Addition of aliskiren to angiotensin receptor blocker improves ambulatory blood pressure profile and cardiorenal function better than addition of benazepril in chronic kidney disease

（慢性腎臓病におけるアンジオテンシン受容体拮抗薬治療へのアリスキレン併用療法は、ベナゼプリル併用療法と比較して24時間自由行動下血圧指標と心・腎機能を改善する）

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1. Introduction

Activation of the renin-angiotensin system (RAS) has been demonstrated to be involved in both the pathogenesis of CKD and its cardiovascular complications, and blockade of the RAS by angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II (Ang II) type 1 receptor (AT1R) blockers (ARB) has been shown to exert various protective effects on CKD progression and cardiovascular complications, at least partially, through a reduction in albuminuria (Ito S, 2010; Holtkamp FA et al., 2011).

Ambulatory blood pressure (BP) monitoring has allowed an accurate diagnosis of hypertension (Hodgkinson J et al., 2011; Lovibond K et al., 2011) and determination of the BP and heart rate (HR) circadian rhythms under different pathophysiological conditions, including hypertension and CKD. Previous studies have shown that an altered ambulatory BP and HR profile is related to renal deterioration and cardiovascular complication in hypertension and CKD patients (Kikuya M et al., 2000; Minutolo R et al., 2011).

In this study, we examined the effects of aliskiren, a direct renin inhibitor, when added to ARB, on the ambulatory BP and HR profile and the cardiorenal function in hypertensive CKD patients with residual albuminuria.

2. Subjects & Methods

Patient were eligible for the study based on following criteria: (1) age of 20 years or older, (2) clinic systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 80 mmHg, (3) albuminuria defined as a UACR ≥ 30 mg/g·creatinine despite already receiving the standard dose of ARB treatment for over 4 weeks before this study. At baseline and 24 weeks after the treatment, 24-h ambulatory BP and HR monitoring and echocardiography, measurements of biochemical parameters were performed. The primary outcomes were comparison of the changes in urinary albumin creatinine ratio (UACR) and left ventricular mass index (LVMI) from baseline
to after 24-weeks treatment between the addition of aliskiren and benazepril. Secondary outcomes were comparison of the changes in ambulatory BP and HR profile, oxidative stress and RAS components between the addition of aliskiren and benazepril.

3. Results

Thirty-six hypertensive CKD patients were randomly assigned to the aliskiren add-on group (n=18) or the benazepril add-on group (n=18). Both the aliskiren and benazepril groups achieved the clinic BP goal (clinic BP<130/80 mmHg), with no significant differences between groups (aliskiren vs benazepril; systolic BP, -9.8±1.8 vs -13.1±2.0, P=0.226; diastolic BP, -6.9±1.5 vs -6.6±1.5, P=0.904). The 24-hr, daytime and nighttime ambulatory systolic/diastolic BP were comparably lowered in the aliskiren and benazepril groups after the 24-weeks treatment period. With respect to the effects of the treatment on short-term BP variability, the nighttime systolic short-term BP variability in the aliskiren add-on group was significantly lower than in the benazepril add-on group after 24 weeks of treatment.

Table 1 shows that change in UACR was more decreased in the aliskiren add-on group than in the benazepril add-on group. The eGFR was comparable in the two groups.

**Table 1.** Comparison of the effects of add-on anti-hypertensive treatments on parameters of renal function, oxidative stress and RAS components

| Parameter                  | Benazepril | Aliskiren | Δ    | Benazepril | Aliskiren | Δ    |
|----------------------------|------------|-----------|------|------------|-----------|------|
| Estimated GFR (mL/min/1.73m²) | 43.1±4.3  | 40.1±4.6  | -2.9±1.8 | 48.2±5.6  | 46.1±5.6  | -2.1±0.9 |
| UACR (mg/g · Cr)           | 1309±456   | 1340±445  | 32±131 | 1824±683   | 1433±589  | -391±135*  |
| Pentosidine (nm/L)         | 40.7±5.0   | 36.7±5.7  | -4.0±6.9 | 32.4±2.8   | 32.3±3.9  | -0.1±3.0  |
| PRA (ng/mL/h)              | 1.9±0.5    | 3.2±1.6   | 1.3±1.7 | 2.0±0.5    | 0.5±0.2*  | -1.5±0.5*  |
| ARC (pg/mL)                | 18.3±4.4   | 46.8±32.4 | 28.5±33.2 | 19.6±3.7   | 136.0±32.8* | 116.4±31.2** |
| PAC (pg/mL)                | 55.9±10.9  | 49.3±9.7  | -6.5±8.3 | 81.3±17.1  | 68.4±11.7 | -13.0±6.7  |
| Serum potassium (mEq/L)    | 4.2±0.2    | 4.2±0.2   | 0.0±0.2 | 4.2±0.1    | 4.3±0.1   | 0.1±0.1   |

Values are means ± SE. RAS, renin-angiotensin system; GFR, glomerular filtration rate; UACR, urinary albumin/creatinine ratio; PRA, plasma renin activity; ARC, active renin...
concentration; PAC, plasma aldosterone concentration. \*P < 0.05 vs benazepril group; **P < 0.01 vs benazepril group.

In addition, LVMI was significantly lower in the aliskiren add-on group than in the benazepril add-on group after treatment. In the aliskiren add-on group, multivariate linear regression analysis showed a significant association between changes in UACR and changes in nighttime systolic BP. Furthermore, there were significant associations between changes in LVMI and changes in daytime HR variability, as well as between changes in the LVMI and changes in the plasma aldosterone concentration in the aliskiren add-on group.

### 4. Discussion

Sympathetic predominance in CKD patients is reported to contribute to the development of cardiac hypertrophy despite antihypertensive treatment (Siddiqi L et al., 2010). Since aliskiren was shown to reduce sympathetic nerve activity with BP lowering in CKD patients in a previous study (Siddiqi L et al., 2011), the results of the present study appear to indicate that aliskiren-mediated inhibition of sympathetic nerve activity, as revealed by the increase in HR variability in the aliskiren group, may be involved in the suppression of cardiac hypertrophy. The results of the “Aliskiren in Left Ventricular Hypertrophy” (ALLAY) study showed that the aliskiren-mediated suppression of aldosterone is involved in the regression of cardiac hypertrophy in hypertension (Pouleur AC et al., 2011), which would be consistent with the results of present study.

The addition of aliskiren to the ARB resulted in an additional reduction in albuminuria in CKD patients in the present study and those with diabetic nephropathy in the “Aliskiren in the Evaluation of Proteinuria in Diabetes” (AVOID) study (Parving HH et al., 2008). On the other hand, there was an increase in adverse events, such as hypotension and hyperkalemia, and no apparent benefits among patients randomized to aliskiren in the “Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints” (ALTITUDE) trial prompted early study termination (Parving HH et al., 2012). In addition, the combination therapy with telmisartan and ramipril reduced albuminuria to a greater extent than ramipril monotherapy, but it worsened the decline in estimated glomerular filtration rate (eGFR) with an increased risk of hypotention, hyperkalemia and acute renal impairment, especially in the subgroup with no history of hypertension, in post hoc analysis of the “Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint” (ONTARGET) trial (Mann JF et al., 2008). Therefore, these dual RAS blockade with combination of the highest dose of RAS inhibitors in high-risk
patients without hypertension might increase hypotenion and not show beneficial effects in these studies.

In this study, it suggest that aliskiren add-on therapy may exert its cardiorenal protective effects, at least partly, through the improvement in ambulatory BP and HR profile and the suppression of aldosterone in hypertensive CKD patients with albuminuria who had been already treated with ARB.

5. References

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6. Publication list

**Ohsawa M**, Tamura K, Kanaoka T, Wakui H, Maeda A, Dejima T, Azushima K, Uneda K, Kobayashi R, Tsurumi-Ikeya Y, Toya Y, Fujikawa T, Umemura S.(2013). Addition of aliskiren to Angiotensin receptor blocker improves ambulatory blood pressure profile and cardiorenal function better than addition of benazepril in chronic kidney disease. *Int J Mol Sci.* 14,15361-15375. doi: 10.3390/IJMS.140815361.
論文目録

I. 主論文
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II. 副論文
なし

III. 参考論文
なし