aortic valve disease: evaluation of ECG criteria by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2009; **1**: 11–18.
18 Morrison I, Clark E, Macfarlane PW. Evaluation of the electrocardiographic criteria for left ventricular hypertrophy. *Anadolu Kardiyol Derg* 2007; **7**: 159–163.
19 Fagard R, Brguljan J, Thijs L, Staessen J. Prediction of the actual awake and asleep blood pressures by various methods of 24 h pressure analysis. *J Hypertens* 1996; **14**: 557–563.
20 Iimuro S, Imai E, Watanabe T, Nitta K, Akizawa T, Matsuo S, Makino H, Ohashi Y, Hishida Afor the Chronic Kidney Disease Japan Cohort Study Group. Clinical correlates of ambulatory BP monitoring among patients with CKD. *Clin J Am Soc Nephol* 2013; **8**: 721–730.
21 Wang C, Zhang J, Liu X, Li C, Ye Z, Peng H, Chen Z, Lou T. Reversed dipper blood-pressure pattern is closely related to severe renal and cardiovascular damage in patients with chronic kidney disease. *PLoS One* 2013; **8**: e55419.
22 Pogue V, Rahman M, Lipkowitz M, Toto R, Miller E, Faulkner M, Rostand S, Hiremath L, Sika M, Kendrick C, Hu B, Greene T, Appel L, Philips RAAfrican American Study of Kidney Disease and Hypertension Collaborative Research Group. Disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease. *Hypertension* 2009; **53**: 20–27.
23 Li X, Li Y, Jia N, Guo S, Chu S, Niu W. Angiotensin-converting enzyme gene deletion allele increases the risk of left ventricular hypertrophy: evidence from a meta-analysis. *Mol Biol Rep* 2012; **39**: 10063–10075.
24 Sethi AA, Nordestgaard BG, Tybjærg-Hansen A. Angiotensinogen gene polymorphism, plasma angiotensinogen, and risk of hypertension and ischemic heart disease: a meta-analysis. *Arterioscler Thromb Vasc Biol* 2003; **23**: 1269–1275.
25 Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER 3rd, Simons-Morton DG, Karanja N, Lin PHDASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med* 2001; **344**: 3–10.
26 Bangash F, Agarwal R. Masked hypertension and white-coat hypertension in chronic kidney disease: a meta-analysis. *Clin J Am Soc Nephrol* 2009; **4**: 656–664.
27 Ligtenberg G, Blankestijn PJ, Oey PL, Klein IH, Dijkhorst-Oei LT, Boomsama F, Wieneke GH, van Huffelen AC, Koomans HA. Reduction of sympathetic hyperactivity by enalapril in patients with chronic renal failure. *N Engl J Med* 1999; **340**: 1321–1328.
28 Terawaki H, Yoshimura K, Hasegawa T, Matsuyama Y, Negawa T, Yamada K, Matsushima M, Nakayama M, Hosoya T, Era S. Oxidative stress is enhanced in correlation with renal dysfunction: examination with the redox state of albumin. *Kidney Int* 2004; **66**: 1988–1993.
29 Sachdeva A, Weder AB. Nocturnal sodium excretion, blood pressure dipping, and sodium sensitivity. *Hypertension* 2006; **48**: 527–533.
30 Jensen LW, Pedersen EB. Nocturnal blood pressure and relation to vasoactive hormones and renal function in hypertension and chronic renal failure. *Blood Press* 1997; **6**: 332–342.
31 Grassi G, Cattaneo BM, Seravalle G, Lanfranchi A, Pozzi M, Morganti A, Carugo S, Mancia G. Effects of chronic ACE inhibition on sympathetic nerve traffic and baroreflex control of circulation in heart failure. *Circulation* 1997; **96**: 1173–1179.
32 Tamura K, Kanaoka T, Ohsawa M, Haku S, Azushima K, Maeda A, Dejima T, Wakui H, Ozawa M, Shigenaga A, Toya Y, Umemura S. Emerging concept of anti-hypertensive therapy based on ambulatory blood pressure profile in chronic kidney disease. *Am J Cardiovasc Dis* 2011; **1**: 236–243.
33 Fujii T, Uzu T, Nishimura M, Takaji M, Kuroda S, Nakamura S, Inenaga T, Kimura G. Circadian rhythm of natriuresis is disturbed in nondipper type of essential hypertension. *Am J Kidney Dis* 1999; **33**: 29–35.
34 Uzu T, Ishikawa K, Fujii T, Nakamura S, Inenaga T, Kimura G. Sodium restriction shifts circadian rhythm of blood pressure from nondipper to dipper in essential hypertension. *Circulation* 1997; **96**: 1859–1862.
35 Wilson DK, Sica DA, Miller SB. Effects of potassium on blood pressure in salt-sensitive and salt-resistant black adolescents. *Hypertension* 1999; **34**: 181–186.
36 Hermida RC, Ayala DE, Fernández JR, Calvo C. Chronotherapy improves blood pressure control and reverts the nondipper pattern in patients with resistant hypertension. *Hypertension* 2008; **51**: 69–76.
37 Hermida RC, Calvo C, Ayala DE, Domínguez MJ, Covelo M, Fernández JR, Mojón A, López JE. Administration time-dependent effects of valsartan on ambulatory blood pressure in hypertensive subjects. *Hypertension* 2003; **42**: 283–290.
38 Portaluppi F, Vergnani L, Manfredini R, degli Uberti EC, Fersini C. Time-dependent effect of isradipine on the nocturnal hypertension in chronic renal failure. *Am J Hypertens* 1995; **8**: 719–726.
39 Hermida RC, Calvo C, Ayala DE, López JE. Decrease in urinary albumin excretion associated with the normalization of nocturnal blood pressure in hypertensive subjects. *Hypertension* 2005; **46**: 960–968.
40 Fukuda M, Munemura M, Usami T, Nakao N, Takeuchi O, Kamiya Y, Yoshida A, Kimura G. Nocturnal blood pressure is elevated with natriuresis and proteinuria as renal function deteriorates in nephropathy. *Kidney Int* 2004; **65**: 621–625.
41 Andersen MJ, Khawandi W, Agarwal R. Home blood pressure monitoring in CKD. *Am J Kidney Dis* 2005; **45**: 994–1001.