Kidney-protective effects of azelnidipine versus a diuretic in combination with olmesartan in hypertensive patients with diabetes and albuminuria: a randomized study

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ABSTRACT

Background. A thiazide diuretic used in combination with be
nazepril is superior to amlodipine plus benazepril in reducing albuminuria in hypertensive patients with diabetes. However, calcium channel blockers have diverse characteristics. Thus, we investigated whether combining an angiotensin receptor blocker with either azelnidipine or a thiazide diuretic produced similar reductions in albuminuria in hypertensive diabetic patients for the same levels of blood pressure achieved.

Methods. Hypertensive patients with type 2 diabetes and albuminuria (30–600 mg/g creatinine) under antihypertensive treatment (mean age 67.0 ± 7.6 years) were instructed to stop all antihypertensive treatment and take a combination of olmesartan (20 mg/day) and amlodipine (5 mg/day) for 3 months (run-in period). Then, patients were randomly assigned to receive either olmesartan plus azelnidipine (16 mg/day; n = 71) or olmesartan plus trichlormethiazide (1 mg/day; n = 72) for an additional 6 months. The primary end point was urinary excretion of albumin at 6 months after randomization.

Results. At the time of randomization, urinary albumin was 116.0 and 107.8 mg/g creatinine (geometric mean) in the azelnidipine and diuretic arms, respectively, and was reduced to a similar extent [79.8 (95% confidence interval 66.4–96.0) and...
89.7 (74.6–107.7) mg/g creatinine, respectively, after adjustment for baseline values. Blood pressure did not differ between the two groups throughout the study period.

**Conclusions.** Azelnidipine is equally effective as a thiazide diuretic in reducing urinary albumin when used in combination with olmesartan.

## INTRODUCTION

Albuminuria is a powerful prognostic predictor of cardiovascular disease as well as end-stage renal disease in patients with hypertension and diabetes [1–6]. The risk of cardiovascular morbidity and mortality increases with increasing urinary albumin excretion without any recognizable threshold or plateau [7–10]; thus, every effort is made to reduce urinary albumin excretion. Reductions in albuminuria following antihypertensive treatment lead to reductions in cardiovascular events [11, 12].

Guidelines for the management of hypertension recommend aggressive blood pressure reduction and the use of renin–angiotensin system inhibitors in hypertensive and diabetic patients with albuminuria [13–15]. However, effective blood pressure control is particularly difficult to achieve in these patients [16], and combinations of two or more agents are frequently necessary to reduce both blood pressure and urinary albumin excretion [16–18]. A recent trial demonstrated that benazepril, an angiotensin-converting enzyme inhibitor, used in combination with a diuretic is superior to the combination of benazepril plus amlodipine (a calcium channel blocker) in reducing urinary albumin excretion in hypertensive patients with diabetes and albuminuria [19]. However, calcium channel blockers have diverse characteristics; some calcium channel blockers that inhibit N- or T-type calcium channels have been shown to have antiproteinuretic effects similar to those of angiotensin-converting enzyme inhibitors [20]. Indeed, the addition of cilnidipine (an N- and L-type calcium channel blocker), but not amlodipine (an L-type calcium channel blocker) reduced urinary protein in patients being treated with renin–angiotensin system inhibitors [21].

Recent reports suggest that the calcium channel blocker azelnidipine has potent antiproteinuretic effects even though it has neither N- nor T-type calcium channel blocking activity [22–26]. Thus, the present study, the Renoprotective effects of Azelnidipine in hypertensive Diabetic patients in Aichi and Mie (RANDAM) study, was designed to test the hypothesis that combining an angiotensin receptor blocker with either azelnidipine or a thiazide diuretic would result in similar reductions in urinary albumin excretion for the same levels of blood pressure achieved and the same degree of blood pressure reduction in patients with hypertension and diabetes mellitus.

## MATERIALS AND METHODS

The RANDAM study was a multicenter 24-week prospective randomized open-blinded end-point study assessing the effects of azelnidipine versus those of a diuretic in combination with olmesartan, an angiotensin receptor blocker, on urinary albumin excretion in hypertensive patients with diabetes and albuminuria. The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Komono Kosei Hospital, the core clinical center of the trial. All patients provided written informed consent prior to participating in the study. The core study center was located at Nagoya City University, which was responsible for data collection and statistical analysis. The recruitment and follow-up of patients were undertaken by each investigator. The RANDAM study is registered with the UMIN Clinical Trial Registry (UMIN 00003451; http://www.umin.ac.jp/ctr).

### Patients

Hypertensive patients with type 2 diabetes and albuminuria who were being treated with antihypertensive medication (one or two classes of drugs used at standard doses) were recruited to the study. Patients were deemed eligible for inclusion in the study if they were 20–75 years of age and had essential hypertension, type 2 diabetes and urinary albumin in the range 30–600 mg/g creatinine. Patients were excluded from the study if they had contraindications for either of the study medications, severe hypertension (≥180/110 mmHg), office blood pressure <130/80 mmHg while being treated with a standard dose of a single class of antihypertensive drug, secondary hypertension, acute coronary syndrome or another cardiovascular event in the past 6 months, uncontrolled diabetes (HbA1c ≥9.0%) and serum creatinine ≥2.0 mg/dL in men or ≥1.5 mg/dL in women. The diagnosis of type 2 diabetes was based on World Health Organization criteria [27]. All patients were treated with oral antidiabetic medications based on a previous diagnosis of diabetes mellitus. Secondary hypertension was excluded on the basis of a medical history and appropriate physical, biochemical and radiological examinations. Blood pressure was measured by a doctor using a semi-automated device that has been calibrated by the auscultation method after patients had been seated for 2 min with their back supported and their arms supported at heart level. Patients were instructed to avoid the intake of caffeine-containing beverages and smoking for the 30 min before blood pressure measurements were made. Three consecutive blood pressure measurements were taken at 2-min intervals and the mean of the second and third measurements was recorded as the blood pressure for that patient.

### Protocol

Patients were instructed to stop all antihypertensive drugs and take a combination of a standard dose of olmesartan (20 mg; after breakfast) and amlodipine (5 mg; after breakfast) for 12 weeks (run-in period; Figure 1a). At the end of the run-in period, baseline evaluations were performed and patients underwent randomization if they had urinary albumin in the range 30–600 mg/g creatinine. As indicated in Figure 1b, 175 patients were registered for the study; of these, 152 patients were randomized to further treatment. A computer-generated random number sequence was obtained in the core center and
If needed, chlormethiazide (1 mg, once daily; diuretic regimen; dose of olmesartan (20 mg, once daily) and a low dose of trichlormethiazide (1 mg, once daily; azelnidipine regimen; n = 75) or a standard dose of olmesartan (20 mg, once daily) and a low dose of trichlormethiazide (1 mg, once daily; diuretic regimen; n = 77) (Figure 1a). Target office blood pressure was <130/80 mmHg and blood pressure was evaluated at each visit (every month); if needed, α- and then β-blockers were added to reach target blood pressure. Clinical data, including blood pressure, heart rate, serum and urine biochemical analyses, and hematologic measurements, were collected at the end of the run-in period and then again 12 and 24 weeks after randomization.

To determine urinary albumin excretion, a morning urine sample was collected. Urinary albumin was measured by a turbidimetric immunoassay test using an automated analyzer (JCA-BM8000; Japan Electron Optics Laboratory, Tokyo, Japan). The sensitivity of the assay was 1.1 mg/L albumin. Urinary albumin excretion was expressed as the ratio of urinary albumin to urinary creatinine (mg/g creatinine). The average urinary albumin excretion over 2 consecutive days was used for analyses.

The primary end point of the study was urinary albumin excretion 24 weeks after randomization. In addition, changes in office blood pressure, serum creatinine levels, serum uric acid levels and HbA1c levels from baseline to 24 weeks after randomization were assessed. GFR was estimated using the Japanese Society of Nephrology formula (eGFR) [28].

**Statistics**

All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). Continuous variables are expressed as the mean ± SD, except for urinary albumin. Because of its extremely skewed distribution, urinary albumin was log-transformed before analysis and is presented as the geometric mean with 95% confidence intervals. Primary end points were analyzed using analysis of covariance (ANCOVA) with achieved urinary albumin as a dependent variable and treatment group and baseline urinary albumin as covariates. In other analyses, differences in continuous variables were assessed using unpaired t-test, whereas the Chi-squared test was used to evaluate categorical variables. In all analyses, except for that of the primary end point, two-tailed P < 0.05 was considered significant.

The present study was planned to prove the non-inferiority of azelnidipine compared with trichlormethiazide treatment when prescribed in combination with olmesartan in terms of their effects on urinary albumin excretion. An inferiority margin of <1.2 in terms of the ratio [urinary albumin (mg/g creatinine) in the azelnidipine regimen]/[urinary albumin in the diuretic regimen] was assumed considering non-significant differences. Based on a previous report, the log-transformed SD of urinary albumin excretion after treatment using the present regimens was assumed to be 0.39 [23]. To achieve a power of 0.8 with a significance level of 0.025 (one-sided), 72 patients were needed in each treatment group to demonstrate the non-inferiority of the azelnidipine regimen. With the added expectation of patients withdrawing from the study (expected dropout rate 5%), we planned to recruit 76 patients to each group.

**RESULTS**

Between August 2010 and November 2011, after a 12-week run-in period consisting of combination treatment with olmesartan plus azelnidipine (baseline), 152 patients were randomly assigned to receive either olmesartan plus azelnidipine or olmesartan plus trichlormethiazide for an additional 6 months (Figure 1a). Four patients in the azelnidipine group and five in the diuretic group dropped out, leaving 143 patients for whom data were available for analysis (Figure 1b). The baseline characteristics of the patients are listed in Table 1. The mean (±SD) age of the 143 patients was 67.0 ± 7.6 years, with mean systolic and diastolic blood pressures of 134.2 ± 12.4 and 74.8 ± 9.3 mmHg, respectively. There were no significant differences in any of the characteristics, except for serum potassium levels, between the azelnidipine and diuretic regimens at baseline.

Replacement of amloidipine with azelnidipine or trichlormethiazide in combination with olmesartan had no significant effects on blood pressure (−2.2 ± 10.2/−1.1 ± 8.3 and −0.9 ± 11.2/−1.3 ± 6.7 mmHg, respectively; Figure 2a). There...
were no significant differences in blood pressure between the two arms of the study throughout the treatment period, with blood pressure at 24 weeks in the azelnidipine and diuretic regimens being 133.1 ± 10.1/74.0 ± 7.9 and 133.6 ± 11.4/73.5 ± 10.2 mmHg, respectively. All patients received the allocated drugs, but 10 patients in the azelnidipine group and 15 patients in the diuretic group (P = 0.38) were prescribed additional classes of antihypertensive drugs in order to reach target blood pressure levels. Heart rate was reduced in the azelnidipine group (–1.6 ± 5.6 b.p.m.; P = 0.01), but not in the diuretic group (–0.5 ± 3.8 b.p.m.; P = 0.30); thus, at the end of the study, patients in the azelnidipine group had a lower heart rate than patients in the diuretic group (Figure 2b).

Urinary albumin excretion was markedly reduced after 24 weeks of treatment with azelnidipine (–29.3%; P = 0.002) or the diuretic (–19.0%; P = 0.02; Figure 3a). After adjustment for baseline urinary albumin values, there were no significant differences in urinary albumin levels between the azelnidipine and diuretic groups throughout the study period (Figure 3b), and the azelnidipine regimen was not inferior to the diuretic regimen in terms of its ability to reduce urinary albumin excretion (non-inferiority margin 1.2; Figure 4). In contrast with the comparable effects of the both regimens on blood pressure and urinary albumin excretion, eGFR was reduced following 24 weeks treatment with the diuretic (–5.3 ± 10.6 mL/min per 1.73 m² from baseline; P < 0.0001) but not azelnidipine (–1.0 ± 10.6 mL/min per 1.73 m² from baseline (P = 0.44); P = 0.02 for the change in eGFR versus the diuretic regimen; Figure 5).

Throughout the study period, there was no change in serum potassium levels in the azelnidipine group, whereas there was a slight, non-significant reduction in potassium levels in the diuretic group (P = 0.05; Table 2). Furthermore, significant increases in serum uric acid were seen only in the

<table>
<thead>
<tr>
<th>Table 1: Patient characteristics at baseline</th>
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<tr>
<td>Azelnidipine regimen (n = 71)</td>
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<tr>
<td>No. of men (%)</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>SBP (mmHg)</td>
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<tr>
<td>DBP (mmHg)</td>
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<tr>
<td>Heart rate (b.p.m.)</td>
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<tr>
<td>Creatinine (mg/dL)</td>
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<tr>
<td>eGFR (mL/min per 1.73 m²)</td>
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<tr>
<td>Potassium (mg/dL)</td>
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<td>Uric acid (mg/dL)</td>
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<td>LDL-C (mg/dL)</td>
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<td>HDL-C (mg/dL)</td>
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<td>HbA1c (%)</td>
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<tr>
<td>Urinary albumin (mg/g creatinine)</td>
</tr>
<tr>
<td>No. smokers (%)</td>
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<tr>
<td>No. with dyslipidemia (%)</td>
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<td>No. (%) with a history of</td>
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<tr>
<td>Cardiac events</td>
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<tr>
<td>Cerebrovascular events</td>
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<td>Disease duration (years)</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Hypertension</td>
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</table>

Data are presented as either the mean ± SD, geometric mean with 95% confidence intervals in parentheses (for urinary albumin) or as the number of patients with percentages in parentheses.

SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein–cholesterol; HDL-C, high-density lipoprotein–cholesterol.

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diuretic group. Although both treatment regimens had no significant effect on glucose metabolism, HbA1c responses to the two regimens tended to differ (P = 0.05; Table 2). The adverse effects observed during the study period are listed in Table 3. There were no serious adverse effects and the frequency of adverse effects did not differ between the two groups.

**DISCUSSION**

The present study demonstrates that both azelnidipine and a thiazide diuretic in combination with the angiotensin receptor blocker olmesartan reduce urinary albumin excretion to the same extent in hypertensive patients with type 2 diabetes and albuminuria. This highlights the importance of the careful selection of calcium channel blockers as additional medication in patients with albuminuria and hypertension who are being treated with an angiotensin receptor blocker.

Blood pressure levels after the replacement of amlodipine with azelnidipine or trichlormethiazide were similar throughout the study period and were not altered after randomization, indicating that the two combinations used in the present study were both as effective as the combination of amlodipine and olmesartan in reducing blood pressure. In contrast with blood pressure, urinary albumin excretion was markedly reduced after randomization to both regimens. Although the present study was not designed to compare the effects of amlodipine with those of azelnidipine or trichlormethiazide as antihypertensive drugs prescribed together with olmesartan, our findings suggest that the combination of olmesartan plus azelnidipine is more effective than that of olmesartan plus amlodipine in reducing urinary albumin, confirming the diverse characteristics of the different calcium channel blockers [21–23, 25]. Furthermore, the fact that after adjustment for baseline data, azelnidipine and trichlormethiazide resulted in similar reductions in urinary albumin proves the hypothesis that combining an angiotensin receptor blocker with either azelnidipine or a thiazide diuretic will produce similar reductions in
urinary albumin excretion for the same levels of blood pressure achieved and the same degree of blood pressure reduction in patients with hypertension and diabetes mellitus. The ultimate goal in managing patients with hypertension is to prevent the occurrence of cardiovascular events. A recent study conducted in high-risk hypertensive patients demonstrated that combining amlodipine rather than a thiazide diuretic with the angiotensin converting enzyme inhibitor benazepril was better for the prevention of composite cardiovascular end points [29], suggesting that, when renin–angiotensin system inhibitors are being used in the management of hypertension, calcium channel blockers may be the best choice for combination therapy. Conversely, the combination of a thiazide diuretic plus benazepril was shown to be more effective in reducing albuminuria than the combination of amlodipine plus benazepril in hypertensive patients with diabetes and albuminuria [19]. Because cardiovascular and total mortality increase with increasing urinary albumin levels, even within the range defined as ‘normal’, without any

**FIGURE 5:** Changes in the estimated glomerular filtration rate (eGFR) after the randomization of patients to either the olmesartan plus azelnidipine (16 mg/day; azelnidipine regimen; n = 71) or olmesartan plus trichlormethiazide (1 mg/day; diuretic regimen; n = 72) arms of the study. Data are the mean ± SD. *P < 0.001, **P < 0.0001 compared with baseline.

### Table 2: Changes in variables during the study period

<table>
<thead>
<tr>
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<th>Baseline</th>
<th>24 weeks</th>
<th>Change</th>
<th>P-value*</th>
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</thead>
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<tr>
<td>Serum potassium (mg/dL)</td>
<td></td>
<td></td>
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<tr>
<td>Azelnidipine regimen</td>
<td>4.4 ± 0.4</td>
<td>4.4 ± 0.4</td>
<td>0.02 ± 0.40</td>
<td>0.10</td>
</tr>
<tr>
<td>Diuretic regimen</td>
<td>4.2 ± 0.4</td>
<td>4.1 ± 0.4</td>
<td>-0.1 ± 0.4</td>
<td></td>
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<tr>
<td>Serum creatinine (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azelnidipine regimen</td>
<td>0.94 ± 0.26</td>
<td>0.95 ± 0.26</td>
<td>0.03 ± 0.38</td>
<td>0.18</td>
</tr>
<tr>
<td>Diuretic regimen</td>
<td>0.87 ± 0.20</td>
<td>0.97 ± 0.27**</td>
<td>0.10 ± 0.16</td>
<td></td>
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<tr>
<td>Serum uric acid (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azelnidipine regimen</td>
<td>5.8 ± 1.3</td>
<td>5.8 ± 1.1</td>
<td>-0.07 ± 1.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diuretic regimen</td>
<td>5.7 ± 1.2</td>
<td>6.3 ± 1.3**</td>
<td>0.70 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azelnidipine regimen</td>
<td>6.9 ± 0.8</td>
<td>6.8 ± 0.9</td>
<td>-0.1 ± 0.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Diuretic regimen</td>
<td>7.0 ± 0.9</td>
<td>7.1 ± 1.0</td>
<td>0.04 ± 0.40</td>
<td></td>
</tr>
</tbody>
</table>

Data are given as the mean ± SD.

*P-values are for comparisons of changes during the study period between the azelnidipine and diuretic groups.

**P < 0.0001 compared with baseline.

### Table 3: Adverse effects

|                        | Azelnidipine regimen | Diuretic regimen | P-value |
|------------------------|                      |                 |         |
| Headache               | 1 (1.4%)             | 0 (0.0%)        | 0.31    |
| Dizziness              | 1 (1.4%)             | 1 (1.4%)        | 0.99    |
| Edema                  | 1 (1.4%)             | 0 (0.0%)        | 0.31    |
| Hypokalemia*           | 0 (0.0%)             | 3 (4.2%)        | 0.08    |

Data show the number patients in each group, with percentages given in parentheses.

*Serum potassium <3.5 mEq/dL
recognizable threshold [7–10], a second-line antihypertensive drug targeting the prevention of cardiovascular events in hypertensive patients with albuminuria being treated with renin–angiotensin system inhibitors has not been proposed. In this context, the findings of the present study may provide evidence that, of the various calcium channel blockers that may be more effective than diuretics in reducing cardiovascular events when used in combination with a renin–angiotensin system inhibitor, azelnidipine exhibits additive effects in reducing urinary albumin, a significant marker of cardiovascular disease and end-stage renal disease.

Although both azelnidipine and trichlormethiazide produced effective reductions in urinary albumin, there were notable differences between the two regimens, specifically the eGFR response. Replacement of amlodipine with azelnidipine did not alter eGFR, whereas eGFR was significantly reduced after the replacement of amlodipine with trichlormethiazide. The difference in eGFR over the study period between the two groups may have reflected additional volume depletion. Although one possible concern is that the reduction in GFR after diuretic treatment may lead to future cardio renal deterioration, the impact of the reductions in GFR observed after 24 weeks of treatment on future cardiovascular and renal outcomes remains unknown. In contrast, eGFR was not reduced in the azelnidipine arm of the study, suggesting that replacement of amlodipine with azelnidipine in patients being treated with olmesartan may not have further reduced intraglomerular pressure.

The mechanisms underlying the considerable reduction in urinary albumin after replacement of amlodipine with azelnidipine (or the similar potency of both regimens in reducing urinary albumin) cannot be determined from the present study. However, one possible explanation is suppression of sympathetic nerve activity by the calcium channel blocker [26, 30, 31]. Azelnidipine has been shown to decrease sympathetic nerve activity via antioxidant effects in the rostral ventrolateral medulla [30] and it attenuates glomerular damage by suppressing sympathetic nerve activity in experimental studies [26]. Indeed, in the present study, heart rate was reduced after the treatment of patients with azelnidipine, confirming the observations reported previously [31]. Anti-inflammatory and endothelial protective effects of azelnidipine may also play a significant role in the reduction in urinary albumin [32] because urinary albumin excretion is closely associated with endothelial dysfunction and systemic inflammation [33–35]. Alternatively, intraglomerular pressure may have been decreased after replacement of amlodipine with azelnidipine, as shown in experimental hypertension [26]; however, because there were no significant reductions in eGFR following azelnidipine treatment in the present study, it is unlikely that this mechanism contributes in any large degree to the beneficial effects of azelnidipine.

There were some notable changes in the biochemical data for patients in the two treatment arms. Uric acid levels were increased in patients treated with the diuretic regimen, and this may indicate a greater risk of cardiovascular events [36–39]. Moreover, glycemic control tended to be worse in patients in the diuretic compared with azelnidipine arm of the study. However, both regimens were generally well tolerated and any adverse effects were mild in severity.

Interpretation of the present study is limited because of the following points. First, reductions in albuminuria in hypertensive patients with type 2 diabetes have not been proven to reduce cardiovascular and renal events. Similarly, different effects on albuminuria among calcium channel blockers have not translated into different effects on cardiovascular or renal outcomes. Indeed, recent large clinical trials, though primary outcomes or study population were different from those in the present study, have demonstrated that reductions in albuminuria or the prevention of the onset of albuminuria do not translate into reductions in cardiovascular and renal events [40–42]. Second, blood pressure was not reduced to the target level defined in the protocol. This may have affected the results, because blood pressure shows close relationship with urinary excretion of albumin.

In conclusion, combination treatment with olmesartan plus azelnidipine is as effective as olmesartan plus a thiazide diuretic in reducing urinary albumin excretion in hypertensive patients with diabetes and albuminuria. Azelnidipine in combination with olmesartan did not reduce eGFR and, so, may be a useful medication for the treatment of these patients.

CONFLICT OF INTEREST STATEMENT

The authors report that they have no conflicts of interest.

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Decline in renal functioning is associated with longitudinal decline in global cognitive functioning, abstract reasoning and verbal memory

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ABSTRACT

Background. Decreased estimated glomerular filtration rate (eGFR) and higher serum creatinine (sCR) levels have been associated with longitudinal decline in global mental status measures. Longitudinal data describing change in multiple domains of cognitive functioning are needed in order to determine which specific abilities are most affected in individuals with impaired renal function.

Methods. We conducted a 5-year longitudinal study with 590 community-living individuals (mean age 62.1 years, 60.2% female, 93.2% white, 11.4% with diabetes mellitus, mean eGFR 78.4 mL/min/1.73 m²) free from dementia, acute stroke and end-stage renal disease. To measure longitudinal change-over-

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