Awaiting the OSCAR subanalysis of subjects according to the presence of proteinuria

To the Editor: We read with great interest the article describing the OSCAR Study:[1] compared with high-dose angiotensin receptor blocker (ARB) monotherapy, the ARB/calcium-channel blocker combination conferred a greater reduction in cardiovascular risk in patients with chronic kidney disease (CKD), as defined by a glomerular filtration rate <60 ml/min per 1.73 m^2.

Our study group proposes the following: (1) high sodium sensitivity originates in impaired renal sodium excretion and thus causes sodium retention to augment the cardiovascular burden and (2) the steady-state amount of sodium intake ($U_{Na}V$, *y*-axis) could be represented as a first-order function of blood pressure (MAP, *x*-axis): $U_{Na}V = B \times (MAP\text{-}A)$, where A and B represent the extrapolated x-intercept and the slope of the pressure-natriuresis curve, respectively.[2] Sodium sensitivity index (SI) was interpreted as the reciprocal of the slope (B) and MAP–A as the net effective filtration pressure gradient across the glomerular capillaries (ΔPF):$(MAP\text{-}A) = \Delta PF = SI \times U_{Na}V$. This equation indicates that patients with high sodium sensitivity, i.e., the cardiovascular burden, are predisposed toward glomerular hypertension, resulting in proteinuria. ARB can achieve a lower steady sodium balance, and the diuretic effect can be enhanced by sodium deprivation.[3] These findings can explain why ARBs prevented the cardiovascular events more effectively, under a lower sodium diet in *post hoc* analysis of the RENAAL and IDNT studies;[4] that is, the effect of ARBs on sodium dynamics is the key to sever cardiorenal connection. Therefore, we eagerly await the OSCAR subanalysis in which subjects are examined according to the presence of proteinuria, a clinical clue to high sodium sensitivity.

1. Kim-Mitsuyama S, Ogawa H, Matsui K *et al.* An angiotensin II receptor blocker–calcium channel blocker combination prevents cardiovascular events in elderly high-risk hypertensive patients with chronic kidney disease better than high-dose angiotensin II receptor blockade alone. *Kidney Int* 2013; **83**: 167–176.
2. Kimura G, Brenner BM. Implications of the linear pressure-natriuresis relationship and importance of sodium sensitivity in hypertension. *J Hypertens* 1997; **15**: 1055–1061.
3. Hall JE, Guyton AC, Smith MJ Jr *et al.* Chronic blockade of angiotensin II formation during sodium deprivation. *Am J Physiol* 1979; **237**: F424–F432.
4. Lambers Heerspink HJ, Holtkamp FA, Parving HH *et al.* Moderation of dietary sodium potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers. *Kidney Int* 2012; **82**: 330–337.

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The Authors Reply: We read with interest the letter by Fukuda and Miura,[1] in response to our article. As they commented, the degree of sodium intake is known to significantly affect the effectiveness of angiotensin II receptor blockers (ARBs) in patients with chronic kidney disease. However, in the OSCAR study, we did not monitor urinary sodium levels and therefore, the role of salt sensitivity in the OSCAR study is unclear. Furthermore, it is unknown whether the elderly patients enrolled in the OSCAR study exhibited glomerular hypertension or not. Unfortunately, measurement of urinary protein or albumin was not performed in the OSCAR study. However, 680 patients of 1164 enrolled patients had urinary protein test by dipstick

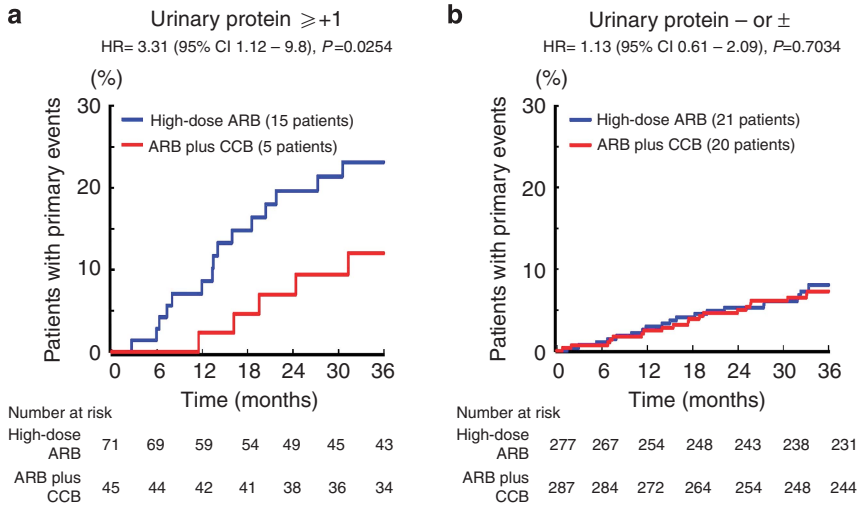

Figure 1 | Kaplan–Meier curves. For primary composite end points during the follow-up period in patients (**a**) with and (**b**) without proteinuria. ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio.

analysis at baseline. According to the request, we present the subgroup analysis data according to the presence or absence of proteinuria at baseline (Figure 1). In patients with urinary protein +1 or greater, more primary events (a composite of cardiovascular events and non-cardiovascular death) occurred in the high-dose ARB group than in the ARB + calcium channel blocker (CCB) group (15 vs 5 events, hazard ratio (HR), 3.31, 95% confidence interval (CI) 1.12–9.8; $P = 0.0254$). On the other hand, in patients with urinary protein – or ±, the incidence of primary events was similar between the two treatments (HR = 1.13, 95% CI 0.61–2.09; $P = 0.7034$). Thus, our subanalysis suggests that ARB + CCB combination, compared to high-dose ARB, conferred greater benefit in prevention of cardiovascular events in patients with proteinuria, being consistent with the findings[2] on patients with estimated glomerular filtration rate of <60 ml/min per 1.73 m^2. The superiority of ARB + CCB combination might be at least in part attributed to the potential improvement of renal blood flow through arterial vasodilation, because the elderly patients are characterized by significant vascular stiffness. However, further clinical study is required to define our proposal, as the number of patients in the OSCAR study is limited.

1. Fukuda M, Miura T. Awaiting the OSCAR subanalysis of subjects according to the presence of proteinuria. *Kidney Int* 2013; **84**: 1047.
2. Kim-Mitsuyama S, Ogawa H, Matsui K *et al.* An angiotensin II receptor blocker-calcium channel blocker combination prevents cardiovascular events in elderly high-risk hypertensive patients with chronic kidney disease better than high-dose angiotensin II receptor blockade alone. *Kidney Int* 2013; **83**: 167–176.

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Why are complements activated in anti-neutrophil cytoplasmic antibody–associated vasculitis?

To the Editor: We read with great interest the recent contribution by Gou *et al.*[1] They investigated the circulating complement activation profiles of patients with anti-neutrophil cytoplasmic antibody–associated vasculitis (AAV) and found that complement activation markers such as plasma levels of C3a, C5a, soluble C5b-9, and Bb were significantly higher in active stage than during remission of AAV.[1] However, they did not explicate the possible mechanisms. We would like to suggest a possible pathomechanism of complement activation in AAV.

Vachino *et al.*[2] previously reported that, in most cancer patients who were treated with high-dose recombinant interleukin-2 (IL-2), pretreatment plasma levels of C3a, Ba, Bb, and SC5b-9 were comparable with those measured in normal donor plasma. However, C3a levels had increased 15.6-fold at the end of the treatment course. Bb and SC5b-9 levels had also increased 5.0-fold.[2] Furthermore, Arranz *et al.*[3] found that the concentrations of serum-soluble interleukin-2 receptor (sIL-2R) were significantly higher in AAV during the active phase than during the inactive phase ($P<0.05$), and serum sIL-2R levels were significantly increased in these patients than a group of healthy subjects ($P<0.05$). In addition, serum sIL-2R levels correlated with serum levels of C-reactive protein ($P<0.05$).[3]

Therefore, there is a possibility that complement systems could be activated by IL-2, which might be increased at the active stage of AAV. However, further studies are necessary to elucidate the exact molecular signaling pathway of IL-2 influence on the complement system and to evaluate why AAV generally does not show hypocomplementemia or complement deposition in the kidney.

1. Gou S-J, Yuan J, Chen M *et al.* Circulating complement activation in patients with anti-neutrophil cytoplasmic antibody–associated vasculitis. *Kidney Int* 2012; **83**: 129–137.
2. Vachino G, Gelfand JA, Atkins MB *et al.* Complement activation in cancer patients undergoing immunotherapy with interleukin-2 (IL-2): binding of complement and C-reactive protein by IL-2-activated lymphocytes. *Blood* 1991; **78**: 2505–2513.
3. Arranz O, Ara J, Rodríguez R *et al.* Serum levels of soluble interleukin-2 receptor in patients with ANCA-associated vasculitis. *J Nephrol* 2000; **13**: 59–64.

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The Authors Reply: We appreciate the interest of Kim *et al.*[1] in our study on complement in ANCA-associated vasculitis (AAV).[2] We agree that further exploration of the mechanisms of complement activation in AAV would be of great interest.

The possible mechanisms of complement activation in AAV have been previously studied by Xiao *et al.*[3] Incubating normal human neutrophils, primed by tumor necrosis factor-α, with