Supplementary data to the study of ESRD Map in Japan

To the Editor: Our recent study [1] has added more convincing evidence for renoprotection of angiotensin-converting enzyme inhibitors (ACEIs) by asking whether the use of ACEIs may explain our previously disclosed important findings [i.e., regional variations in incidence of end-stage renal disease (ESRD)] in Japan [2]. In this study, we used the amounts of expense spent on ACEIs as an explanation. This was, however, a surrogate marker for a real use of ACEIs. Therefore, we next retrieved data regarding the real use of ACEIs from Nephro-Database in one large nephrology care center in Japan (Kimitsu Hospital) [3]. The rationale for using this database was that the hospital was the only nephrology center in its catchment area, excluding patients and hospital-based bias, and, more importantly, that the age-, sex- and underlying disease-adjusted cumulative incidence of ESRD was significantly higher than other areas in Japan, for example, in 1997, 178.9 per 1 million in the area, and 127.1 in Japan as a whole, allowing us to compare ACEIs with other potential risk factors in the area where progression of renal failure was far accelerated. We conducted a retrospective chart review of 74 consecutive patients who had started renal replacement therapy (RRT) between January 1993 and December 2000. Multiple logistic regression analysis clearly demonstrated an independently favorable role of “a usage of ACEIs (dose over the least officially recommended one)” against inception of RRT among antihypertensive agents (Table 1). Thus, we could confirm the conclusion [1] in a local area of Japan on a micro level, as well.

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Table 1. Multivariate logistic regression analysis of risk factors associated with inception of renal replacement therapy

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (vs. female)</td>
<td>1.3 (1.1–2.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Age (vs. &lt;40)</td>
<td>1.3 (1.0–2.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Late referral (vs. no)</td>
<td>3.4 (1.4–6.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Baseline data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (vs. &lt;1.3 mg/dL)</td>
<td>2.1 (1.1–2.3)</td>
<td>0.004</td>
</tr>
<tr>
<td>Proteinuria level (vs. &lt;1 g)</td>
<td>1.7 (1.9–2.5)</td>
<td>0.013</td>
</tr>
<tr>
<td>Hypertension (vs. no)</td>
<td>2.4 (1.1–3.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia (vs. not on erythropoietin)</td>
<td>1.6 (1.2–2.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Use of ACEI as antihypertensive agents (vs. below recommended dose)</td>
<td>0.5 (0.3–0.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Diet adherence (vs. good)</td>
<td>1.3 (1.8–4.6)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

1. Late referral was defined as a case that started renal replacement therapy within six months after an initial consult to renal outpatient clinic in the Kimitsu Hospital
2. Patients who had sitting systolic diastolic blood pressure over 140/90 mm Hg, or who were receiving antihypertensive drugs were judged hypertensive
3. Dietary adherence (good adherence was defined as daily urinary protein intake less than 0.7 g and sodium intake less than 7 g, otherwise allocated to poor adherence)

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Stopping progression in familial juvenile hyperuricemic nephropathy with benzbromarone?

To the Editor: In a recent issue of *Kidney International*, a landmark paper on familial juvenile hyperuricemic nephropathy (FJHN) was published. Bleyer et al [1] describe a large family with the disease, which is caused by a uromodulin gene mutation. Chronic and progressive renal failure was the most prominent clinical feature. Despite treatment with allopurinol, loss of creatinine clearance (CrCl) exceeded 3 mL/min/year.

Hyperuricemia in FJHN is caused by reduced fractional excretion of uric acid (FEUA). Whereas allopurinol does not affect FEUA, benzbromarone normalizes it in FJHN [2]. We treated two FJHN patients with a combination of allopurinol adjusted to renal function and benzbromarone...
100 mg a day for 68 months. The patients, a mother and son, had a heterozygous 481T→C mutation in the uromodulin gene, causing a C126R amino acid change predicted to disrupt the tertiary structure of Tamm-Horsfall glycoprotein [3]. The mother, age 53, had a CrCl of 38 mL/min, which decreased to 16 mL/min within one year. After introduction of benz bromarone 100 mg her renal function stabilized and her actual CrCl was 17 mL/min. The 32-year-old son had a CrCl of 58 mL/min. His renal function also remained stable under benz bromarone 100 mg, with an actual CrCl of 60 mL/min. We think that a trial of benz bromarone is justified in patients with FJHN. If benz bromarone proves to be effective this would also imply that reduced FEUA is of pathogenetic importance. There is nothing to be lost, but possibly much to win using benz bromarone in FJHN.

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Submaximal dose of trandolapril in the COOPERATE trial?

To the Editor: In the recent study published in Kidney International by Jacobsen et al [1], the authors considered the dose of angiotensin-converting enzyme inhibitor used in the COOPERATE trial [2] to be submaximal. With regard to this issue, however, we disagree with the authors. Trandolapril at a dose of 3 mg is sufficient. First, the baseline renal function of the enrollee was moderately reduced (mean serum creatinine level, 265 ± 12.5 mmol/L). In Japan, the recommended maximum dose of trandolapril is 2 mg, mainly for patients with uncomplicated essential hypertension. Thus, pharmacies strongly request us to reduce the dose in patients with renal dysfunction.

Second, during a run-in period, we had confirmed the individual maximal anti-proteinuric efficacy of trandolapril using an up-titration scale from 0.5 to 6.0 mg. Of 301 patients, 240 showed dose-response reactions up to 3 mg. Above this dose, however, no additional anti-proteinuric benefit was obtained. Third, the more a dose was increased, the higher the tendency for side effects, including hypotension, gastrointestinal symptoms, and acute renal decline or low compliance of the patients. Fourth, compared with the previous study asking the efficacy of 4 mg trandolapril in chronic renal disease [3], the anti-proteinuric efficacy obtained in the COOPERATE was not less. Lastly, according to the official reports of pharmacokinetic and pharmacodynamic variables of trandolapril in Japanese patients with renal dysfunction [4], these variables after 7 days’ consecutive use of even 1 mg are three times greater than those of patients with congestive heart failure who have been treated with 4 mg trandolapril.

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Reply from the Author

We appreciate the important additional information from the COOPERATE trial [1] in the letter by Dr. Nakao regarding the dose of trandolapril used. We recognize that 3 mg of trandolapril seems to be the optimal dose in this Japanese population with nondiabetic renal disease. This further supports the findings of an additional renoprotective effect of treatment with both ACE inhibitors (ACE-I) and angiotensin II receptor antagonists (ARB) in patients with renal disease found in our own study of diabetic nephropathy [2], as well as in the COOPERATE trial [1]. However, it should be mentioned that the maximal recommended dose of trandolapril is 4 mg daily in Europe and various renal diseases and ethnic groups [3] have different degrees of renal and systemic activation of