ARTICLE

Normotensive non-dipping blood pressure profile does not predict the risk of chronic kidney disease progression

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Abstract

The lack of a decrease in nocturnal blood pressure is a risk factor for the progression of chronic kidney disease (CKD); however, it currently remains unknown whether it is a risk factor in normotensive CKD patients. We conducted a retrospective cohort study and enrolled 676 CKD patients who underwent ambulatory blood pressure monitoring (ABPM). According to their nocturnal blood pressure dipping pattern (>10%: dipper or <10%: non-dipper) and average 24-h systolic blood pressure (>130/80 mmHg: hypertension or <130/80 mmHg: normotension), patients were divided into four groups. The estimated glomerular filtration rate (eGFR) decline over 2 years and relevant clinical parameters were analyzed among groups. Among all participants, 82.7% were non-dippers and half of them were normotensive. The eGFR decline was the most rapid in hypertensive non-dipper patients (4.73 ± 0.45 ml/min/1.73 m^2/2 years), and was not significantly different between normotensive non-dipper (1.31 ± 0.49 ml/min/1.73 m^2/2 years) and dipper patients (1.69 ± 0.80 ml/min/1.73 m^2/2 years). A multivariate regression analysis revealed that the amount of urinary protein (95% confidence interval (CI): 1.51–2.63), 24-h systolic blood pressure (95% CI 1.13–1.45), and eGFR (95% CI 1.02–1.44) were associated with a rapid eGFR decline. We conclude that, according to the ABPM-based analysis, a non-dipping blood pressure pattern in normotensive CKD patients does not predict the risk of a rapid decline in eGFR. This suggests that the control of blood pressure, rather than its circadian rhythm, is essential for the preservation of eGFR.

Keywords ambulatory blood pressure monitoring · circadian rhythm · chronic kidney disease

Introduction

Due to an aging society and the high prevalence of patients with hypertension and diabetes mellitus (DM), the number of patients with chronic kidney disease (CKD) is increasing

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[1]. Previous epidemiological observations showed that CKD is a risk factor not only for developing end-stage kidney disease, but also cardiovascular diseases [2]. Various risk factors for alterations in kidney function in CKD patients have already been proposed [3], and high blood pressure (BP) is regarded as a strong predictor among these factors.

International guidelines from different organizations have highlighted the importance of lowering BP in CKD patients in order to prevent the progression of CKD as well as cardiovascular diseases [4–7]. However, the establishment of a target BP is still being debated, particularly the reliability or reproductivity of conventional clinical BP measurements, which most previous clinical trials used. Previous studies showed that BP measured outside the clinic, such as self-measurements at home or ambulatory BP monitoring (ABPM), correlated better with the incidence of cardiovascular diseases and the future decline of kidney function [8, 9]. In particular, nocturnal BP measured by ABPM is the strongest predictor of renal and cardiovascular events [10–13].

ABPM allows not only the detection of white-coat or masked hypertension, but also the classification of the daily BP profile [14]. BP generally decreases during nighttime, and is termed the "dipper" pattern; however, some populations exhibited less or an absence of dipping BP during nighttime, and, thus, it is termed the "non-dipper" pattern which is frequently observed in patients with CKD [15–17]. In addition, clinical observations showed that the non-dipper BP profile pattern, which is frequently complicated by a nocturnal high BP, predicted end-organ damage, including left ventricular hypertrophy [18] and urinary albumin excretion [19], a potent predictor of the progression of renal insufficiency [20].

However, due to the lack of sufficient evidence, particularly interventional clinical trials with ABPM-based controls, the target BP of ABPM has not yet been established. Furthermore, although the non-dipper BP pattern is regarded as a risk factor for the progression of kidney disease and cardiovascular diseases in CKD patients [21–24], it currently remains unclear whether a normotensive non-dipper pattern is still a risk factor for the progression of CKD. Given the recent studies demonstrating that non-dipping pattern of BP is associated with renal arteriosclerosis even in normotensive patients with IgA nephropathy, it is possible that normotensive non-dipper is a risk for developing kidney disease [25, 26]. In the present study, according to ABPM findings, i.e., 24-h BP values and BP dipping patterns, we divided CKD patients into four categories and compared the estimated glomerular filtration rate (eGFR) decline among these groups.

Materials and methods

Patients and study protocol

This is a retrospective cohort study that was conducted in the Omihachiman Community Medical Center in Shiga Prefecture, Japan. We consecutively enrolled 937 CKD patients who underwent ABPM between October 2006 and May 2014. CKD was diagnosed according to the criteria of the National Kidney Foundation defined as eGFR < 60 ml/min/1.73 m^2 [27]. A total of 261 patients were excluded from the present study due to the lack of results for blood or urine examinations 6, 12, or 24 months after the ABPM procedure. As a result, 676 patients were recruited for this study (Fig. 1). All clinical characteristics were collected from medical records, including age, gender, complications, laboratory results, and the measurement of BP. eGFR was calculated according to the following formula, which was provided by the Japanese Society of Nephrology [28] "194 × [age (years)]$^{-0.287}$ × [serum creatinine (mg/dl)]$^{-1.094}$ × [0.739 if female]". Body mass index (BMI) was
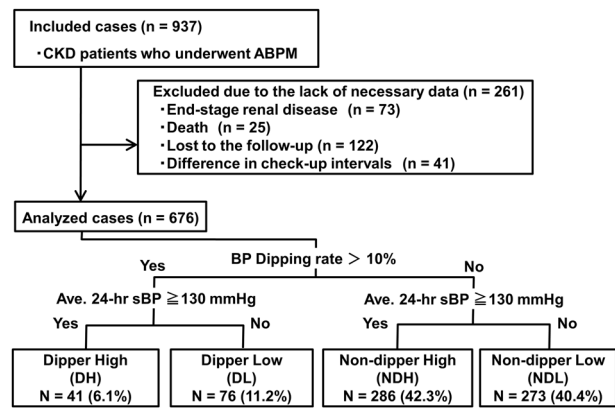

Fig. 1 Flowchart of the process of patient recruitment. A Patient with a less than 10% nocturnal decline in systolic BP was defined as a non-dipper. The diagnosis of hypertension was made by an average 24-h systolic BP higher than 130 mmHg. A total of 82.7% of patients were categorized as non-dippers

calculated as [weight (kg)]/[height (meter)] [2]. We calculated eGFR decline from baseline in each group 6, 12, and 24 months after the ABPM procedure. The protocol for this study was approved by the Ethics Committee of the Omihachiman Community Medical Center. The entire protocol of this study was designed in accordance with the Declaration of Helsinki.

ABPM procedure and definition of BP profiles

ABPM devices (FB-270, Fukuda Denshi Co., Ltd., Tokyo, Japan) were fit between 15:00 and 16:00 and removed at 15:30 the next day. During the day (07:00–22:00), measurements were taken at 30-min intervals, whereas night measurements (22:00–07:00) were taken hourly.

The average 24-h BP was measured by ABPM. Non-dipper or dipper and high or low BP were classified by the guidelines submitted by American Heart association [4]. Non-dipper was defined when the average diurnal systolic BP (sBP) was not 10% higher than the average nocturnal sBP. Hypertension was defined when the average 24-h BP was higher than 130/80 mmHg (Fig. 1).

Statistical analysis

Data are expressed as the mean ± standard error (SE). Comparisons of two groups were performed by Welch's t-test for continuous variables and by Fisher's exact test for categorical variables. Multiple comparisons among the four groups were performed by the Steel-Dwass test for continuous variables and by the Bonferroni correction for categorical variables.

Multiple regression analyses were performed in order to assess variables associated with a faster eGFR decline using

Table 1 Average BP profiles of each group for all patients

	Total	Dipper high	Dipper low	Non-dipper high	Non-dipper low
24 h (mmHg)					
Systolic blood pressure	129.7 ± 17.0	140.0 ± 8.8	116.4 ± 9.3	143.9 ± 12.4	116.9 ± 8.9
Diastolic blood pressure	76.2 ± 9.9	79.3 ± 8.7	71.0 ± 7.1	81.6 ± 9.7	71.5 ± 7.5
P value vs. NDH		0.16	< 0.0001	–	< 0.0001
Daytime (mmHg)					
Systolic blood pressure	131.3 ± 16.7	148.4 ± 9.7	123.0 ± 9.9	143.6 ± 12.6	118.2 ± 9.6
Diastolic blood pressure	78.0 ± 10.0	83.8 ± 9.2	75.6 ± 7.4	82.5 ± 10.0	73.0 ± 7.9
P value vs. NDH		0.0032	< 0.0001	–	< 0.0001
Nighttime (mmHg)					
Systolic blood pressure	127.7 ± 19.1	128.4 ± 8.8	106.2 ± 9.0	144.3 ± 14.4	116.1 ± 10.0
Diastolic blood pressure	73.8 ± 10.9	72.8 ± 8.6	63.4 ± 7.4	80.3 ± 10.6	70.0 ± 8.0
P value vs. NDH		< 0.0001	< 0.0001	–	< 0.0001
Blood pressure dipping (%)	2.7 ± 7.8	13.4 ± 2.3	13.6 ± 3.2	−0.6 ± 7.0	1.6 ± 5.9

gender, age, the nocturnal sBP dipping rate, and factors considered to have a significant relationship. We defined the cutoff value as the mean value of the eGFR decline by aging in healthy Japanese adults aged 40 years or older [29]. We examined the relationship between the eGFR decline over 2 years and the sBP dipping rate or average 24 h, daytime and nighttime sBP using a linear correlation model. A *P* value <0.05 was considered to be significant. Statistical analyses were performed using JMP version 9.0.3 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

High prevalence of the non-dipping BP profile in CKD patients

We consecutively enrolled 937 CKD patients who underwent ABPM between October 2006 and May 2014 (Fig. 1). Due to the lack of follow-up data 6, 12, or 24 months after ABPM, 261 patients were excluded from this analysis. The reasons for the loss of data were as follows: reaching end-stage renal disease for 73 patients, death by any cause for 25, lost to the follow-up during the observation period for 122, and lacking data at the indicated time points for 41. The baseline characteristics and ABPM profile of patients with end-stage renal disease and death during the observational period were summarized in Supplementary Table 1 and Supplementary Table 2. After the exclusion of these patients from the analysis, 676 patients were recruited in the present study (Fig. 1).

According to the general definition of dipper and ABPM-based hypertension as an average 24-h BP of higher than 130/80 mmHg [4], we divided 676 patients into four groups as follows: non-dipper with high BP (NDH 42.3%), non-dipper with low BP (NDL 40.4%), dipper with high BP

(DH 6.1%), and dipper with low BP (DL 11.2%) (Fig. 1). The average nocturnal BP decline was 2.7 ± 7.8%, and a high prevalence of the non-dipping BP pattern (82.7%) was observed (Table 1).

Regarding the clinical characteristics of participants, no significant differences were observed in age, sex, renal function, hemoglobin values, or the usage rate of RAS inhibitors, diuretics, and β-blockers among each group (Table 2). The percentage of patients with DM, the usage rate of the calcium blocker, and values for the body mass index, serum calcium, and albumin were significantly lower in DL and NDL patients than in NDH patients. Regarding the urinary protein, one of the strong predictor of future eGFR decline in CKD patients, the NDH group exhibited the highest value (1.53 ± 0.13 g/day), and that of NDL group (0.54 ± 0.07 g/day) was similar to that of DL group (0.51 ± 0.13 g/day) were similar.

BP profiles in each group (Table 1) showed that the average sBP was similar in NDH and DH patients (143.9 ± 12.4 mmHg vs. 140.0 ± 8.8 mmHg, *P* = 0.16). The average sBP in DL and NDL patients were also similar (116.4 ± 9.3 mmHg vs. 116.9 ± 8.9 mmHg, *P* = 0.99). Due to the lack of a BP decline during the nighttime in non-dipper patients, the average nocturnal BP was significantly higher in NDH and NDL patients than in DH and DL patients, respectively.

Non-dipping BP with appropriate controls does not accelerate the eGFR decline

Changes in eGFR from baseline were calculated 6, 12, and 24 months after the ABPM procedure. In the all patient analysis, eGFR decreased by 2.93 ± 0.30 ml/min/1.73 m^2 during the observational period (Fig. 2a). In the separate analysis according to BP dipping and 24-h BP, a significant difference in the eGFR decline was observed between the NDH and normotensive groups (DL and NDL) 6 months

Table 2 Patient characteristics of each group for all patients

	Total	Dipper high	Dipper low	Non-dipper high	Non-dipper low
Number	676	41	76	286	273
Men (%)	67.8	68.3	67.1	66.8	68.9
Age (years old)	68.4 ± 11.7	68.7 ± 11.6	70.8 ± 11.1	68.4 ± 11.3	67.6 ± 12.3
Body mass index	23.80 ± 4.02	24.03 ± 4.33	23.27 ± 3.49	24.28 ± 4.21	23.41 ± 3.88*
Diabetes mellitus (%)	39.5	41.5	31.6	47.9	32.6*
Creatinine (mg/dL)	2.12 ± 1.16	2.32 ± 1.29	2.00 ± 1.03	2.18 ± 1.06	2.07 ± 1.20
eGFR (ml/min/1.73 m^2)	29.33 ± 12.92	27.74 ± 14.33	30.70 ± 13.98	28.36 ± 12.60	30.21 ± 12.70
Blood urea nitrogen (mg/dL)	32.43 ± 15.60	37.29 ± 17.68	32.24 ± 16.33	31.48 ± 14.45	32.74 ± 16.15
Urinary protein (g/day)	0.98 ± 0.07	0.93 ± 0.17	0.51 ± 0.13[†]	1.53 ± 0.13	0.54 ± 0.07*,[‡]
Calcium (mg/dL)	8.94 ± 0.53	8.80 ± 0.56	9.06 ± 0.69	8.86 ± 0.51	9.02 ± 0.47*
Potassium (mg/dL)	4.58 ± 0.55	4.70 ± 0.63	4.61 ± 0.56	4.52 ± 0.54	4.61 ± 0.55
Albumin (g/dL)	3.83 ± 0.45	3.85 ± 0.42	3.90 ± 0.30[†]	3.72 ± 0.49	3.91 ± 0.42*
Hemoglobin (g/dL)	11.58 ± 2.05	11.69 ± 2.38	11.47 ± 2.12	11.41 ± 2.03	11.71 ± 1.99
LDL-cholesterol (mg/dL)	103.0 ± 32.3	114.1 ± 51.2	104.1 ± 26.5	105.8 ± 32.1	98.0 ± 29.5
Calcium channel blocker (%)	67	80.5	61.8	75.2	57.9*,[‡]
RAS inhibitor (%)	71.6	73.2	59.2	75.2	71.1
Diuretics (%)	32.1	43.9	21.1	36.7	28.6
β-blocker (%)	19.4	19.5	11.8	23.4	17.2

*$P < 0.05$ between NDH and NDL

[†]$P < 0.05$ between NDH and DL

[‡]$P < 0.05$ between NDL and DH

after recruitment, and these differences became larger over the observational period (Fig. 2b). No significant difference was noted between the DL and NDL groups throughout the observational period. These results indicate that the 24-h BP value is more important for detecting the future progression of kidney disease. Of note, in contrast to previous findings showing the risk of the non-dipping BP profile on the progression of kidney disease [21], our results indicated that the normotensive non-dipper BP profile is not a risk factor for the progression of kidney disease.
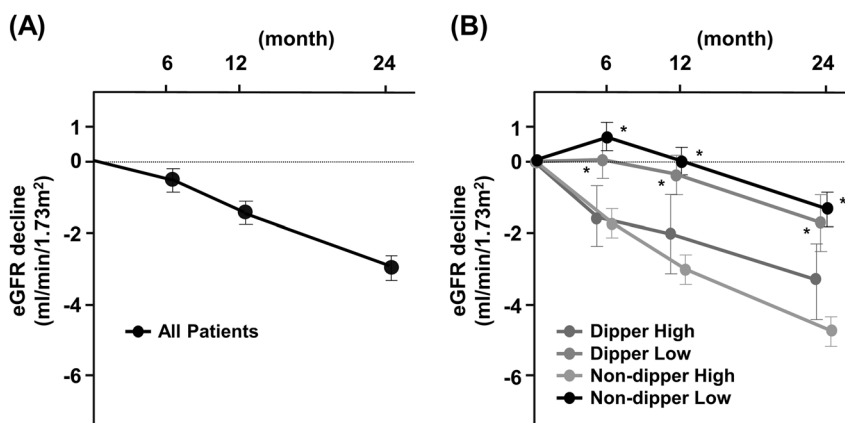
Since a previous study demonstrated that the average eGFR decline rate in a Japanese general population was 0.36 ml/min/1.73 m^2/year [29], we performed a logistic regression analysis adjusted by gender, age, the nocturnal BP decline rate, and factors considered to have a significant relationship with a faster eGFR decline than this value. The analysis identified the average 24-h sBP (95% CI 1.13–1.45), proteinuria (95% CI 1.51–2.63), and eGFR at baseline (95% CI 1.02–1.44) as significant factors associated with the worsening of eGFR (Fig. 3). We also examined the linear correlation between the eGFR decline over 2 years and BP dipping rate or average 24-h sBP. The eGFR decline correlated linearly with 24-h sBP ($P < 0.001$, $r = 0.26$, Fig. 4a), whereas no correlation was observed between the BP dipping rate and eGFR decline ($P = 0.074$,

$r = -0.069$, Fig. 4b). Given the previous observational investigation demonstrating the nighttime BP was strongest correlation with future incidence of cardiovascular diseases [10–12], we further analyzed the linear relationship between the eGFR decline and average nighttime of daytime BP. eGFR decline correlated linearly with both nighttime and daytime BP ($P < 0.0001$, $r = 0.251$, $P = 0.0001$, $r = 0.254$, Suppl Fig) and there was no big difference between these linearities.

Discussion

CKD patients are more likely to exhibit a non-dipping BP profile pattern [15–17], as observed in our investigation. The non-dipper profile is a risk factor for the development of kidney disease [21]; however, it is challenging to normalize not only the actual BP value, but also its diurnal rhythm. Thus, our experiment was performed in order to elucidate the impact of the non-dipping BP pattern on the decline in kidney function in normotensives. Three major results were obtained in the present study: ABPM data in our analysis showed an extremely high prevalence of the non-dipping BP profile pattern in CKD patients. The non-dipping BP profile pattern did not predict future declines in

Fig. 2 Change in eGFR from baseline over the observational period. **a** Average eGFR in all patients gradually decreased over 2 years. **b** The separate analysis demonstrated that the eGFR decline was significantly more rapid in the NDH group than in the NDL group. Asterisks indicate $P < 0.05$ vs. NDH at each timepoint
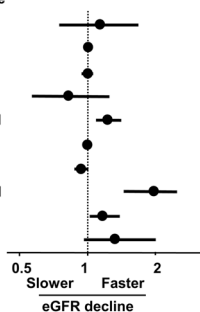

Fig. 3 Proteinuria and 24-h sBP are relevant for the eGFR decline. A multiple regression model for the identification of factors associated with the eGFR decline rate. A larger amount of proteinuria, high 24-h sBP, and high baseline eGFR correlated with the eGFR decline

Fig. 4 Relationship between the eGFR decline over the observational period and the BP dipping rate or 24-h sBP. **a** Twenty-four-hour sBP correlated with the eGFR decline. **b** No correlation was observed between the eGFR decline and BP dipping rate

kidney function in normotensive CKD patients. 24 h BP, rather than its circadian rhythm, is more important for predicting future eGFR decline.

Regarding the relationship between the BP diurnal rhythm and renal outcomes in normotensive subjects, few studies have focused only on urinary albumin excretion and the actual decline in kidney function remains unknown. Previous studies showed that the dipping BP pattern slightly correlated with the left ventricular mass index [30], but not with urinary albumin excretion [31, 32] in normotensives. Consistent with these findings, the present results showed that there was no significant difference in proteinuria between NDL and DL. Regarding the eGFR decline, previous studies demonstrated that nocturnal BP was the strongest predictor of the progression of kidney disease [19, 21, 22, 33]. In the present study, although average nocturnal BP was higher in the NDL group than in the DL group, no significant difference was noted in the eGFR decline between these groups. This result indicates that there is a certain threshold of nocturnal BP and that a lower BP than the threshold does not appear to be a risk factor for developing kidney disease; however, the present results did not provide an actual value for this.
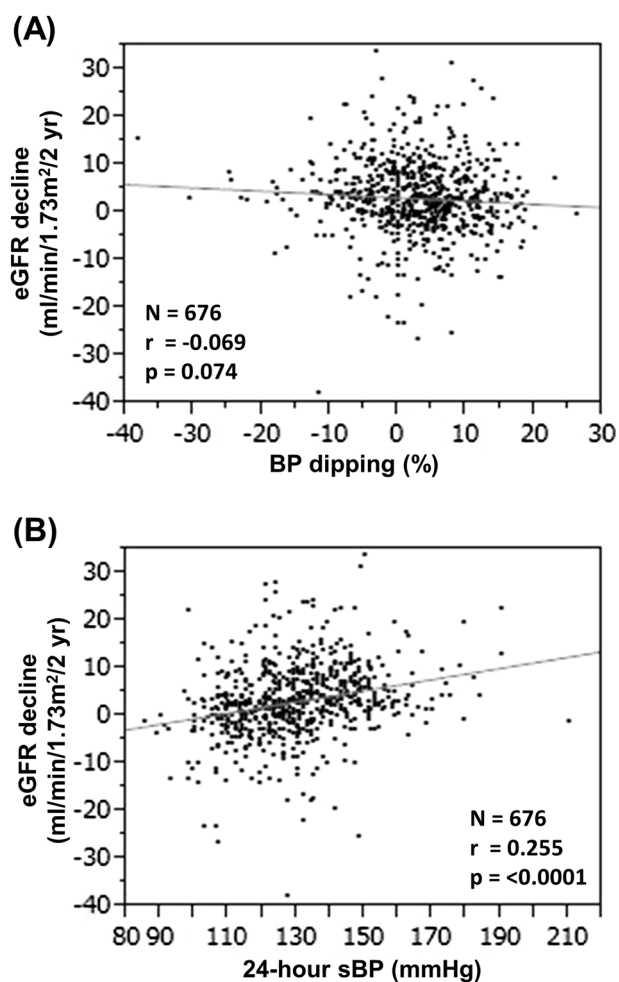
Due to the lack of sufficient evidence, it currently remains unclear whether shifting the BP from non-dipper to dipper by the administration of anti-hypertensives potentiates renoprotective effects. Regarding the change

in the BP profile, Crespo et al. showed that a bedtime hypertension treatment for CKD patients lowered the average nocturnal BP as well as the percentage of non-dipper patients [34]. Several clinical observations have revealed that normalizing the diurnal rhythm of BP by the administration of anti-hypertensives not only improved urinary albumin excretion for early diabetic kidney disease [35, 36], but also reduced the incidence of cardio-vascular diseases [37–39]. However, concerning actual renal outcomes, only one study showed that ABPM-based BP control for pediatric CKD patients reduced the incidence of end-stage renal disease or ameliorated the eGFR decline [40]. Although our ABPM-based analysis is an observational investigation, the results obtained suggest that shifting from non-dipper to dipper in normotensive patients might not be beneficial for preventing the progression of kidney disease.

The present study includes several limitations. We only assessed ABPM once for each patient on recruitment. The reproducibility of ABPM is sometimes a limiting factor because ABPM itself disturbs the sleeping status and reduces daytime activity, which induces a higher nocturnal BP and lower daytime BP than usual. Previous studies showed that some individuals exhibited a different circadian BP pattern in serial ABPM, even with intervals of several weeks [41, 42]. The 48-h ABPM may reflect the BP status more reliably [43]; however, it is less convenient for usual clinical practice. In addition, because we did not assess BP control using ABPM or other methods for BP measurements at later time points during the observational period, the impact of BP control at the later time points on the future eGFR decline remains unclear.

Another limitation is the low prevalence of patients with the dipping BP pattern; the small sample size may have affected the significance of differences. Furthermore, although we found that the non-dipping profile in normotensive patients was not a risk factor for developing kidney disease, we did not provide the actual value of the risk threshold for BP. In order to establish a target BP, a prospective interventional study that includes multiple tests of ABPM is necessary. Previous studies showed that the self-measurement of home BP correlated well with ABPM and is an alternative method for predicting end-organ damage [8, 44]. However, the timing of BP measurements that precisely reflect the dipping BP pattern as well as the average values of BP during daytime and nighttime remains unclear.

Additionally, although a previous community-based cohort study demonstrated that the eGFR decline over 1 year was associated with an increased risk of end-stage renal disease [45], the eGFR decline over 2 years in our analysis may be less accurate for predicting future renal outcomes. Moreover, since it is impossible to calculate

the precise eGFR decline rate, we excluded patients who progressed to end-stage renal disease or died during the observation period. Among these populations, there were a few DL patients, and a lower frequency of NDL patients and higher frequency of NDH patients than those in the main analysis were noted. Thus, although the results of the DL and NDL groups in the main analysis were not affected by this exclusion, we may have underestimated the eGFR decline rate in the NDH group. Since data collection in the present study was retrospective and the eGFR decline over only two years was a surrogate marker of future kidney dysfunction, prospective observations for a longer period using a hard endpoint such as end-stage renal disease, renal death, or a 40% increase in serum creatinine may be required to resolve this limitation.

In conclusion, according to our ABPM-based analysis, a non-dipping BP pattern in normotensive CKD patients does not predict a risk for a rapid decline in eGFR. In hypertensive CKD patients, the non-dipping BP pattern is a higher risk factor for developing kidney disease than in dipping patients. These results suggest that the control of BP, rather than its circadian rhythm, is essential for the preservation of eGFR. A larger scale study and longer period of observation are required in order to elucidate the impact of the diurnal rhythm of BP on the future prognosis of kidney disease in normotensives.

Compliance with ethical standards

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