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

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Abstract

The use of renin-angiotensin system (RAS) inhibitors, such 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

Core tip: The use of renin-angiotensin system (RAS) inhibitors, such 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[6]. 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[20] 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

Onuigbo[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 inconsistence 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[7] and IDNT[8]), 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 nondiabetic CKD patients) suggested a blood pressure of < 130/80 mmHg with protein excretion > 0.3 g/d. 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[42]. Patients with a mean age of > 65 years were participated in the Telmisartan Randomized AssessmeNt Study in ACE iNtolerant Subjects with Cardiovascular Disease[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*[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*[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*[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*[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, β 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*[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[48-51]. There is some evidence indicating that ARBs could reverse LVH and might confer cardiovascular event risks beyond lowering blood pressure[52-54]. Yang *et al*[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[65-68].

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.

REFERENCES

1 **Gross JL**, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. *Diabetes Care* 2005; **28**: 164-176 [PMID: 15616252 DOI: 10.2337/diacare.28.1.164]

2 **Saruta T**. [The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004)]. *Nihon Rinsho* 2005; **63**: 952-958 [PMID: 15948375]

3 KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int* 2013; **3**: 1-119 [DOI: 10.1038/kisup.2012.73]

4 **Mancia G**, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; **31**: 1281-1357 [PMID: 23817082 DOI: 10.1097/01.hjh.0000431740.32696]

5 **James PA**, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC Jr, Svetkey LP, Taler SJ, Townsend RR, Wright JT Jr, Narva AS, Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; **311**: 507-520 [PMID: 24352797 DOI: 10.1001/jama.2013.284427]

6 **Shimamoto K**, Ando K, Fujita T, Hasebe N, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ishimitsu T, Ito M, Ito S, Itoh H, Iwao H, Kai H, Kario K, Kashihara N, Kawano Y, Kim-Mitsuyama S, Kimura G, Kohara K, Komuro I, Kumagai H, Matsuura H, Miura K, Morishita R, Naruse M, Node K, Ohya Y, Rakugi H, Saito I, Saitoh S, Shimada K, Shimosawa T, Suzuki H, Tamura K, Tanahashi N, Tsuchihashi T, Uchiyama M, Ueda S, Umemura S. The Japanese Society of Hypertension Guidelines for the Management of

Hypertension (JSH 2014). *Hypertens Res* 2014; **37**: 253-390 [PMID: 24705419 DOI: 10.1038/hr.2014.20]
7 **Brenner BM**, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; **345**: 861-869 [PMID: 11565518 DOI: 10.1056/NEJMoa011161]
8 **Lewis EJ**, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; **345**: 851-860 [PMID: 11565517 DOI: 10.1056/NEJMoa011303]
9 **Suzuki H**, Kanno Y, Ikeda N, Nakamoto H, Okada H, Sugahara S. Selection of the dose of angiotensin converting enzyme inhibitor for patients with diabetic nephropathy depends on the presence or absence of left ventricular hypertrophy. *Hypertens Res* 2002; **25**: 865-873 [PMID: 12484510 DOI: 10.1291/hypres.25.865]
10 **Israili ZH**. Clinical pharmacokinetics of angiotensin II (AT1) receptor blockers in hypertension. *J Hum Hypertens* 2000; **14** Suppl 1: S73-S86 [PMID: 10854085 DOI: 10.1038/sj.jhh.1000991]
11 **Staessen JA**, Thijs L, Li Y, Kuznetsova T, Richart T, Wang J, Birkenhäger WH. 'Beyond blood pressure' means multiple risk factor intervention, not pleiotropic antihypertensive drugs. *Curr Opin Cardiol* 2007; **22**: 335-343 [PMID: 17556887 DOI: 10.1097/HCO.0b013e3281eb8e8d]
12 **Staessen JA**, Wang JG, Birkenhäger WH. Outcome beyond blood pressure control? *Eur Heart J* 2003; **24**: 504-514 [PMID: 12643883 DOI: 10.1016/S0195-668X(02)00797-2]
13 **Lewington S**, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**: 1903-1913 [PMID: 12493255 DOI: 10.1016/S0140-6736(02)11911-8]
14 **Turnbull F**. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003; **362**: 1527-1535 [PMID: 14615107 DOI: 10.1016/S0140-6736(03)14739-3]
15 **de Zeeuw D**, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, Snapinn S, Cooper ME, Mitch WE, Brenner BM. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. *Kidney Int* 2004; **65**: 2309-2320 [PMID: 15149345 DOI: 10.1111/j.1523-1755.2004.00653.x]
16 **Atkins RC**, Briganti EM, Lewis JB, Hunsicker LG, Braden G, Champion de Crespigny PJ, DeFerrari G, Drury P, Locatelli F, Wiegmann TB, Lewis EJ. Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. *Am J Kidney Dis* 2005; **45**: 281-287 [PMID: 15685505 DOI: 10.1053/j.ajkd.2004.10.019]
17 **Levey AS**, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003; **139**: 137-147 [PMID: 12859163 DOI: 10.7326/0003-4819-139-2-200307150-00013]
18 **Tsalamandris C**, Allen TJ, Gilbert RE, Sinha A, Panagiotopoulos S, Cooper ME, Jerums G. Progressive decline in renal function in diabetic patients with and without albuminuria. *Diabetes* 1994; **43**: 649-655 [PMID: 8168641 DOI: 10.2337/diab.43.5.649]
19 **Perkins BA**, Ficociello LH, Roshan B, Warram JH, Krolewski AS. In patients with type 1 diabetes and new-onset microalbuminuria the development of advanced chronic kidney disease may not require progression to proteinuria. *Kidney Int* 2010; **77**: 57-64 [PMID: 19847154 DOI: 10.1038/ki.2009.399]
20 **Rocco MV**, Berns JS. KDOQI clinical practice guideline for diabetes and CKD: 2012 Update. *American Journal of Kidney Diseases* 2012; **60**: 850-886 [DOI: 10.1053/j.ajkd.2012.07.005]
21 **Onuigbo MA**. Causes of renal failure in patients with type 2 diabetes mellitus. *JAMA* 2003; **290**: 1855; author reply 1855-1856 [PMID: 14532312 DOI: 10.1001/jama.290.14.1855-a]
22 **Strippoli GF**, Craig M, Deeks JJ, Schena FP, Craig JC. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. *BMJ* 2004; **329**: 828 [PMID: 15459003 DOI: 10.1136/bmj.38237.585000.7C]
23 **Casas JP**, Chua W, Loukogeorgakis S, Vallance P, Smeeth L, Hingorani AD, MacAllister RJ. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet* 2005; **366**: 2026-2033 [PMID: 16338452 DOI: 10.1016/S0140-6736(05)67814-2]
24 **de Zeeuw D**, Lewis EJ, Remuzzi G, Brenner BM, Cooper ME. Renoprotective effects of renin-angiotensin-system inhibitors. *Lancet* 2006; **367**: 899-900; author reply 900-902 [PMID: 16546533 DOI: 10.1016/S0140-6736(06)68374-8]
25 **Balamuthusamy S**, Srinivasan L, Verma M, Adigopula S, Jalandhara N, Hathiwala S, Smith E. Renin angiotensin system blockade and cardiovascular outcomes in patients with chronic kidney disease and proteinuria: a meta-analysis. *Am Heart J* 2008; **155**: 791-805 [PMID: 18440325 DOI: 10.1016/j.ahj.2008.01.031]
26 **Sarafidis PA**, Stafylas PC, Kanaki AI, Lasaridis AN. Effects of renin-angiotensin system blockers on renal outcomes and all-cause mortality in patients with diabetic nephropathy: an updated meta-analysis. *Am J Hypertens* 2008; **21**: 922-929 [PMID: 18535536 DOI: 10.1038/ajh.2008.206]
27 Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 2000; **355**: 253-259 [PMID: 10675071 DOI: 10.1016/S0140-6736(99)12323-7]
28 **Marre M**, Lievre M, Chatellier G, Mann JF, Passa P, Ménard J. Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). *BMJ* 2004; **328**: 495 [PMID: 14960504 DOI: 10.1136/bmj.37970.629537.0D]
29 **Sarafidis PA**, Ruilope LM. Aggressive blood pressure reduction and renin-angiotensin system blockade in chronic kidney disease: time for re-evaluation? *Kidney Int* 2014; **85**: 536-546 [PMID: 24048382 DOI: 10.1038/ki.2013.355]
30 **American Diabetes Association**. Standards of medical care in diabetes--2013. *Diabetes Care* 2013; **36** Suppl 1: S11-S66 [PMID: 23264422 DOI: 10.2337/dc13-S011]
31 **Roscioni SS**, Heerspink HJ, de Zeeuw D. The effect of RAAS blockade on the progression of diabetic nephropathy. *Nat Rev Nephrol* 2014; **10**: 77-87 [PMID: 24296623 DOI: 10.1038/nrneph.2013.251]
32 **Onuigbo MA**, Onuigbo NT. Late-onset renal failure from RAAS blockade. *Kidney Int* 2006; **70**: 1378-1379 [PMID: 16988746 DOI: 10.1038/sj.ki.5001648]
33 **Onuigbo MA**, Onuigbo NT. Late-onset renal failure from angiotensin blockade (LORFFAB) in 100 CKD patients. *Int Urol Nephrol* 2008; **40**: 233-239 [PMID: 18196471 DOI: 10.1007/s11255-007-9299-2]
34 **Onuigbo MA**. Reno-prevention vs. reno-protection: a critical re-appraisal of the evidence-base from the large RAAS blockade trials after ONTARGET--a call for more circumspection. *QJM* 2009; **102**: 155-167 [PMID: 19098074 DOI: 10.1093/qjmed/hcn142]
35 **Onuigbo MA**. Is renoprotection with RAAS blockade a failed paradigm? Have we learnt any lessons so far? *Int J Clin Pract* 2010; **64**: 1341-1346 [PMID: 20716141 DOI: 10.1111/j.1742-1241.2010.02448.x]
36 **Suissa S**, Hutchinson T, Brophy JM, Kezouh A. ACE-inhibitor use and the long-term risk of renal failure in diabetes. *Kidney Int* 2006; **69**: 913-919 [PMID: 16518351 DOI: 10.1038/sj.ki.5000159]
37 **Imai E**, Horio M, Watanabe T, Iseki K, Yamagata K, Hara S, Ura N, Kiyohara Y, Moriyama T, Ando Y, Fujimoto S, Konta T, Yokoyama H, Makino H, Hishida A, Matsuo S. Prevalence of chronic kidney disease in the Japanese general population. *Clin Exp Nephrol* 2009; **13**: 621-630 [PMID: 19513802 DOI: 10.1007/s10157-009-0199-x]
38 **Coresh J**, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P,

Van Lente F, Levey AS. Prevalence of chronic kidney disease in the United States. *JAMA* 2007; **298**: 2038-2047 [PMID: 17986697 DOI: 10.1001/jama.298.17.2038]

39 **O'Hare AM**, Hailpern SM, Pavkov ME, Rios-Burrows N, Gupta I, Maynard C, Todd-Stenberg J, Rodriguez RA, Hemmelgarn BR, Saran R, Williams DE. Prognostic implications of the urinary albumin to creatinine ratio in veterans of different ages with diabetes. *Arch Intern Med* 2010; **170**: 930-936 [PMID: 20548004 DOI: 10.1001/archinternmed.2010.129]

40 **Gullion CM**, Keith DS, Nichols GA, Smith DH. Impact of comorbidities on mortality in managed care patients with CKD. *Am J Kidney Dis* 2006; **48**: 212-220 [PMID: 16860186 DOI: 10.1053/j.ajkd.2006.04.083]

41 **O'Hare AM**, Choi AI, Bertenthal D, Bacchetti P, Garg AX, Kaufman JS, Walter LC, Mehta KM, Steinman MA, Allon M, McClellan WM, Landefeld CS. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol* 2007; **18**: 2758-2765 [PMID: 17855638 DOI: 10.1681/ASN.2007040422]

42 **Winkelmayer WC**, Zhang Z, Shahinfar S, Cooper ME, Avorn J, Brenner BM. Efficacy and safety of angiotensin II receptor blockade in elderly patients with diabetes. *Diabetes Care* 2006; **29**: 2210-2217 [PMID: 17003295 DOI: 10.2337/dc06-0570]

43 **Mann JF**, Schmieder RE, Dyal L, McQueen MJ, Schumacher H, Pogue J, Wang X, Probstfield JL, Avezum A, Cardona-Munoz E, Dagenais GR, Diaz R, Fodor G, Maillon JM, Rydén L, Yu CM, Teo KK, Yusuf S. Effect of telmisartan on renal outcomes: a randomized trial. *Ann Intern Med* 2009; **151**: 1-10, W1-2 [PMID: 19451556 DOI: 10.7326/0003-4819-151-1-200907070-00122]

44 **Ahmed AK**, Kamath NS, El Kossi M, El Nahas AM. The impact of stopping inhibitors of the renin-angiotensin system in patients with advanced chronic kidney disease. *Nephrol Dial Transplant* 2010; **25**: 3977-3982 [PMID: 19820248 DOI: 10.1093/ndt/gfp511]

45 **Hsu TW**, Liu JS, Hung SC, Kuo KL, Chang YK, Chen YC, Hsu CC, Tarng DC. Renoprotective effect of renin-angiotensin-aldosterone system blockade in patients with predialysis advanced chronic kidney disease, hypertension, and anemia. *JAMA Intern Med* 2014; **174**: 347-354 [PMID: 24343093]

46 **Heerspink HJ**, Ninomiya T, Zoungas S, de Zeeuw D, Grobbee DE, Jardine MJ, Gallagher M, Roberts MA, Cass A, Neal B, Perkovic V. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials. *Lancet* 2009; **373**: 1009-1015 [PMID: 19249092 DOI: 10.1016/S0140-6736(09)60212-9]

47 **Iseki K**, Shoji T, Nakai S, Watanabe Y, Akiba T, Tsubakihara Y. Higher survival rates of chronic hemodialysis patients on anti-hypertensive drugs. *Nephron Clin Pract* 2009; **113**: c183-c190 [PMID: 19672117 DOI: 10.1159/000232600]

48 **Faul C**. Fibroblast growth factor 23 and the heart. *Curr Opin Nephrol Hypertens* 2012; **21**: 369-375 [PMID: 22531163 DOI: 10.1097/MNH.0b013e32835422c4]

49 **Quinn U**, Tomlinson LA, Cockcroft JR. Arterial stiffness. *JRSM Cardiovasc Dis* 2012; **1**: pii: cvd.2012.012024 [PMID: 24175072 DOI: 10.1258/cvd.2012.012024]

50 **Sano M**. Multifaceted approach to analyzing the pathogenesis of cardiovascular disease. *Circ J* 2012; **76**: 2521-2529 [PMID: 23037324 DOI: 10.1253/circj.CJ-12-1063]

51 **Wright J**, Hutchison A. Cardiovascular disease in patients with chronic kidney disease. *Vasc Health Risk Manag* 2009; **5**: 713-722 [PMID: 19756163 DOI: 10.2147/VHRM.S6206]

52 **Barrios V**, Calderón A, Escobar C, Barrios S, Navarro-Cid J, González-Pedel V, Vegazo O, Fernandez R. Electrocardiographic left ventricular hypertrophy regression induced by an angiotensin receptor blocker-based regimen in daily clinical practice: the SARA study. *J Hypertens* 2007; **25**: 1967-1973 [PMID: 17762663 DOI: 10.1097/HJH.0b013e3282257145]

53 **Barrios V**, Escobar C, Calderón A, Echarri R, Barrios S, Navarro-Cid J. Electrocardiographic left ventricular hypertrophy regression induced by an angiotensin receptor blocker-based regimen in hypertensive patients with diabetes: data from the SARA study. *J Renin Angiotensin Aldosterone Syst* 2009; **10**: 168-173 [PMID: 19651760 DOI: 10.1177/1470320309343596]

54 **Inaba S**, Iwai M, Furuno M, Kanno H, Senba I, Okayama H, Mogi M, Higaki J, Horiuchi M. Temporary treatment with AT1 receptor blocker, valsartan, from early stage of hypertension prevented vascular remodeling. *Am J Hypertens* 2011; **24**: 550-556 [PMID: 21293390 DOI: 10.1038/ajh.2011.6]

55 **Yang LY**, Ge X, Wang YL, Ma KL, Liu H, Zhang XL, Liu BC. Angiotensin receptor blockers reduce left ventricular hypertrophy in dialysis patients: a meta-analysis. *Am J Med Sci* 2013; **345**: 1-9 [PMID: 23018492 DOI: 10.1097/MAJ.0b013e318249d387]

56 **Tai DJ**, Lim TW, James MT, Manns BJ, Tonelli M, Hemmelgarn BR. Cardiovascular effects of angiotensin converting enzyme inhibition or angiotensin receptor blockade in hemodialysis: a meta-analysis. *Clin J Am Soc Nephrol* 2010; **5**: 623-630 [PMID: 20133488 DOI: 10.2215/CJN.07831109]

57 **Peritoneal Dialysis Adequacy Work Group**. Clinical practice guidelines for peritoneal dialysis adequacy. *Am J Kidney Dis* 2006; **48** Suppl 1: S98-129 [PMID: 16813998]

58 **Peritoneal Dialysis Adequacy 2006 Work Group**. Clinical practice guidelines for peritoneal adequacy, update 2006. *Am J Kidney Dis* 2006; **48** Suppl 1: S91-S97 [PMID: 16813997 DOI: 10.1053/j.ajkd.2006.05.016]

59 **Imai Y**, Hosaka M, Elnagar N, Satoh M. Clinical significance of home blood pressure measurements for the prevention and management of high blood pressure. *Clin Exp Pharmacol Physiol* 2014; **41**: 37-45 [PMID: 23763494 DOI: 10.1111/1440-1681.12142]

60 **Kario K**. Orthostatic hypertension-a new haemodynamic cardiovascular risk factor. *Nat Rev Nephrol* 2013; **9**: 726-738 [PMID: 24189649 DOI: 10.1038/nrneph.2013.224]

61 **Krakoff LR**. Ambulatory blood pressure improves prediction of cardiovascular risk: implications for better antihypertensive management. *Curr Atheroscler Rep* 2013; **15**: 317 [PMID: 23423525 DOI: 10.1007/s11883-013-0317-9]

62 **Krause T**, Lovibond K, Caulfield M, McCormack T, Williams B. Management of hypertension: summary of NICE guidance. *BMJ* 2011; **343**: d4891 [PMID: 21868454 DOI: 10.1136/bmj.d4891]

63 **Niiranen TJ**, Mäki J, Puukka P, Karanko H, Jula AM. Office, home, and ambulatory blood pressures as predictors of cardiovascular risk. *Hypertension* 2014; **64**: 281-286 [PMID: 24842916 DOI: 10.1161/HYPERTENSIONAHA.114.03292]

64 **Stergiou GS**, Asayama K, Thijs L, Kollias A, Niiranen TJ, Hozawa A, Boggia J, Johansson JK, Ohkubo T, Tsuji I, Jula AM, Imai Y, Staessen JA. Prognosis of white-coat and masked hypertension: International Database of HOme blood pressure in relation to Cardiovascular Outcome. *Hypertension* 2014; **63**: 675-682 [PMID: 24420553 DOI: 10.1161/HYPERTENSIONAHA.113.02741]

65 **Suzuki H**, Nakamoto H, Okada H, Sugahara S, Kanno Y. Self-measured systolic blood pressure in the morning is a strong indicator of decline of renal function in hypertensive patients with non-diabetic chronic renal insufficiency. *Clin Exp Hypertens* 2002; **24**: 249-260 [PMID: 12069356 DOI: 10.1081/CEH-120004229]

66 **Cohen DL**, Huan Y, Townsend RR. Ambulatory blood pressure in chronic kidney disease. *Curr Hypertens Rep* 2013; **15**: 160-166 [PMID: 23595357 DOI: 10.1053/j.ajkd.2013.12.015]

67 **Okada T**, Nakao T, Matsumoto H, Nagaoka Y, Tomaru R, Iwasawa H, Wada T. Prognostic significance of home blood pressure control on renal and cardiovascular outcomes in elderly patients with chronic kidney disease. *Hypertens Res* 2009; **32**: 1123-1129 [PMID: 19816503 DOI: 10.1038/hr.2009.165]

68 **Uchida HA**, Nakamura Y, Norii H, Kaihara M, Hanayama Y, Sada KE, Wada J, Shikata K, Makino H. Insufficient control of morning home blood pressure in Japanese patients with hypertension associated with diabetes mellitus. *J Diabetes Investig* 2010; **1**: 266-272 [PMID: 24843442 DOI: 10.1111/j.2040-1124.2010.00056.x]

69 **Li L**, Astor BC, Lewis J, Hu B, Appel LJ, Lipkowitz MS, Toto RD, Wang X, Wright JT, Greene TH. Longitudinal progression trajectory of GFR among patients with CKD. *Am J Kidney Dis* 2012; **59**: 504-512 [PMID: 22284441 DOI: 10.1053/j.ajkd.2011.12.009]

70 **Rosansky SJ**. Renal function trajectory is more important than

chronic kidney disease stage for managing patients with chronic kidney disease. *Am J Nephrol* 2012; **36**: 1-10 [PMID: 22699366 DOI: 10.1159/000339327]

71 **Morishita Y**, Kusano E. Direct Renin inhibitor: aliskiren in chronic kidney disease. *Nephrourol Mon* 2013; **5**: 668-672 [PMID: 23577328 DOI: 10.5812/numonthly.3679]

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