Time to re-evaluate effects of renin-angiotensin system inhibitors on renal and cardiovascular outcomes in diabetic nephropathy

Hiromichi Suzuki, Tomohiro Kikuta, Tsutomu Inoue, Ukihiro Hamada

Hiromichi Suzuki, Tomohiro Kikuta, Tsutomu Inoue, Ukihiro Hamada, Department of Nephrology and Community Health Science Center, Saitama Medical University, Saitama 350-0495, Japan

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Correspondence to: Hiromichi Suzuki, MD, PhD, Department of Nephrology and Community Health Science Center, Saitama Medical University, 38 Moroyama-machi, Iruma-gun, Saitama 350-0495, Japan. iromichi@saitama-med.ac.jp
Telephone: +81-49-2957338
Fax: +81-49-2761620
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Abstract
The use of renin-angiotensin system (RAS) inhibitors, such as angiotensin converting enzyme inhibitors/angiotensin-Ⅱ receptor blockers, to slow progression of chronic kidney disease (CKD) in a large group dominated by elderly people in the real world is not supported by available evidence. Large-scale clinical trials had many faults, among them a lack of focus on the elderly. However, it would be difficult to conduct clinical trials of a similar scale in elderly CKD patients. Besides, progression of kidney disease is often slow in elderly persons, and the vast majority of older adults with CKD will die before reaching end stage renal disease. Moreover, since it is not clear that progression of kidney disease, and even of proteinuric diabetic nephropathy, is not inhibited through the use of RAS inhibitors, the most patient-centric goal of therapy for many elderly individuals should be individualized.

Key words: Angiotensin converting enzyme inhibitors; Angiotensin receptor blockers; Dialysis; Chronic kidney disease

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Core tip: The use of renin-angiotensin system (RAS) inhibitors, such as angiotensin converting enzyme inhibitors/angiotensin-Ⅱ receptor blockers, to slow progression of chronic kidney disease in a large group dominated by elderly people in the real world is not supported by available evidence. Since it is not clear that progression of kidney disease, and even of proteinuric diabetic nephropathy, is not inhibited through the use of RAS inhibitors, the most patient-centric goal of therapy for many elderly individuals should be individualized.

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INTRODUCTION
Renin-angiotensin system (RAS) inhibitors [angiotensin
converting enzyme inhibitors (ACEI) and angiotensin-II receptor blockers (ARBs)] have been recommended for reduction of proteinuria and prevention of the progresses of diabetic nephropathy (DN) by national and international guidelines[1-6]. Especially, two landmark trials, the Reduction of Endpoints in non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL)[7] and the Irbesartan Diabetic Nephropathy Trial (IDNT)[8], established the use of ARBs as first-line drugs for hypertensive patients with DN. In line with evidence presented in these trials, ARBs are now widely used for any stage of DN. However, our developed society, examples of which are European countries, the United States, and Japan, is facing a growing elderly population. The evidence referred to in the guidelines was produced more than 10 to 20 years ago when the diabetic population was mainly 50 to 60 years of age. At present, patients with DN are older than previously, suggesting that evidence accumulated earlier does not always hold true. As a general concept, renal function in elderly people is at risk of abrupt and complete inhibition of RAS. Previously, our group proposed that in patients with advanced stage chronic kidney disease (CKD), dose reduction of ACEi was required, especially in elderly patients[9]. In comparison with ACEI, all ARBs are mainly excreted from the bile instead of the kidney[10], supporting the concept that no dose modification is needed for ARBs in advanced stage CKD patients, such as stages 4 and 5 CKD. However, recently, a small dose of ARBs was recommended for patients with advanced stages of CKD[11]. With these issues in mind, this is the best time to reconsider the role of ARBs in the choice of treatment for hypertensive patients with DN. In this mini review, the authors re-examined previous reports that discussed the effects of ARBs on renal and cardiovascular outcomes.

ARE THERE REALLY EFFECTS OF ARBS BEYOND BLOOD PRESSURE LOWERING?

During the past 10 years, in addition to their use for blood pressure reduction, ARBs and ACEI have been administered to reduce proteinuria and to inhibit the progression of renal disease. In both the RENAAL[7] and IDNT[8], unexpectedly, there were very small reductions in blood pressure in patients receiving ARBs compared with patients receiving a placebo. However, in spite of this small reduction in blood pressure, conclusions were drawn regarding factors beyond the blood pressure lowering effects of ARBs on the assumption of a similar blood pressure reduction in both placebo and ARB groups. The possibility cannot be denied that a difference in blood pressure reduction, no matter how small, between groups is important in a large-scale clinical trial[11,12]. Considering these factors, small but not significant average blood pressure changes in a large number of patients cannot be neglected. Between the levels of blood pressure and the frequencies of cardiovascular events[13] there was the log-linear association, indicating that reduction in a systolic blood pressure of 5 mmHg is producing the stroke events by 40% and myocardial infarction by 20% reduction respectively[14]. The cardiovascular endpoints reduction seen in placebo-controlled trials of ACEi or ARBs use is expected from their blood pressure lowering effects, opposing pleiotropic effects of RAS inhibitors on cardiovascular disease (CVD) events. Therefore, it is unlikely that RAS inhibition produces effects beyond lowering blood pressure.

IS THERE A CLOSE RELATION BETWEEN THE LEVELS OF PROTEINURIA OR ALBUMINURIA AND PROGRESSION OF DN?

In the RENAAL, there were a linear relationship between baseline proteinuria and the risk of the primary outcome. Furthermore, every 50% reduction in albuminuria in the first 6 mo produced a reduction of 36% in the primary endpoint and a reduction of 45% in end stage renal disease (ESRD) at the end of study. The authors proposed the renoprotection as reducing proteinuria of losartan but not their lowering blood pressure[15]. Similarly, in the IDNT, every 2-fold increase from the baseline urinary excretion of protein doubled the risk of the primary endpoint. In either treatment groups, this risk was not achieved in half with every 50% reduction in proteinuria at 1 year. These results indicated the amount of proteinuria represented as an intermediate outcome in hypertensive patients with DN[16].

In line with this evidence, an old fashioned dogmatic hypothesis assuming a course of progression of DN stated that, first, microalbuminuria appears as DN and then the estimated glomerular filtration rate (eGFR) starts to decrease[17]. This central dogmatic hypothesis was adopted by the first edition of the CKD guideline of the Kidney Disease Outcomes Quality Initiative[17] and prevailed throughout the nephrology and diabetology world. However, in spite of this guideline, in the real world, general practitioners have been suspicious of this schema. Indeed, Tsalamandris et al[18] in 1994 demonstrated that in 40 hypertensive patients with DN followed for more than 7 years, they found 3 different courses of progression of DN over the long term. The first was that in spite of no decrease in the GFR, albuminuria increased; the second was that decreases in the GFR and increases in albuminuria progressed in parallel; and the third was that without any increases in albuminuria the GFR decreased progressively. Similar findings showed that DN is easily able to progress without albuminuria[19]. These data clearly suggest that destruction of other tissue pathways might produce the
decline in renal function. Ten years after the first edition of the CKD guideline, the second version revised and accepted the concept that the levels of albuminuria and progression of DN are not always in parallel and sometimes independently change. This notion should be more greatly emphasized for general practitioners because a larger population of CKD patients with diabetes in the real world is treated by general practitioners than by specialists.

**FLAWS IN LARGE-SCALE CLINICAL TRIALS**

Onuogo[21] proposed several serious concerns about randomized controlled trials. First, the discontinuation rates of the trial drugs have been remarkably high. In the RENAAL trial[7], the discontinuation rate of both losartan and placebo was unacceptably high. More than 45% of patients on losartan and more than 50% on placebo discontinued their drug, indicating that the outcome of the trial was not reliable. In contrast, in the ALLHAT trial, only 3.5% of enrolled subjects dropped out throughout the study. In addition to these flaws, both the RENAAL and IDNT trials failed to demonstrate statistically significant reductions in all-cause mortality by ARBs as well as the rate of introduction of dialysis therapy. Secondly, since in the RENAAL there were statistically inconsistency and apparently failed in substantial risk reductions of the doubling of serum creatinine and ESRD and a relatively higher rate of death in the losartan group compared with the placebo group were observed. Thirdly, there has been selection bias for participated patients with preserved renal function at the start of study. Finally, adverse effects, especially potential nephrotoxicity of the trial drug, was not correctly reported.

**INCONSISTENCIES IN META-ANALYSES OF RAS INHIBITION IN CKD PATIENTS**

Many meta-analyses and review articles have been published with regard to RAS inhibition in CKD patients. Strippoli et al[22] evaluated the effects of ACEI/ARBs on renal outcome and all-cause mortality in hypertensive patients with DN. In their analysis, ACEI significantly reduced all-cause mortality (RR = 0.79, 95%CI: 0.67-0.99, P = 0.04) compared with placebo but ARBs did not, although there was strong supportive evidence that ARBs were beneficial, showing a 22% reduction in risk of ESRD and a 42% increase of regression from microalbuminuria to normoalbuminuria. Besides, the effect of all renal outcomes was estimated for favor of ACEI compared with ARBs. Similar findings were reported for CVD outcomes in comparison between ACEI and ARBs. The benefit of ACEI but not of ARBs on all-cause mortality could probably be due to the experimental evidences that bradykinin antagonism of ACEI but not of ARBs, and the selectivity of ARBs could not have an advantage. Despite these findings in 2004, ARBs have been widely used in clinical practice for treatment of patients with DN.

One year after publication of Strippoli et al.[22], in 2005 Cases et al.[23] reported a systematic review and meta-analysis of the effect of RAS inhibitors and other antihypertensive drugs on renal outcomes. In their report, comparisons of ACEi or ARBs with other antihypertensive drugs showed a doubling of creatinine (RR = 0.71, 95%CI: 0.49-1.04) and a small benefit on ESRD (RR = 0.89, 95%CI: 0.75-0.99). In hypertensive patients with DN, there was no benefit found in comparative trials of either ACEi or ARBs on the doubling of serum creatinine (RR = 1.09, 95%CI: 0.55-2.15), ESRD (RR = 0.89, 95%CI: 0.74-1.07), GFR, or creatinine values. They proposed that blood pressure lowering effect was a major actions of ACEI/ARBs on renal outcomes conducted as placebo-controlled trials. Therefore, in patients with DN, beyond blood pressure lowering effects still remain unclear. However, considering their data, including data from patients with diabetes in ALLHAT[24], which was not originally designed to investigate the effects of antihypertensive agents for treatment of kidney diseases, it is likely that the mixture of diabetic nephropathy and hypertensive nephrosclerosis could account for the unfavorable effects shown for ACEI. Thus, the importance of the ALLHAT may cancel any effect shown in patients with true DN; therefore, the validity should be cautiously interpreted.

Balamuthusamy et al[25] reported a meta-analysis of studies using RAS inhibitors and CVD outcomes in hypertensive CKD patients with proteinuria, which included data from ACEI and ARBs. In that meta-analysis, RAS inhibitors decreased the risk for heart failure (RR = 0.63, 95%CI: 0.47-0.86, P = 0.003) in patients with DN in comparison with the control group. Although there was a decreased risk for myocardial infarction (RR = 0.89, 95%CI: 0.79-1.01, P = 0.06) and an increased risk of stroke (RR = 1.75, 95%CI: 0.96-3.17, P = 0.07) with inhibitors of RAS, the findings were not statistically significant. Based on their analysis, the authors concluded beneficial usage with RAS inhibitors for reduction of the risk of CV outcomes and heart failure in hypertensive patients with DN in comparison with placebo. Moreover, the authors recommended that the RAS inhibitors should be used as the first line antihypertensive drugs for hypertensive patients with diabetes mellitus and proteinuria. However, these results could be cautiously interpreted because a bias with larger numbers affected the findings.

Sarafidis et al[26] demonstrated in their meta-analysis that RAS inhibition with ACEI/ARBs in hypertensive patients with DN was related with reductions in the risk for ESRD and the doubling of serum creatinine in comparison with regimens that do not include RAS inhibitors. In addition, these agents did not produce
a reduction of the risk of all-causes mortality was not brought by these agents. In their study, ARBs were reported to reduce the risk of ESRD and the doubling of serum creatinine by 22% and 21% with significance, respectively. In contrast, ACEi were not significantly associated with reduction of 30% for the risk of ESRD but was significantly done with reduction of 29% for the risk of the doubling of serum creatinine. These findings favoring ARBs over ACEi should be interpreted with caution, because the effect on both ESRD and the doubling of serum creatinine were lower in ACEi in comparison with ARBs. These discrepancies might be caused by the two pairs of studies occupying the reported effects of ACEi (Micro-HOPE[27] and DIABHYCAR[28]) and ARBs (RENAAL[10] and IDNT[36]), which are completely different in primary outcomes, participated populations and its study design.

Recently, Sarafidis et al[29] summarized that in patients with DN, data from observational analyses and surrogate outcomes (and excluding the data from non diabetic CKD patients) suggested a blood pressure of <130/80 mmHg with protein excretion > 0.3 g/dl. In non-proteinuric patients with diabetes, the main determinant of blood pressure goals leads to cardioprotection. Diastolic blood pressure <80 mmHg is warranted, whereas the optimal systolic blood pressure target lies between 130 and 140 mmHg and should be decided on an individual basis, balancing the benefits of stroke reduction and unfavorable risks of hypotension and acute renal failure[30]. However, they proposed that there is no decisive evidence for combined therapy using RAS inhibitors for any type of CKD. Furthermore, sub-analyses from cardiovascular trials suggested no clear-cut benefit of RAS inhibition in hypertensive patients with normo-albuminuria and preservation of eGFR and sometimes produced harm in susceptible individuals.

More recently, Roscioni et al[31] postulated that the value of the RAS in the progression of DN has promoted the marketing of a therapeutic strategy to aim every step in the RAS cascade. Blockade of angiotensin II by means of ACEi or ARBs is currently considered as the best option to treat DN because the renoprotective capabilities of these agents were well-established.

Among a large number of review articles, the well-designed larger studies dominated the results, whereas small studies had total weights accounting for a small percent of the total results. Thus, even if conclusions of several small studies differed from those of large-scale studies, the results of the large-scale clinical studies would prevail because of the large number of participants.

**WHY ARE ARBS NOT RENOPROTECTIVE?**

In several reports, Onuigbo of the Mayo Clinic noted that the administration of RAS inhibitors to patients with CKD sometimes produced acute kidney injury (AKI)[32-35]. He could not point out any clear-cut identifiable factors for this phenomenon, although he mentioned that many factors, such as heart failure, hypertension, infections, dehydration, etc. were found to be associated with worsening of renal failure in patients with CKD.

Suissa et al[36] assessed the long-term effect of ACEi on the risk of ESRD. They analyzed the data from a population-based cohort of all diabetic patients treated with antihypertensive drugs in the Province of Saskatchewan, Canada, between 1982 and 1986. The patients were followed up to the end of 1997 and identified as cases of end-stage renal failure. Using a nested case-control with the controls matched to each case for age, diabetes type, and duration of follow-up were analyzed. Of 6102 subjects, the 102 cases that developed ESRD were matched to 4129 controls. The adjusted RR of ESRD in relation to thiazide diuretic use, 2.5 (95%CI: 1.3-4.7) for ACEi, 0.8 (95%CI: 0.5-1.4) for blockers and 0.7 (95%CI: 0.4-1.3) for calcium channel blockers were reported. During the first 3 years after the start of follow-up, the RR of ESRD with ACEi use was 0.8 (95%CI: 0.3-2.5), but increased to 4.2 (95%CI: 2.0-9.0) after 3 years. From these data, it is clear that use of ACE-inhibitor use does not reduce the long-term risk of ESRD in diabetes. Their data also suggested that ACEi might actually produce this risk, which contribute to the continuing increases in incidence of ESRD owing to diabetes. These data coming from the real world do not validate the usefulness of ACEi in prevention of progression of DN. In the real world, a recent growth of the proportion of the elderly population is becoming worldwide. Moreover, higher number of elderly patients is brought by the increasing longevity of humans and it is producing subjects with multiple chronic diseases such as hypertension, diabetes, and CKD. These problems increase in morbidity and mortality in the elderly. More than one third of adults in the general population are 70 years over and half of them have CKD[37,38]. Whether evidence supporting current guidelines for the use ACEi/ARBs in patients with CKD can be extrapolated to this large group is unknown. O’Hare et al[39] tried to address this question and found that current guidelines addressing ACEi/ARBs use in patients with CKD are funded on evidence with limited relevance to most persons older than 70 years suffered from with CKD. Use of these agents to slow progression in this large group is not supported by available evidence. It is also not clear that slowing the progression of kidney disease represents the most patient-centric goal of therapy for many of these individuals. In elderly persons, renal function is slowly deteriorated and the vast majority of older adults with CKD will die before reaching ESRD[40,41]. In a subgroup analysis among patients who were 65 years over and enrolled in the RENAAL trial, losartan was propagated to show renoprotective effect on these older participants. This suggested that this agent has equal efficacy for elderly albuminuric patients. However, the patients in this study was less than 74 years old, indicating that it cannot be applicable for those findings
to patients who are 75 years over\textsuperscript{[42]}. Patients with a mean age of > 65 years were participated in the Telmisartan Randomized Assessment Study in ACE iNtolerant Subjects with Cardiovascular Disease\textsuperscript{[43]}. In this study, the investigators analyzed patients with organ damage but without macroalbuminuria or heart failure who could not tolerate ACEis. Either an ARB (telmisartan) or a placebo were administered to patients in addition to standard treatment and composite renal outcomes (ESRD, doubling of serum creatinine changes in eGFR, or the levels of albuminuria) were examined. Increases in albuminuria were less in patients treated with telmisartan than with placebo (32% vs 63%; \( P < 0.001 \)). Furthermore, there was no significant difference in the composite renal outcome between telmisartan and placebo (1.96% vs 1.55%). Therefore, it is unlikely that RAS inhibition is effective for patients with DN.

**CONCURRENT THERAPY WITH ARBS CAUSES UNRECOGNIZED WORSENING OF RENAL FAILURE IN ADVANCED STAGE OF CKD**

Onuigbo et al\textsuperscript{[33]} reported that the discontinuation of ACEi and/or ARBs produced reversible AKI in 100 CKD patients and that 75% of these patients were 65 years over, and 23% of these were 80 years over. Also, they examined prospectively the syndrome of worsening renal failure in CKD patients hemodynamically. In 19 of 20 patients the eGFR was increased from 27.8 ± 9.5 to 39.7 ± 14.9 mL/min per 1.73 m\(^2\) after stopping RAS inhibitors. Further, they found that ESRD in the older CKD patients (average age 75.3 years) was frequently coming from patients suffered from unilateral renal artery stenotic lesions with dual kidneys. Similar findings were reported by Ahmed et al\textsuperscript{[44]} in 52 patients with advanced stage CKD. Their mean age was 73.3 ± 1.8 years, their average eGFR 16.38 ± 1 mL/min per 1.73 m\(^2\) and urinary excretion of protein 77 ± 20 mg/gCr. Besides, 40 percent had diabetes mellitus. Twelve months after cessation of RAS inhibitors the eGFR increased significantly to 26.6 ± 2.2 mL/min per 1.73 m\(^2\). Of these patients, 61.5% had a more than 25% increase and 36.5% had an increase exceeding 50% in eGFR, although a significant decline in the eGFR slope (-0.39 ± 0.07) in the 12 mo before cessation of RAS inhibitors were found. From these findings in combination, cessation of either ACEi or ARBs could delay the progression of ESRD in the majority of those patients. It is therefore likely that ACEI/ARBs should be used in elderly hypertensive patients with CKD with great caution.

**ARE ACEI/ARBs STILL EFFECTIVE IN PREDIALYSIS PATIENTS?**

Hsu et al\textsuperscript{[45]} examined safety and the adverse effects of ASCI/ARB use for hypertensive patients with advanced CKD and anemia by a population-based longitudinal cohort study. They selected subjects who had a primary diagnosis of CKD and received an erythropoietin stimulating agent. Inclusion criteria was their baseline values for serum creatinine > 6 mg/dL and hematocrit < 28%. From January 2000 through June 30, 2009, 28497 patients were selected. Results showed that use of ACEi/ARB inhibitors significantly reduced the risk of long-term dialysis and the composite outcome, with a hazard ratio (HR) of 0.94 (95%CI: 0.92-0.97) after adjustment for various confounders. In this study, even in patients with DN, ACEi/ARB use reduced the HR of ESRD and the composite outcome of ESRD or death. However, a higher rate of hyperkalemia-associated hospitalization was found among patients treated with ACEi/ARB inhibitors than among nonusers (9.2% vs 6.7%), indicating that the use of RAS inhibitors for elderly patients with DN might be dangerous.

**ARE ARBS EFFECTIVE IN PATIENTS RECEIVING DIALYSIS?**

Heerspink et al\textsuperscript{[46]} reported a systematic review and meta-analysis of assessment of blood pressure lowering effects in dialyzed patients. In their analysis, treatment with antihypertensive agents was more closely related with lower risks of CVD events (RR = 0.71, 95%CI: 0.55-0.92, \( P = 0.009 \)), all-cause mortality (RR = 0.80, 95%CI: 0.66-0.96, \( P = 0.014 \)), and CVD mortality (RR = 0.71, 95%CI: 0.50-0.99, \( P = 0.044 \)) than control regimens. Also, their data indicated that there were no differences in blood pressure lowering effects among RAS inhibitors, \( \beta \) blockers, and calcium channel blockers in patients on dialysis. They concluded that the choice of antihypertensive agents might be chosen on the grounds of their tolerability, their side-effect, and other related variables. No specific drugs were recommended. Recently, Iseki et al\textsuperscript{[47]} reported that olmesartan, an ARB, did not lower the risks of major CV events or death among patients with hypertension on chronic dialysis. Combining these data, it is suggested that ARBs are not the only antihypertensive drug suitable for patients receiving dialysis. Left ventricular hypertrophy (LVH) is a well-established marker for future occurrence of CVD and an independent predictor of CV events\textsuperscript{[55,58-54]}. There is some evidence indicating that ARBs could reverse LVH and might confer cardiovascular event risks beyond lowering blood pressure\textsuperscript{[52,54,58-54]}. Yang et al\textsuperscript{[55]} undertook a meta-analysis to assess the effect of ARBs vs placebo or other treatments, as well as ARBs and ACEi in combination, on LVH in patients receiving dialysis. Their study demonstrated that among dialysis patients the ARBs presented a greater regression in the LVM index when compared with the non-ARB users while there was no significant difference in the left ventricular ejection fraction (LVEF) between the two groups. The ARB group had a greater therapeutic value for the left ventricular mass (LVM) index or LVEF without achieving...
significance when compared with the ACEI group. No significant alterations were found in the LVM index and LVEF between the ARB and ACEI in combination and the ARB. The authors concluded that ARBs produced a greater reduction in LVH in patients on dialysis. The ARB therapy tended to have favorable effectiveness similar to ACEI; however, the treatment with ARBs and ACEI in combination did not produce additional benefit for LVH in patients on HD. Tai et al.\(^{56}\) reported a meta-analysis to examine whether ACEI/ARBs reduced fatal and non-fatal CV events and the LVM in patients receiving HD. In their analysis, in comparison with the control groups, use of ACEI/ARBs did not produce any significant reduction of CV events. ACEI/ARB use resulted in a statistically significant reduction in the LVM (RR = 15.4, 95%CI: 7.4-23.5; P < 0.001). From these data, it could be suggested that ACEI/ARBs were effective in reducing the LVM index in patients with CKD accompanied by CVD. These data indicated that ACEI/ARBs are effective to reduce the LVM index in patients receiving HD. While ACEI/ARB use is advocated in peritoneal dialysis (PD) patients, (http://www.kidney.org/PROFESSIONALS/kdoqi/guideline_upHD_PD_VA/index.htm)\(^{57,58}\) supporting evidence is unclear. Akbari in attempting to answer questions about the efficacy of ACEI/ARBs in patients on PD carried out a systematic review with analysis of randomized controlled trials, in which treatment with ACEI/ARB inhibitors was compared with that with other antihypertensive agents. Their review revealed that there remains no clear cut evidence for the use of ACEI/ARBs for the reduction of mortality and CV events in PD patients; limited data suggested that these agents induce a slow decrease in residual renal function loss. With these facts in mind, ACEI/ARBs can be carefully used in patients on PD.

**FUTURE DIRECTIONS**

**Blood pressure measurements**

That measurements of blood pressure in these clinical trials were performed in outpatient clinic might produce erroneous results. Recently, it was shown that blood pressure measurements in medical offices can be considered to be unreliable\(^{59-61}\) because the mixture of white coat phenomenon and/or masked hypertension cannot be avoided. The recently issued NICE guidelines\(^{62}\) recommended ambulatory blood pressure monitoring instead of measurement of blood pressure in medical offices\(^{63,64}\). Therefore, blood pressure in elderly CKD patients should be measured using home blood pressure\(^{65,66}\).

**Assessment of progression of renal disease**

To date, most studies looking at outcomes related to renal disease have not used the renal trajectory as an endpoint. Most previous studies have been employing either a doubling of serum creatinine or time to start of renal replacement therapy. The latter is at most subjective assessment of trajectory\(^{69}\), Rosansky\(^{70}\) proposed the following: change in a patient's eGFR over time (renal function trajectory) is potentially more important when deciding initiation of RRT. In the elderly CKD 4 population with several comorbidities and slow decrease in renal function, the likelihood of death or cardiovascular events prior to the need for RRT should be expected before making arteriovenous access for dialysis.

**Newly developed direct renin inhibitor aliskiren**

Recently Morishita and Kusano assessed the efficacy of aliskiren on blood pressure control and renoprotection in CKD patients whose proteinuria was not reduced less than 1.0 g daily in spite of administration of ARBs\(^{71}\). It is therefore possible that aliskiren produces different action compared with ARBs in hypertensive patients with DN.

**CONCLUSION**

I would like to propose that it is time for re-evaluation of the use of ACEI/ARBs for patients with DN and that new individualized therapies for elderly people in the real world should be developed.

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