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【 ORIGINAL ARTICLE 】

Prediction of Acute Glomerular Filtration Rate Reductions Following Renin-angiotensin System Blockade in Chronic Kidney Disease: A Possible Application of Ultrasonography in Clinical Practice

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Abstract:

Objective Renal arteriolosclerosis is a risk factor for acute reductions in the glomerular filtration rate (GFR) when renin-angiotensin system (RAS) inhibitors are administered. Renal arteriolosclerosis can be detected by an increase in the resistive index (RI) on Doppler ultrasonography. The purpose of the present study is to determine whether or not the RI can predict acute GFR reductions following RAS blockade in chronic kidney disease (CKD).

Methods We surveyed all CKD patients who were hospitalized in Otemae Hospital from January 2008 to December 2017. One hundred and eight patients who had been newly treated with RAS inhibitors were able to be followed for 14 weeks. The end point was an acute reduction in the GFR, defined as a decrease of ≥30%.

Results Twenty-three of the 108 patients presented with acute GFR reductions. The cumulative probability of acute GFR reductions was 3.3% and 53% in patients with RI ≤0.70 and RI >0.70, respectively ($p<0.001$). A univariate Cox proportional-hazards analysis showed that the RI, age, GFR, systolic blood pressure, urinary protein excretion, diabetic kidney disease, coronary artery disease, and use of diuretics were significant variables. Multivariate hazard ratios were calculated from the RI and three established variables (age, GFR, diuretics), and the RI and use of diuretics were shown to be significant risk factors for acute GFR reductions.

Conclusion These results suggest that an increase in the RI, as well as the use of diuretics, may be risk factors for acute GFR reductions following RAS blockade.

Key words: chronic kidney disease, Doppler ultrasonography, resistive index, renin-angiotensin system inhibitors, acute GFR reductions

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Introduction

Doppler ultrasonography noninvasively provides information on the morphology and hemodynamics of patients with kidney disease. The resistive index (RI) has been commonly used to assess the vascular stiffness in the kidneys. It is a simple parameter calculated as follows: (peak-systolic velocity - end-diastolic velocity)/peak-systolic velocity (Fig. 1). The normal range of the RI has been reported to be ≤0.70 (1-3). Recent studies have shown the clinical usefulness of the RI in chronic kidney disease (CKD). Tubulointerstitial injury in glomerular diseases can be evaluated by the RI (4), the accurate interpretation of which allows for the early identification of chronic tubulointerstitial nephritis (5). The RI correlates well with renal arteriolosclerosis (6), arteriosclerosis, and peritubular capillary loss (7). We previously showed that the RI was able to estimate the renal prognosis in CKD in 2- and 4-year follow-up studies (8, 9).

The number of CKD patients is increasing worldwide. The growing population of aged people has led to an increase in nephrosclerosis as an etiology of CKD, especially

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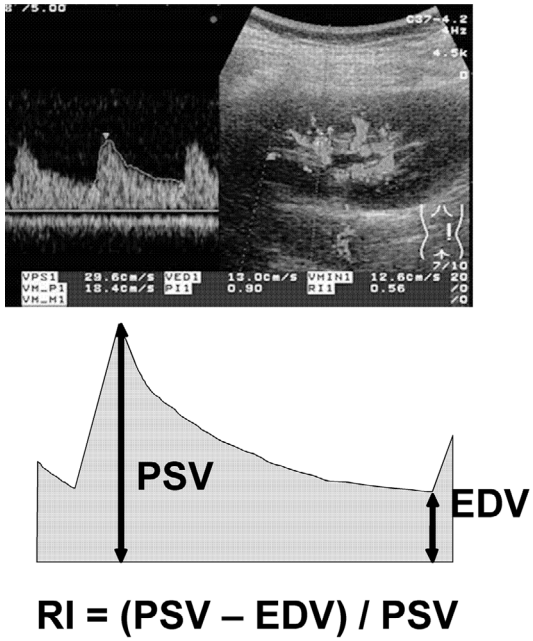

Figure 1. Doppler ultrasonography and a schematic illustration of the RI. The resistive index (RI) is calculated as follows: (peak-systolic velocity - end-diastolic velocity)/peak-systolic velocity. PSV: peak-systolic velocity, EDV: end-diastolic velocity

in Japan. Renin-angiotensin system (RAS) inhibitors, which exert renoprotective and antiproteinuric effects, are recommended as the first-line antihypertensive drugs for CKD with proteinuria (10, 11). These effects are thought to result mainly from the attenuation of glomerular hypertension. However, nephrosclerosis with proteinuria is often accompanied by severe arteriolosclerosis and/or arteriosclerosis (12), and the glomerular capillary pressure in this setting is not as high as that in primary glomerular diseases. As such, sclerosis of resistant vessels, such as afferent arterioles and interlobular arteries, may increase the risk of an acute reduction in the glomerular filtration rate (GFR) and/or normotensive acute kidney injury when RAS inhibitors are administered (13).

In this setting, an increase in the renal RI, which reflects advanced arteriolosclerosis in the kidneys, may be associated with a high incidence of acute GFR reduction following RAS blockade. The purpose of this study was to determine whether or not a high RI was a risk factor for an acute GFR reduction when RAS inhibitors are administered to CKD patients.

Materials and Methods

Patients and clinical evaluation

We retrospectively surveyed all of the CKD patients who were hospitalized in Otemae Hospital between January 2008 and December 2017. One hundred and eight (31 women and 77 men) were newly treated with RAS inhibitors, as follows: telmisartan (36 patients), losartan potassium (23 patients), olmesartan medoximil (21 patients), candesartan cilexetil (15 patients), and imidapril hydrochloride (13 patients). No patients were treated with dual or triple blockade of RAS inhibitors. Twenty-four of the 108 patients were treated with diuretics. The eligibility criteria for CKD were a reduced kidney function (GFR <60 mL/min/1.73 m^2) and/or persistent proteinuria (urinary protein >0.15 g/g creatinine), continuing for at least 3 months. No patients showed rapidly progressive kidney dysfunction (a decrease in GFR >10% per month) nor renal artery stenosis [peak systolic velocity >200 cm/s, side-to-side difference of the RI >0.05, or extended acceleration time >0.07 sec on Doppler ultrasonography (14)]. None of the 108 patients underwent renal replacement therapy during their hospitalization.

The patients were able to be followed for at least 14 weeks after the initiation of RAS inhibitors. The end point was an acute GFR reduction, defined as a decrease in the GFR ≥30%, until the end of the follow-up. We accepted this definition because most guidelines recommend that RAS inhibitors be discontinued if serum creatinine concentrations increase by ≥30% (i.e., GFR decreases by ≥30%) (10, 11). Data concerning the estimated GFR (eGFR), protein/creatinine ratio in spot urine samples, and blood pressure were available for all patients just before the initiation of RAS inhibitors and at least six times (twice a month for three months) until the end of the follow-up. Doppler ultrasonography findings of both kidneys on hospital admission were available for all patients. Serum creatinine was measured by an enzymatic assay. The GFR was estimated from the serum creatinine (s-Cr) level and age with the revised Japanese equation as follows: $194 \times s\text{-}Cr^{-1.094} \times Age^{-0.287}$ ($\times 0.739$ for women) (15).

This study was approved by the ethics committee in the hospital, and informed consent was obtained from each participant. All procedures were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with 1975 Declaration of the Helsinki, as revised in 2008.

Doppler sonography

A real-time ultrasound device with color Doppler capacity (AplioXG, SSA-790A; Toshiba Medical, Tokyo, Japan) and a 3.5-MHz convex-type probe were used. The scan showing the maximum longitudinal dimension was chosen for measurement. After observation of the intrarenal arteries by color Doppler ultrasonography, the blood flow velocities in the segmental arteries were measured by pulsed Doppler ultrasonography. The signals were obtained from segmental arteries since clear signals could be obtained reliably from these vessels (16). The RI was calculated as follows: (peak-systolic velocity - end-diastolic velocity)/peak-systolic velocity (Fig. 1).

The measurements were performed twice by one well-trained ultrasonographer who was unaware of the study, and the average of the two measurements was accepted. We used

Table 1. Characteristic of 108 Patients at Baseline.

	All patients (n=108)	Acute GFR reductions		
		Yes (n=23)	No (n=85)	p value
Age (years)	60±13	67±11	58±13	<0.01
Women (%)	28.7	26.1	29.4	0.96
RI	0.69±0.10	0.79±0.08	0.66±0.09	<0.001
Kidney size (major axis, mm)	104±15	103±13	105±19	0.82
eGFR (mL/min/1.73 m^2)	43.4±25.3	26.0±14.5	48.1±25.6	<0.001
Blood pressure (mmHg)				
Systolic	148±19	160±17	145±18	<0.001
Diastolic	85±15	79±16	86±14	0.23
Urinary protein (g/g Cr)	2.44±2.53	4.14±2.67	1.98±2.23	<0.001
Clinical diagnosis				
Glomerulonephritis (%)	39.8	26.1	43.5	0.15
DKD (%)	27.8	47.8	22.3	<0.05
BNS (%)	25.9	21.7	27.1	0.79
Others (%)	6.5	4.4	7.1	>0.99
Use of				
Diuretics (%)	22.2	43.5	16.5	<0.05
CCBs (%)	47.2	65.2	42.3	0.09
Statins (%)	49.1	60.9	45.9	0.3
Current or past smoking (%)	45.4	60.9	41.1	0.15
CAD (%)	18.5	39.1	12.9	<0.05

Values are expressed as mean±SD or percentage of numbers. Mann-Whitney U test was used to assess differences between two groups of continuous variables. Fisher's exact test was used to assess differences between two groups shown as numbers of patients.

RI: resistive index, eGFR: estimated glomerular filtration rate, Cr: creatinine, DKD: diabetic kidney disease, BNS: benign nephrosclerosis, CCBs: calcium channel blockers, CAD: coronary artery disease

the average value between the right and the left kidneys for the RI. To eliminate the influence of an abnormal aortic flow on the renal RI, we examined the aortic waveform simultaneously. No patients proved to have insufficient aortic flow.

Data analyses

Results are shown as the mean±standard deviation (SD) unless stated otherwise. Wilcoxon's signed-rank test was used to compare two related samples. The Mann-Whitney U test was used to assess differences between the two groups. A Kaplan-Meier analysis was used to estimate the cumulative probability of events using the log-rank test. A Cox proportional-hazards analysis was used to calculate hazard ratios as estimates of relative risks. A logistic regression analysis was used to calculate odds ratios. A p value less than 0.05 was accepted as indicating statistical significance.

Results

Clinical characteristics of the patients

The clinical characteristics of the 108 CKD patients at baseline are listed in Table 1. Each parameter in all patients and in the groups with or without acute GFR reductions is shown in the table. The age, RI, eGFR, systolic blood pressure, urinary protein excretion, morbidity of diabetic kidney disease (DKD), use of diuretics, and morbidity of coronary artery disease were significantly different between the groups with and without acute GFR reductions.

Table 2 shows the eGFR, systolic and diastolic blood pressure, and urinary protein excretion at the end of the follow-up period. Each parameter in all patients and in the groups with or without acute GFR reductions is shown in the table. All of these parameters at the end of the follow-up were decreased significantly compared with the baseline. Significant differences were evident in the eGFR, diastolic pressure, and urinary protein at the end of the follow-up between patients with acute GFR reductions and those without such reductions.

The RI and acute GFR reductions by RAS inhibitors

Overall, 23 of 108 patients presented with acute GFR reductions by treatment with RAS inhibitors. Fig. 2 shows the results of the Kaplan-Meier analysis of the renal outcomes according to the initial RI value: RI≤0.70 (normal RI) and RI>0.70 (high RI). The cumulative probability of acute GFR reductions at 14 weeks was 3.3% and 53% in patients with RI≤0.70 and RI>0.70, respectively. The log-rank test showed a significant difference between the 2 groups (p<0.001).

Table 2. eGFR, Blood Pressure, and Urinary Protein at the End of Follow-up.

	Baseline			End of follow-up		
		Acute GFR reductions			Acute GFR reductions	
	All patients (n=108)	Yes (n=23)	No (n=85)	All patients (n=108)	Yes (n=23)	No (n=85)
eGFR (mL/min/1.73 m^2)	43.4±25.3	26.0±14.5[#1]	48.1±25.6	39.9±25.8[a]	16.3±9.4[a, c]	46.3±25.1[b]
Blood pressure (mmHg)						
Systolic	148±19	160±17[#1]	145±18	134±18[a]	136±15[a]	132±19[a]
Diastolic	85±15	79±16	86±14	81±12[b]	75±13[#2]	82±12[b]
Urinary protein (g/g Cr)	2.44±2.53	4.14±2.67[#1]	1.98±2.23	1.74±2.53[a]	2.89±2.94[b, #1]	1.43±2.33[b]

Values are expressed as mean±SD. Wilcoxon signed-rank test was used to assess differences between two related samples (a: p<0.001, b: p<0.01 vs. baseline value). Mann-Whitney U test was used to assess differences between unrelated two groups (#1: p<0.001, #2: p<0.05 vs. patients without acute GFR reductions).
eGFR: estimated glomerular filtration rate, Cr: creatinine

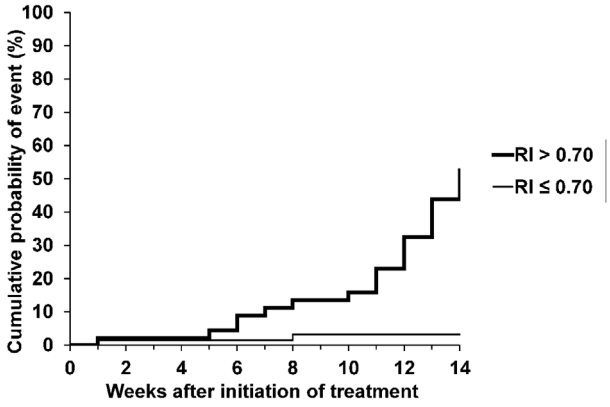

Figure 2. Cumulative probabilities of acute GFR reductions following RAS blockade. A Kaplan-Meier analysis according to the initial resistive index (RI). The bold line denotes RI >0.70, and the fine line denotes RI≤0.70. The cumulative probability of acute GFR reductions at 14 weeks was 3.3% and 53% in patients with RI≤0.70 and RI>0.70, respectively. Log-rank test, p<0.001. An acute GFR reduction was defined as a decrease in GFR of ≥30%.

While a high RI was associated with a high incidence of acute GFR reductions, the etiology of CKD was heterogeneous in the present cohort. In particular, the proportion of DKD was significantly higher in the group with acute GFR reductions than in the group without such reductions (Table 1), suggesting that the significance of the RI on acute GFR reductions might differ based on the presence of DKD.

To address this issue, we stratified the cohort by DKD. Fig. 3 shows the results of a Kaplan-Meier analysis of the renal outcomes stratified by DKD. Both groups equally showed significant differences in the cumulative probability of events between patients with RI>0.70 and those with RI ≤0.70. These results indicate that the RI can be used to predict acute GFR with or without DKD, possibly regardless of any underlying kidney disease.

Predictors of acute GFR reductions

While DKD was not shown to interfere with the association between a high RI and high incidence of acute GFR reductions, we suspected that other parameters might be confounding factors. We therefore selected parameters that were significantly different between the two groups with or without acute GFR reductions as the variables in the analyses: RI, age, eGFR, systolic blood pressure, urinary protein, DKD, coronary artery disease, and use of diuretics. We suspected that these factors might have an effect on the reduction in the GFR following RAS blockade and should be taken into account when evaluating the association between the RI and acute GFR reductions.

To evaluate the effects of these factors, including the RI on acute GFR reductions, we performed a Cox proportional-hazards analysis and calculated the hazard ratios. We used five continuous variables and three categorical variables. The continuous variables investigated were the RI×100 (i.e., a hazards ratio for an increase in RI of 0.01), age, eGFR, systolic blood pressure, and urinary protein excretion ×10 (i.e., a hazard ratio for an increase in urinary protein of 0.1 g/g creatinine). The categorical variables were DKD, coronary artery disease, and the use of diuretics. Fig. 4 shows the univariate hazard ratios for acute GFR reductions calculated from continuous or categorical variables. All variables investigated here proved to be significant.

In previous studies, several risk factors were shown to be associated with acute GFR reductions after RAS blockade, including old age, a reduced renal function, and the use of diuretics (17, 18). In the present study, we constructed a multivariate Cox model with the RI and the above three factors, as only 23 events occurred, which restricted the number of predictor variables that could be included (19). Table 3 shows the multivariate hazard ratios for acute GFR reductions calculated from the RI and established variables. While univariate analyses showed that all of these variables - an increase in RI, an increase in age, a decrease in eGFR, and the use of diuretics - were significant risk factors, the multivariate analysis showed that only an increase in the RI and the use of diuretics were significant.

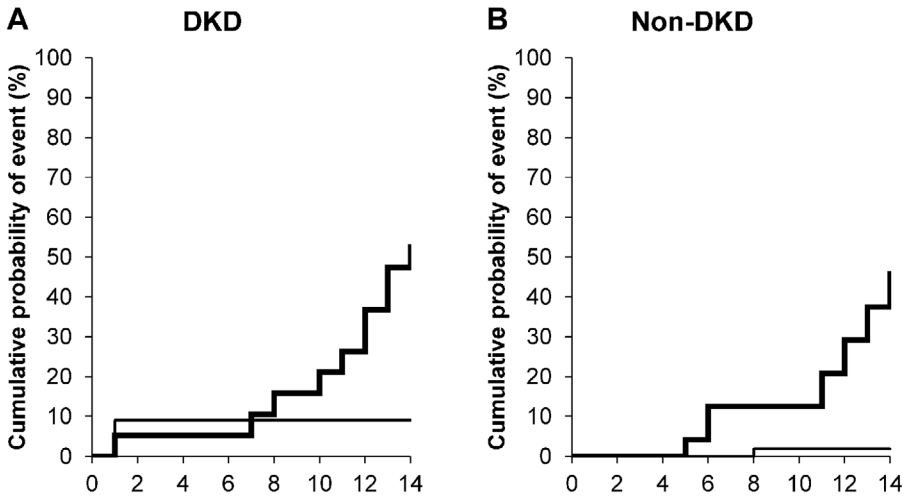

Figure 3. **Cumulative probabilities of acute GFR reductions following RAS blockade stratified by DKD. A Kaplan-Meier analysis according to the initial resistive index (RI) stratified by diabetic kidney disease (DKD). The bold line denotes RI>0.70 and the fine line denotes RI≤0.70. (A) DKD. The cumulative probability of acute GFR reductions at 14 weeks was 9.1% and 53% in patients with RI ≤0.70 and RI>0.70, respectively. Log-rank test, p<0.05. (B) non-DKD. The cumulative probability of acute GFR reductions at 14 weeks was 1.9% and 46% in patients with RI≤0.70 and RI>0.70, respectively. Log-rank test, p<0.001. An acute GFR reduction was defined as a decrease in GFR of ≥30%.**

Blood pressure at the end point and acute GFR reductions

The diastolic blood pressure at the end of the follow-up was significantly lower in the group with acute GFR reductions than in the group without such reductions (Table 2). To evaluate the effect of achieved diastolic blood pressure (i.e., diastolic pressure at the end of the follow-up), we performed a logistic regression analysis. Fig. 5 shows the univariate and multivariate odds ratios for acute GFR reductions. The variables investigated were the RI×100 and achieved diastolic pressure. A univariate analysis showed that both an increase in the RI and a decrease in the diastolic pressure were significant risk factors. However, the multivariate analysis showed that the achieved diastolic pressure had no effect on acute GFR reductions.

Verification of cutoff

Fig. 6 shows the receiver operating characteristic (ROC) curve for RI. The curve shows that the RI has a sufficient discriminatory power to identify patients likely to develop acute GFR reductions. The highest sensitivity and specificity were attained at an RI of 0.70, where the sensitivity was 91% (21/23, number/total number) and the specificity was 69% (59/85, number/total number), indicating that 0.70 was suitable as the cutoff value. The area under the curve (AUC) was 0.85, showing moderate accuracy for predicting acute GFR reductions.

Discussion

The number of patients with CKD is increasing worldwide. While primary glomerular diseases have decreased as a cause of CKD, diabetic kidney disease now accounts for the greatest proportion of CKD in Japan (20). Recently, the aging of society has led to an increase in nephrosclerosis as a cause of CKD (20). Diabetic kidney disease and nephrosclerosis share some characteristics in common, such as renal arteriolosclerosis and arteriosclerosis.

Blood pressure control is important for attenuating the progression of CKD (21). RAS inhibitors are recommended as the first-line therapy in CKD with proteinuria (10). In the early years of the 21st century, reducing the blood pressure as far as possible was thought to the best way to preserve the renal function in CKD (22). However, this theory has been reconsidered since the concept of "normotensive acute kidney injury" was reported in 2007 (13). CKD patients with severe renal arteriolosclerosis and arteriosclerosis can easily develop acute GFR reductions without a significant decrease in their blood pressure when RAS inhibitors are administered. This event is called normotensive acute kidney injury and is thought to occur as result of an excessive reduction in glomerular capillary pressure. The increase in CKD patients with diabetic kidney disease and/or nephrosclerosis can therefore increase the risk of acute GFR reductions following RAS blockade. Being able to identify individuals at risk of acute GFR reductions would be of great benefit to ensuring their timely treatment.

In the present study, an increase in the RI, as well as the use of diuretics, was shown to be a risk factor for acute GFR reductions after RAS blockade. Diuretics can induce hypovolemia, through which RAS inhibitors can easily provoke acute GFR reductions (17, 18). Why then is a high RI associated with acute GFR reductions when RAS inhibitors

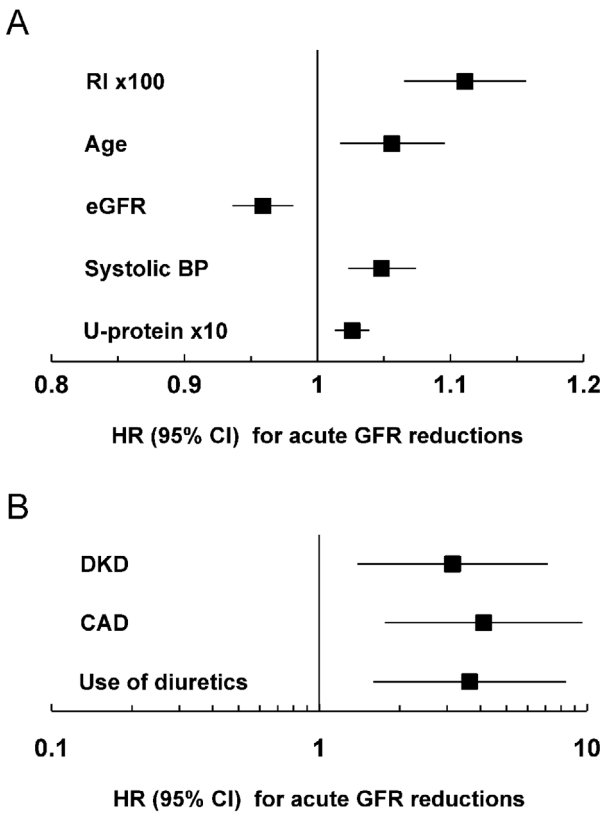

Figure 4. **Univariate hazard ratios for acute GFR reductions. A Cox proportional-hazards analysis was used to calculate the hazard ratio as estimates of relative risks of acute GFR reductions, defined as in the legend to Fig. 2. The figure shows hazard ratios with 95% confidence intervals. The variables investigated were RI×100 (i.e., an increase in RI of 0.01), age, eGFR, systolic blood pressure, urinary protein excretion ×10 (i.e., an increase in urinary protein of 0.1 g/g creatinine), diabetic kidney disease, coronary artery disease, and use of diuretics. All of these variables proved to be significant risk factors for acute GFR reductions. HR: hazard ratio, CI: confidence interval, RI: resistive index, eGFR: estimated glomerular filtration rate, BP: blood pressure, U-protein: urinary protein, Cr: creatinine, DKD: diabetic kidney disease, CAD: coronary artery disease**

Table 3. **Multivariate Hazard Ratios for Acute GFR Reductions Calculated from RI and Established Variables.**

Variables	HR	95% CI	p value
Univariate analysis			
RI×100	1.11	1.07-1.16	<0.001
Age	1.06	1.02-1.10	<0.01
eGFR (mL/min/1.73 m^2)	0.96	0.94-0.98	<0.001
Use of diuretics	3.65	1.59-8.36	<0.01
Multivariate analysis			
RI×100	1.07	1.01-1.13	<0.05
Age	1.00	0.96-1.14	0.97
eGFR (mL/min/1.73 m^2)	0.98	0.95-1.00	0.08
Use of diuretics	2.64	1.08-6.45	<0.05

Cox proportional-hazards analysis was used to calculate hazard ratio as estimates of relative risks of acute GFR reductions. The variables investigated were RI×100 (i.e., an increase in RI of 0.01), age, eGFR, and the use of diuretics.

HR: hazard ratio, CI: confidence interval, RI: resistive index, eGFR: estimated glomerular filtration rate

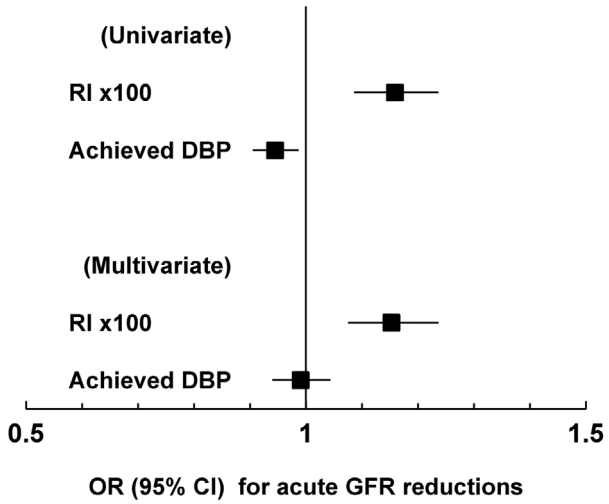

Figure 5. **Univariate and multivariate odds ratios of achieved diastolic blood pressure for acute GFR reductions. A logistic regression analysis was used to calculate the odds ratio for acute GFR reductions, defined as in the legend to Fig. 2. The figure shows odds ratios with 95% confidence intervals. The variables investigated were RI×100 (i.e., an increase in RI of 0.01) and achieved diastolic blood pressure (i.e., diastolic pressure at the end of follow-up). The achieved diastolic pressure had no effect on acute GFR reductions. OR: odds ratio, CI: confidence interval, RI: resistive index, DBP: diastolic blood pressure**

are administered? One reason is that a high RI reflects progression of renal arteriolosclerosis and arteriosclerosis (3, 4). Another possible reason is that an impaired cardiovascular function affects the renal function because a high RI reflects an increase in systemic vascular stiffness (23-26).

RI is the most well examined parameter in studies of renal Doppler ultrasonography. However, what the renal RI really reflects is still under debate. The RI may reflect systemic vascular stiffness as well as renal arteriosclerosis / arteriolosclerosis, as described above. A previous report suggested that the RI might be a long-term imprint of hypertensive organ damage in the same way that glycated hemoglobin is a long-term imprint of glycemic control (24). We confirmed a significant correlation between the RI and the duration of diabetes mellitus and/or hypertension in the present cohort (data not shown), suggesting that the RI could be an atherosclerotic result of long-standing diabetes and/or hypertension. The renal artery branches into segmental arteries, which in turn branch into interlobar arteries and then into arcuate arteries in the kidneys. While the absolute velocities of the blood flow decrease continuously from the upstream

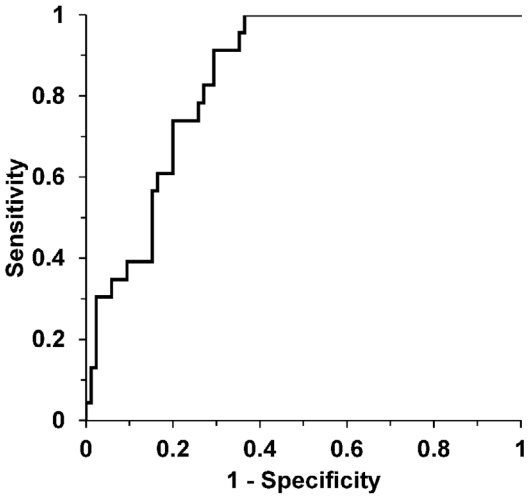

Figure 6. Receiver operating characteristic (ROC) curve for the RI. The highest sensitivity and specificity were attained at RI of 0.70, where the sensitivity was 91% (21/23, number/total number) and the specificity was 69% (59/85, number/total number), showing that 0.70 was suitable as the cutoff value. The area under the curve (AUC) was 0.85, showing moderate accuracy for predicting acute GFR reductions.

of a renal artery to the downstream of arcuate arteries, the RI does not change along this blood stream (i.e., the RI of the arcuate arteries is almost the same value as that of the upstream arteries) (27). This suggests that an increase in the RI may reflect increased stiffness and/or resistance of more peripheral vessels, namely interlobular arteries or afferent arterioles. These vessels are the resistant vessels in kidneys (12) and sclerosis of them can lead to impaired glomerular perfusion and an increased risk of acute GFR reductions (13).

We defined a decrease in GFR of ≥30% as an acute GFR reduction by RAS blockade in the present study. Most guidelines recommend that RAS inhibitors be discontinued if serum creatinine concentrations increase by ≥30% (i.e., if the GFR decreases by ≥30%) (10, 11). This is because acute increases in serum creatinine of up to 30% by RAS inhibitors have been shown to be associated with the long-term preservation of the renal function (28). The long-term renoprotective effects of RAS blockade may be great in patients with acute decreases in GFR, as reductions in intraglomerular pressure are associated with both an initial decrease in the GFR and long-term renal benefits (29). However, smaller reductions in the GFR (i.e., <30%) following RAS blockade have been shown to be associated with poor renal and cardiovascular outcomes in recent studies (29, 30), suggesting that decreases in GFR below 30% may not be safe. This is an area that requires further research. At present, it is recommended to follow the current guidelines, which allows a GFR reduction within 30%.

We described a reduction in the GFR within 14 weeks as an acute recuciton, which may be inappropriate, as a reduction in the GFR generally occurs soon after RAS blockade. We used the term "acute" here because such GFR reductions reflect hemodynamic changes following RAS blockade. We confirmed two piece of evidence indicating GFR reductions to be hemodynamic in the present cohort (data not shown): 1) the GFR recovered in all 23 cases with renal events after the doses of RAS inhibitors were reduced, 2) a smaller reduction in the GFR had occurred earlier in the follow-up after RAS blockade.

Several limitations associated with the present study warrant mention. First, this was a retrospective study and the number of patients was relatively small. As knowledge regarding the appropriate management of CKD spreads throughout the medical community, CKD patients more frequently present to our hospital after RAS inhibitors have already been initiated. This hampers the accumulation of data on the initiation of RAS inhibitors.

In the present study, only 23 patients were assessed for the outcome, as the cohort number was small (n=108). This may make it difficult to construct multivariate analysis. Because the rule of thumb that multivariate model should be constructed with a minimum of 10 outcome events per predictor can be relaxed (19), we performed a multivariate analysis with the RI and 3 established variables: the age, eGFR, and use of diuretics. We were unable to include the systolic blood pressure, urinary protein, DKD, and coronary artery disease in the multivariate analyses, even though these were shown to be significant variables in the univariate analysis. Regarding these variables, the systolic blood pressure was not included in the multivariate analysis because the degree of reduction in systolic blood pressure was associated with acute GFR reduction (Table 2). Furthermore, we found that DKD, urinary protein, and the use of diuretics were interrelated (data not shown). The urinary protein level was higher in the patients with DKD than in those without DKD and was also higher in the patients using diuretics than in those not using diuretics. Patients using diuretics were also more frequent among diabetic patients than among non-diabetic patients. Since we selected the use of diuretics as an established risk factor, setting DKD or urinary protein as variables in the multivariate analysis might reduce the statistical power. Coronary artery disease seems likely to be a mere complication of atherosclerotic diseases and unlikely to be a direct cause of acute GFR reductions.

We were able to see acute GFR reductions earlier after RAS blockade when we relaxed the end-point to GFR reductions of ≥10%, although the significance of GFR reductions of ≥10% is controversial in clinical settings (29, 30). We also confirmed in this setting that a high RI was associated with a high incidence of acute GFR reductions (data not shown). In this setting, the total number of events increased to 47, which allowed us to include more variables in the multivariate analyses. We performed multivariate Cox proportional-hazard analyses with DKD and the same variables used in the present study and confirmed that only the RI and diuretics were significant variables while DKD was not.

We reported in a 4-year follow up study that the RI could predict renal prognosis in CKD (9). Of note, the cohort in the previous study was as heterogeneous as that in the present study, indicating that the etiology of CKD, especially DKD, did not interfere with the estimated RI of CKD. Taken together, these findings suggest that the RI might be a universal marker of renal arteriosclerosis/arteriolosclerosis, as the eGFR is a marker of the glomerular function and N-acetyl-glucosaminidase/β2-microglobulin are markers of tubulointerstitial damage. The RI may therefore be able to predict acute GFR reductions regardless of etiology of CKD.

Despite these limitations, the present study provides an additional means to identify CKD patients at high risk of acute GFR reductions using a relatively easy-to-perform and common method of ultrasonography. It is notable that an RI >0.70 was able to predict acute GFR reductions following RAS blockade in such a heterogeneous cohort, suggesting that we can use an RI >0.70 in patients with any type of CKD, regardless of their underlying kidney disease, GFR, age, etc. This flexibility may be a great advantage in daily clinical practice. While the RI might not be the most important factor, the fact that RI was superior to established risk factors (GFR and age) in predicting acute GFR reductions after RAS blockade is interesting. The significance of the RI should be confirmed by further research.

In summary, we found that a high RI, as well as the use of diuretics, were risk factors for acute GFR reductions following RAS blockade. While a prospective study with a large cohort will be needed, Doppler ultrasonography might be useful diagnostic and prognostic tool in CKD.

The authors state that they have no Conflict of Interest (COI).

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