

## Analysis of the Difference in the Pressure-Natriuresis Relationship Based on the Class of Medication Using Spot Urine Tests in Hypertensive Patients

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Received date: May 25, 2014; Accepted date: June 23, 2014; Published date: June 28, 2014

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### Abstract

**Objective:** We estimated the daily sodium intake using a spot urine method in hypertensive patients, and investigated the differences in the pressure-natriuresis relationship depending on the type of medications and the involvement of renal function in this relationship.

**Methods:** This study included 356 spot urine samples of hypertensive patients at our cardiology outpatient clinic. Daily sodium intake was estimated by the spot urine tests at the time of study enrolment. We examined the difference in the relationships among estimated daily sodium intake, mean blood pressure (mBP), and estimated glomerular filtration rate (eGFR) with each medication.

**Results:** In multivariate analysis, the eGFR and mBP were significantly associated with estimated daily sodium intake. The slope of the pressure-natriuresis relationship was steeper in patients treated with renin-angiotensin system inhibitors (RAS-I) plus diuretics, and lower in patients treated with RAS-I plus calcium-channel blockers (CCB) than in those treated with CCB or who were not treated. eGFR was higher in patients with higher daily sodium intake than in those with lower daily sodium intake in association with higher mBP, except for patients treated with CCB alone.

**Conclusions:** Estimated daily sodium intake in hypertensive patients was positively correlated with eGFR and mBP. The slope of the pressure-natriuresis relationship curve was different depending on the class of medication. In hypertensive patients with higher sodium intake, the relationship between mBP and eGFR may be important when selecting the type of medication.

**Keywords:** Hypertension; Medication; Natriuresis; Renal function; Sodium intake

### Introduction

Sodium intake is related to blood pressure, and is an established risk factor for heart disease and chronic kidney disease (CKD). Hypertension is frequently caused by excessive sodium intake. However, sodium reduction is very difficult if the daily sodium intake of individual patients is unknown. Some published methods for the estimation of daily sodium intake show promise [1,2], but individual estimates of sodium intake are highly variable [3]. Ji et al. suggest that 24-h urine collection for sodium excretion measurement is the preferred tool for assessing sodium intake compared with methods using spot urine samples [4]. The biological basis for the variability between 24-h and other methods remains unclear [5]. However, estimation of sodium intake using a spot urine test is useful for motivating patients to reduce their sodium intake and blood pressure [6]. Furthermore, a spot urine method is a low-burden, low-cost alternative to 24-h urine collections for the estimation of sodium intake, although the latter may be more suitable for population-based studies [7].

In ordinary practice, hypertensive patients receiving medications periodically undergo blood sampling and urinalysis when spot urine

sodium/creatinine concentrations can be evaluated. The spot urine method is reliable for evaluating daily sodium intake, even in patients taking antihypertensive medication [8]. Therefore, in this study, we investigated factors affecting the estimated daily sodium intake using a spot urine method in hypertensive patients. We particularly examined the differences in the pressure-natriuresis relationship curve based on the type of hypertensive medications and the involvement of renal function in that relationship.

### Methods

A total of 356 spot urine samples taken from random hypertensive patients (age,  $69 \pm 10$  years) who visited our outpatient cardiology clinic were analyzed in this study. There were one or more spot urines per patient. The urine was collected at random times. For the purpose of this retrospective study, patients taking antihypertensive drugs or those with a clinical history of hypertension were classified as hypertensive. The percentage whose hypertension was under control was close to 100% in the hypertensive patients with medications. Daily dietary sodium intake was estimated based on the sodium and creatinine concentrations determined by the spot urine test at the time of enrolment [1]. Spot urinary sodium/creatinine ratio was also evaluated in case of the comparison with renal function. Patients taking loop diuretics were excluded from this study. Blood pressure and heart rate were measured at the time of urine sampling. It was just

a spot measurement after a defined resting period. Blood samples were used for the measurement of the creatinine level and estimated glomerular filtration rate (eGFR: men;  $194 \times \text{serum creatinine (mgdL}^{-1})^{-1.094} \times \text{age (years)}^{-0.287}$ , women;  $194 \times \text{serum creatinine (mgdL}^{-1})^{-1.094} \times \text{age (years)}^{-0.287} \times 0.739$ ). Baseline characteristics such as medical history and medications were recorded. Hypercholesterolemia was defined as a low-density lipoprotein cholesterol concentration of  $>140 \text{ mg}\cdot\text{dL}^{-1}$ . Patients taking antihypercholesterolemic drugs were also classified as having hypercholesterolemia. Patients were classified as having diabetes if they reported a history of diabetes, irrespective of whether treatment was received. We compared the estimated daily sodium intake with age, sex, body mass index, mean blood pressure (mBP), heart rate, eGFR, incidence of diabetes or hypercholesterolemia, and medications in hypertensive patients. mBP was calculated as  $[\text{diastolic pressure} + (\text{systolic pressure} - \text{diastolic pressure})/3]$ . We also investigated the factors that affected the correlation between estimated daily sodium intake and eGFR or mBP. In particular, we examined the differences in the correlations between estimated daily sodium intake and mBP and eGFR based on the type of hypertensive medications. The entire investigation conformed to the principles outlined in the Declaration of Helsinki, and was confirmed by the institutional review board at our hospital.

## Statistical Analysis

Univariate analysis for the difference between sexes was performed using the Student's t test. The correlation between estimated daily sodium intake and other factors was evaluated using a Pearson product moment correlation coefficient, and the p value was examined with regression analysis. Multivariate analysis was also performed using logistic regression analysis. A p value  $<0.05$  was considered significant.

## Results

Table 1 shows the clinical profiles of hypertensive patients in all urine samples, and the differences in the clinical profiles between patients with and without medications and between men and women. In all urine samples, the estimated daily sodium chloride intake determined by the spot urine method was  $9.0 \pm 2.5 \text{ g}\cdot\text{day}^{-1}$ . There was no difference in the estimated daily sodium intake between men and women. Compared with women, although the men in this study were significantly younger ( $p=0.003$ ) with a lower heart rate ( $p<0.001$ ), no differences were observed in eGFR ( $p=0.268$ ) and mBP ( $p=0.102$ ).

	All samples	Medication		P value	Men	Women	P value
		(-)	(+)				
N	356	28	328		230	126	
Age, years	69 ± 10	61 ± 15	70 ± 10	<0.001	68 ± 10	71 ± 10	0.003
Men, n (%)	230 (65)	15 (54)	215 (66)	0.143	230 (100)	0 (0)	-
DM, n (%)	111 (31)	10 (36)	101 (31)	0.372	80 (35)	31 (25)	0.031
HL, n (%)	207 (58)	11 (39)	196 (60)	0.028	118 (51)	89 (71)	<0.001
BMI, kg/m <sup>2</sup>	24.6 ± 3.6	25.4 ± 3.8	24.6 ± 3.6	0.268	24.7 ± 3.0	24.5 ± 4.5	0.615
SBP, mmHg	130 ± 15	142 ± 14	129 ± 14	<0.001	130 ± 15	131 ± 14	0.842
DBP, mmHg	74 ± 11	85 ± 9	73 ± 11	<0.001	75 ± 11	72 ± 10	0.013
mBP, mmHg	93 ± 11	104 ± 9	92 ± 10	<0.001	93 ± 11	92 ± 10	0.102
HR, bpm	73 ± 9	73 ± 8	73 ± 9	0.855	72 ± 9	75 ± 8	<0.001
eGFR, ml/min/1.73m <sup>2</sup>	64.7 ± 19.9	78.7 ± 22.6	63.5 ± 19.2	<0.001	63.9 ± 18.7	66.3 ± 21.9	0.268
NaCl, g/day	9.0 ± 2.5	10.5 ± 2.0	8.8 ± 2.5	<0.001	9.0 ± 2.5	8.9 ± 2.6	0.587
BB, n (%)	71 (20)	0 (0)	71 (20)	-	54 (23)	17 (13)	0.017
CCB, n (%)	236 (66)	0 (0)	236 (66)	-	153 (67)	83 (66)	0.497
Diuretics, n (%)	42 (12)	0 (0)	42 (12)	-	31 (13)	11 (9)	0.124
RAS-I, n (%)	246 (69)	0 (0)	246 (69)	-	174 (76)	72 (57)	<0.001

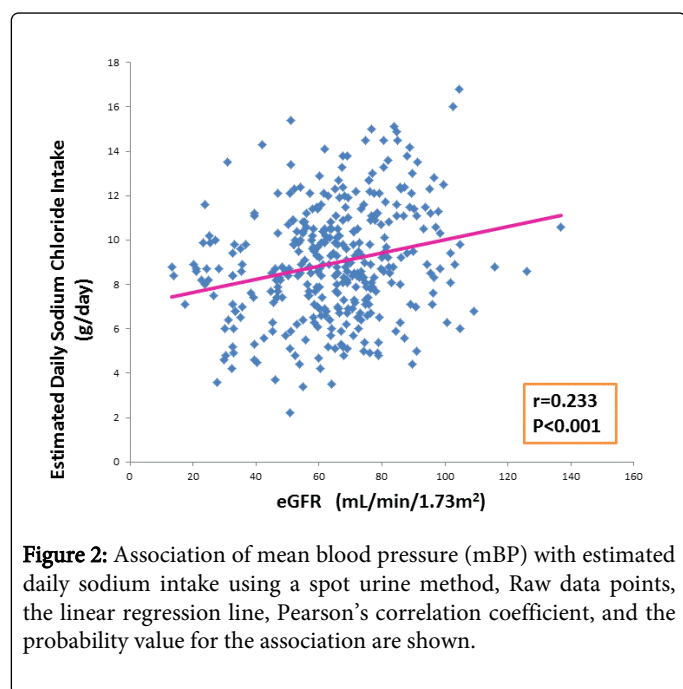
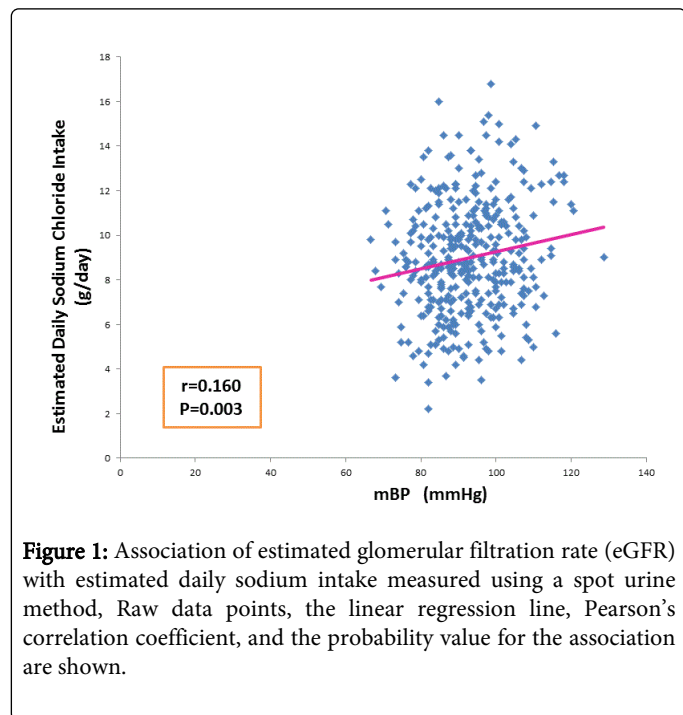
**Table 1:** Clinical profile of hypertensive patients

DM: diabetes mellitus, HL: hyperlipidemia; BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, mBP: mean blood pressure, HR: heart rate, eGFR: estimated glomerular filtration rate, NaCl: sodium chloride, BB: beta blockers, CCB: calcium-channel blockers, RAS-I: renin-angiotensin system inhibitors.

## Factors correlated with estimated daily sodium intake

Estimated daily sodium intake was positively correlated with eGFR ( $r=0.233$ ;  $p<0.001$ , Figure 1) and mBP ( $r=0.160$ ,  $p=0.003$ , Figure 2), but negatively correlated with age ( $r=-0.136$ ,  $p=0.010$ ) (Table 2). Other

factors such as heart rate, body mass index, incidence of diabetes mellitus or hypercholesterolemia, and medications used at the time of enrolment did not correlate with estimated daily sodium intake. When multivariate analysis was performed using these three significant indices in univariate analysis, eGFR ( $p < 0.001$ ) and mBP ( $p = 0.045$ ), but not age, were significantly associated with estimated daily sodium intake (Table 2).



	R value	P value	Multivariate
			P value
Age	-0.136	0.010	0.952
Mean blood pressure	0.160	0.003	0.045
Heart rate	-0.057	0.283	-
Body mass index	0.103	0.053	-
eGFR	0.233	<0.001	<0.001
Diabetes mellitus	-	0.206	-
Hypercholesterolemia	-	0.115	-
Beta blockers	-	0.095	-
Calcium-channel blockers	-	0.327	-
Diuretics	-	0.928	-
RAS-I	-	0.472	-

**Table 2:** Factors related to estimated daily sodium intake using spot urine method

### Factors that affect the correlation between estimated daily sodium intake and eGFR

We examined the factors that affect the correlation between estimated daily sodium intake and eGFR. In patients aged  $< 70$  years, a significant and positive correlation was observed between estimated daily sodium intake and eGFR ( $r = 0.325$ ,  $p < 0.001$ ). However, the correlation was not significant in patients aged  $> 70$  years ( $r = 0.069$ ,  $p = 0.341$ ). A significant correlation between urinary sodium/creatinine ratio and eGFR was found in patients aged  $> 70$  years ( $r = 0.142$ ,  $p = 0.049$ ) and  $< 70$  years ( $r = 0.255$ ,  $p = 0.001$ ). Similar significant correlations were found between estimated daily sodium intake and eGFR in men ( $r = 0.257$ ,  $p < 0.001$ ) and women ( $r = 0.203$ ,  $p = 0.022$ ).

### Factors affecting the correlation between estimated daily sodium intake and mBP

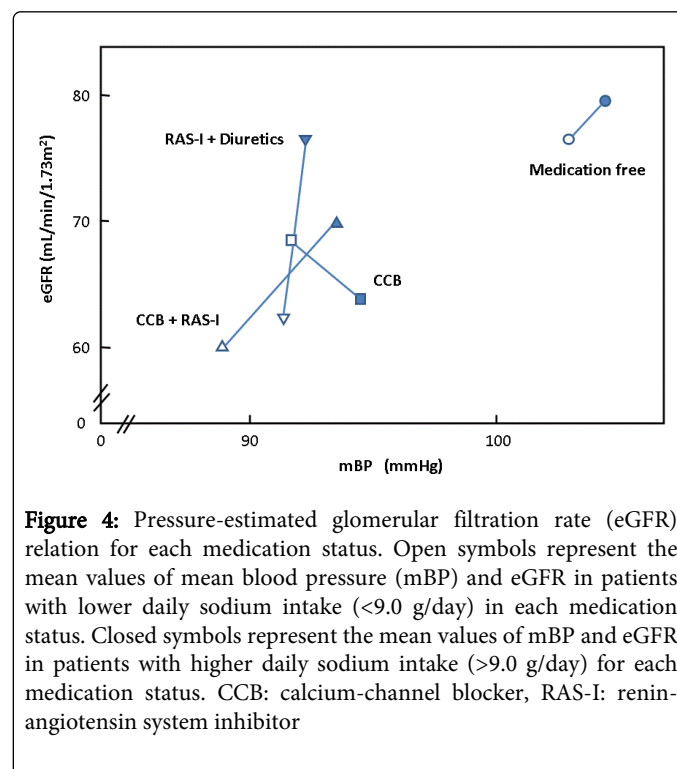
We also examined the factors that affect the correlation between estimated daily sodium intake and mBP. In patients aged  $< 70$  years, a significant and positive correlation was observed between estimated daily sodium intake and mBP ( $r = 0.260$ ,  $p < 0.001$ ). However, no significant correlation was seen in patients aged  $> 70$  years ( $r = 0.011$ ,  $p = 0.878$ ). No significant correlation was seen between urinary sodium/creatinine ratio and mBP in patients aged  $> 70$  years ( $r = 0.025$ ,  $p = 0.728$ ) or  $< 70$  years ( $r = 0.143$ ,  $p = 0.069$ ). A significant correlation between estimated daily sodium intake and mBP was seen in men ( $r = 0.177$ ,  $p = 0.007$ ) but not women ( $r = 0.121$ ,  $p = 0.177$ ), and in patients with an eGFR  $> 60$  mL $\cdot$ min $^{-1}$  $\cdot$ 1.73 m $^{-2}$  ( $r = 0.160$ ,  $p = 0.017$ ), but not  $< 60$  mL $\cdot$ min $^{-1}$  $\cdot$ 1.73 m $^{-2}$  ( $r = 0.048$ ,  $p = 0.581$ ).

### Involvement of medications in the relationship between estimated daily sodium intake and mBP and eGFR

Figure 3 shows the pressure-natriuresis relationship in patients treated with each medication. Because the mean value of the estimated daily sodium chloride intake was 9.0 g $\cdot$ day $^{-1}$  and no difference in estimated daily sodium chloride intake was observed between sexes,

we divided patients into two groups based on estimated daily sodium chloride intake:  $>9.0 \text{ g}\cdot\text{day}^{-1}$  or  $<9.0 \text{ g}\cdot\text{day}^{-1}$ . In patients not on antihypertensive medications, mBP was higher in patients with a higher daily sodium intake than in those with a lower daily sodium intake. In patients treated with calcium-channel blockers (CCB) alone, mBP was lower both in patients with lower and higher daily sodium intake than in those not receiving any medication. The slopes of the relationship curves between mBP and estimated daily sodium intake were comparable both in patients not receiving medication and in those treated with CCB. In patients treated with CCB plus renin-angiotensin system inhibitors (RAS-I), mBP was lower in patients with both lower and higher daily sodium intake than in those treated with CCB alone. However, the slope of the relationship curve in patients treated with CCB plus RAS-I was lower than that in patients treated with CCB alone; the difference in mBP between patients treated with CCB plus RAS-I and those treated with CCB alone was smaller in those with higher daily sodium intake than in those with lower daily sodium intake, possibly showing "sodium-sensitivity." The slope of the relationship curve in patients treated with RAS-I plus diuretics was steeper, and a smaller difference in mBP was observed between patients with lower and higher sodium intake, possibly showing "sodium-resistance." There were no differences in age, eGFR, mBP and estimated daily sodium intake among each medication status (data not shown).

with higher sodium intake than in those with lower sodium intake, irrespective of higher mBP, in those treated with CCB alone.



**Figure 4:** Pressure-estimated glomerular filtration rate (eGFR) relation for each medication status. Open symbols represent the mean values of mean blood pressure (mBP) and eGFR in patients with lower daily sodium intake ( $<9.0 \text{ g/day}$ ) in each medication status. Closed symbols represent the mean values of mBP and eGFR in patients with higher daily sodium intake ( $>9.0 \text{ g/day}$ ) for each medication status. CCB: calcium-channel blocker, RAS-I: renin-angiotensin system inhibitor

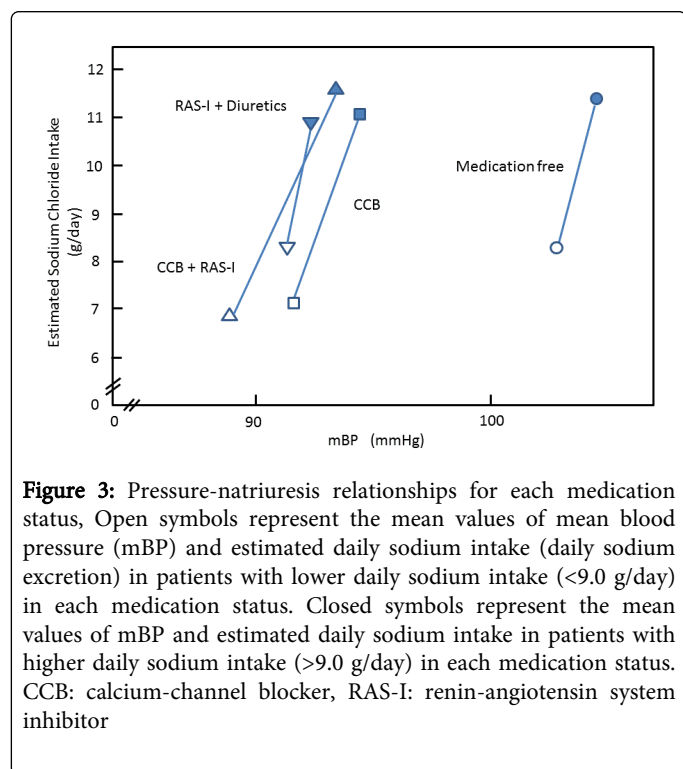
## Discussion

Despite the effects of sodium intake on blood pressure and response to antihypertensive medication, sodium intake is rarely evaluated by 24-h urine collection in the clinical setting. A spot urine method based on the sodium and creatinine concentrations is reliable for evaluating daily sodium intake [1,2].

### Factors that affect estimated daily sodium intake measurements using the spot urine method

Overnight spot urine samples show lower sodium concentrations than those obtained at other times (morning, afternoon, and evening), although urine creatinine concentration does not differ depending on the timing of collection [9]. The strongest correlation between predicted and actual 24-h sodium excretion has been observed in samples obtained in the late afternoon or early evening before dinner and adjusted for 24-h creatinine excretion [10]. In this study, at our outpatient cardiology clinic, spot urine samples were obtained early morning, or before lunch.

We found that the estimated daily sodium intake was significantly and positively associated with eGFR. In previous studies, spot urinary sodium concentration was found to be a simple and effective determinant of sodium intake even in patients with impaired renal function [11-13]. The 24-h sodium excretion and spot urine sodium values are significantly lower in patients with more advanced CKD [14]. The correlation coefficient between sodium intake and spot urine sodium concentration is significantly higher than that between sodium intake and spot urinary sodium/creatinine ratio in patients with CKD [14]. These results indicate that the reduction of estimated sodium



**Figure 3:** Pressure-natriuresis relationships for each medication status. Open symbols represent the mean values of mean blood pressure (mBP) and estimated daily sodium intake (daily sodium excretion) in patients with lower daily sodium intake ( $<9.0 \text{ g/day}$ ) in each medication status. Closed symbols represent the mean values of mBP and estimated daily sodium intake in patients with higher daily sodium intake ( $>9.0 \text{ g/day}$ ) in each medication status. CCB: calcium-channel blocker, RAS-I: renin-angiotensin system inhibitor

A significant and positive correlation was found between mBP and eGFR in patients with higher ( $n=164$ ,  $r=0.194$ ,  $p=0.013$ ) and lower ( $n=192$ ,  $r=0.252$ ,  $p<0.001$ ) sodium intake. However, the relationship between mBP and eGFR differed depending on the type of medication, especially in patients with higher sodium intake (Figure 4). The eGFR was higher in patients with higher sodium intake than in those with lower sodium intake in patients not receiving any medication, and those treated with CCB plus RAS-I or RAS-I plus diuretics, in association with higher mBP. However, eGFR was lower in patients

intake in patients with CKD may be due to the changes in urinary creatinine excretion.

### Renal function and the pressure-natriuresis relationship

Hypertension may be an inevitable consequence of the reduced ability of the kidney to excrete sodium load to promote natriuresis, and maintain a normal sodium balance [15]. mBP was higher in patients with higher sodium intake than in those with lower sodium intake for each type of medication used in this study (Figure 3). The slope of the pressure-natriuresis relationship curve was significantly lower in sodium-sensitive than in sodium-resistant patients [16,17]. In fact, the slope of the pressure-natriuresis relationship curve was steeper in patients treated with RAS-I plus diuretics. Similarly, it was lower in patients treated with CCB plus RAS-I than in those treated with CCB alone or those not treated with any medication, although the differences in the slopes between medications did not appear striking. This evidence supports the role of the sympathetic nervous system in the development of sodium-related hypertension in sodium-sensitive patients. A high sodium diet has been shown to stimulate rather than suppress sympathetic nervous system activity in sodium-sensitive patients [18]. An increase in renal sympathetic nerve activity could shift the pressure-natriuresis relationship towards higher pressures and may be responsible for sodium retention [19]. In contrast, the blood pressure response to angiotensin II is greater in sodium-sensitive than in sodium-resistant patients with low, not high, sodium intake; the greater pressor response to angiotensin II in patients with a low-sodium diet may be due to upregulation of angiotensin II receptors because sodium-sensitive patients usually have suppressed levels of renin [20]. Therefore, reduction of mBP is greater in patients with low sodium intake than that in those with high sodium intake when patients are treated with CCB plus RAS-I.

Although a significant correlation between mBP and eGFR was found in patients with both higher and lower sodium intake, a difference in the relationship between mBP and eGFR was observed with different medications. In patients on a high sodium diet, sodium-resistant hypertensive patients have increased renal blood flow and decreased filtration fraction, whereas sodium-sensitive hypertensive patients have decreased renal blood flow and increased filtration fraction and intraglomerular pressure [20]. For patients treated with CCB plus RAS-I or RAS-I plus diuretics, mBP was higher in those with higher sodium intake than in those with lower sodium intake, in association with high eGFR. In patients treated with CCB alone, mBP was also higher in patients with higher sodium intake than in those with lower sodium intake; however, eGFR was lower in patients with higher sodium intake than in those with lower sodium intake. The involvement of renal function in the pressure-natriuresis relationship may be different in case of CCB, the mechanism of which remains to be seen. These results suggest that careful selection of medications may be necessary in hypertensive patients with higher sodium intake.

### Limitations

The use of the spot urine method for estimating daily sodium intake has its limitations. Many factors such as posture [21] and day-to-day variance in sodium intake [3] or blood pressure level affect the results as well as the methodological limitations. Our findings reflect the difference in the relationships among daily sodium intake, eGFR, and mBP with each medication at the time of enrolment. The variation in the pressure-natriuresis relationship with the duration and administered dose of individual medications remains to be elucidated.

The causal effect of medications on this relationship was not investigated in this study.

### Conclusions

Estimated daily sodium intake measured using the spot urine method in hypertensive patients in clinical practice was positively correlated with eGFR and mBP. The slope of the pressure-natriuresis relationship curve differed based on the type of medication. Selecting medication based on the relationship between mBP and eGFR may be important, especially in hypertensive patients with higher sodium intake.

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