*Original Article*

# Microalbuminuria Reduction with Telmisartan in Normotensive and Hypertensive Japanese Patients with Type 2 Diabetes: A Post-Hoc Analysis of the Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy (INNOVATION) Study

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**The Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy (INNOVATION) study previously showed that treatment with telmisartan, an angiotensin II receptor blocker, effectively reduced the transition from incipient to overt nephropathy in Japanese type 2 diabetic patients. However, that large study included both normotensive and hypertensive patients. In the present post hoc analysis, we aimed to assess whether or not telmisartan elicits beneficial effects on the progression of microalbuminuria in normotensive patients. We randomized 163 microalbuminuric (urinary albumin-to-creatinine ratio: UACR of 100 to 300 mg/g creatinine) normotensive type 2 diabetic patients to treatment with telmisartan (40 or 80 mg once daily) or placebo over 52 weeks. The patients treated with either dose of telmisartan showed lower transition rates from microalbuminuria to overt nephropathy compared to the placebo group. In addition, more patients on telmisartan reverted to normoalbuminuria (UACR < 30 mg/g creatinine): 15.5% of the 40 mg group, 19.6% of the 80 mg group, and 1.9% of the placebo group. In normotensive patients treated with telmisartan, changes in UACR were not significantly correlated with changes in blood pressure. Side effects did not differ among the groups. The present study demonstrates that telmisartan prevents the progression of microalbuminuria (in some cases induces remission of albuminuria) in normotensive Japanese patients with type 2 diabetes. Telmisartan is shown to be safe and well tolerated in these patients. (*Hypertens Res* 2008; 31: 657–664)**

***Key Words*: albuminuria, type 2 diabetes, telmisartan**

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## Introduction

The progression of proteinuria in type 2 diabetes increases the risk of renal and cardiovascular diseases (*1*), and prevention of the development of proteinuria is thus a key treatment goal for diabetic nephropathy (*2*, *3*). Effects of angiotensin II blockade with angiotensin II type 1 ($AT_1$) receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEIs) on the progression of proteinuria are widely recognized in patients with type 2 diabetic nephropathy (*4–11*). Although epidemiological and familial studies indicate that there are obvious different genetic susceptibilities to end-stage renal disease among ethnic groups (*11–15*), most national guideline groups have recommended ARBs or ACEIs instead of other antihypertensive agents in hypertensive patients with diabetic nephropathy (*16–19*).

Recent studies also provide evidence that treatment with ARBs or ACEIs results in long-term stabilization or normalization of albuminuria in normotensive type 2 diabetic patients (*8–10*, *20*, *21*). However, no comprehensive large-scale study has investigated whether or not angiotensin blockade prevents the progression of albuminuria in normotensive Japanese patients with type 2 diabetes. This investigation should be particularly important because it has been revealed that Japanese diabetic patients are much more susceptible than Caucasians to end-stage renal disease (*11–15*). We recently reported on the Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy (INNOVATION) study to examine the effect of telmisartan, an ARB, on the progression of microalbuminuria in Japanese patients with type 2 diabetes (*22*, *23*). This large study included 163 normotensive and 351 hypertensive patients. The major finding was that telmisartan treatment effectively reduced the transition rate from incipient to overt nephropathy in Japanese type 2 diabetic patients.

In the present post-hoc analysis of the INNOVATION study, we aimed to assess whether or not telmisartan elicits beneficial effects on the progression of microalbuminuria in Japanese normotensive patients with type 2 diabetes. Accordingly, we analyzed the data of normotensive subjects from the INNOVATION study and compared them to those obtained from hypertensive subjects. We also determined the time course of telmisartan's effects on albuminuria and blood pressure, as well as its optimal dose, safety, and tolerability in these patients.

## Methods

The INNOVATION study was a randomized, placebo-controlled, double-blind, multicenter study, as previously reported (*22*, *23*). The protocol, patient information form, and informed consent form were reviewed and approved by the local institutional review board at each study center. The trial was carried out in compliance with the protocol and with the principles laid down in the Declaration of Helsinki (1996 Version), in accordance with the ICH (International Conference on Harmanisation) Harmonised Tripartite Guideline for Good Clinical Practice (GCP), and in accordance with the Japanese GCP (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

### Study Population

The study involved both male and female Japanese patients with type 2 diabetes with incipient nephropathy, ranging in age from 30 to 74 years at the time of screening. Both normotensive and hypertensive patients were included in this study. Incipient nephropathy was identified by a first morning voided urinary albumin-to-creatinine ratio (UACR) of 100 to 300 mg/g creatinine at two measuring points during the run-in period. The other inclusion criterion was a serum creatinine level of $<1.5$ mg/dL in males or $<1.3$ mg/dL in females. Patients were excluded if they had had a diagnosis of type 2 diabetes mellitus before the age of 30 years, type 1 diabetes mellitus, or nondiabetic renal disease, HbA1c $\geq 9\%$, or seated systolic/diastolic blood pressure (SBP/DBP) $\geq 180/100$ mmHg. Other exclusion criteria included unstable angina, myocardial infarction, coronary artery bypass graft surgery, or percutaneous transluminal coronary angioplasty within the previous 6 months; a transient ischemic attack or stroke within the previous 6 months; or any history of heart failure before enrollment. Pregnant or possibly pregnant women were ineligible. The current definition of hypertension is a blood pressure higher than 140/90 mmHg, although a recently recommended blood pressure–lowering target is less than 130/80 mmHg in hypertensive patients with diabetes mellitus (*16–19*). Patients who had received any antihypertensive medications were also defined as hypertensive patients.

During the 6-week screening period, hypertensive patients continued to receive their standard antihypertensive therapy. If they were treated with any ARBs and/or ACEIs, these medications were discontinued and replaced by alternative open-label medication (calcium-channel blockers [CCBs]; diuretics, except potassium-sparing agents; $\alpha$- or $\beta$-blockers). After the run-in period, eligible patients were randomly assigned to treatment of 40 or 80 mg telmisartan (once daily) or to a matching placebo group in a 1:1:1 ratio based on a dynamic allocation procedure, following stratification according to baseline UACR, blood pressure, HbA1c, gender, age, *etc*. (*22*, *23*).

### Treatment

The initial dose of telmisartan was 20 mg, which was uptitrated to 40 or 80 mg at 2 or 4 weeks. If the seated SBP/DBP was $>130/85$ mmHg, then patients could receive available concomitant antihypertensive agents. Concomitant antidiabetic agents and alternative antihypertensive medications other than ARBs and ACEIs were allowed throughout the study.

**Table 1. Baseline Characteristics of Patients in the Full Analysis Population**

| | Normotensive patients | | | Hypertensive patients | | |
|---|---|---|---|---|---|---|
| | Placebo | Telmisartan 40 mg | Telmisartan 80 mg | Placebo | Telmisartan 40 mg | Telmisartan 80 mg |
| *N* | 54 | 58 | 51 | 120 | 114 | 117 |
| Age, years | 59.5 | 61.5 | 61.3 | 62.6 | 61.8 | 62.0 |
| Male, % | 81.5 | 79.3 | 72.5 | 68.3 | 71.1 | 73.5 |
| BMI, kg/m$^2$ | 24.6±3.6 | 24.6±3.1 | 25.4±3.9 | 25.7±3.9 | 25.6±4.6 | 26.0±4.0 |
| Weight, kg | 65.8±11.5 | 64.6±10.1 | 65.6±11.9 | 66.8±11.5 | 67.0±13.4 | 68.4±12.3 |
| Duration of DM, years | 9.6±7.3 | 9.1±8.4 | 7.7±7.3 | 8.8±7.1 | 9.4±7.3 | 8.4±7.3 |
| SBP, mmHg | 128±13.5 | 131±13.0 | 133±13.0 | 140±14.0 | 140±14.1 | 140±15.0 |
| DBP, mmHg | 73±8.6 | 75±9.5 | 78±8.9 | 78±11.1 | 79±10.2 | 79±10.7 |
| HbA1c, % | 7.1±0.9 | 7.0±0.9 | 7.2±0.7 | 6.9±0.9 | 7.0±0.9 | 7.0±1.0 |
| UACR, mg/g | 164±40.3 | 173±50.6 | 168±48.6 | 178±48.9 | 172±47.5 | 175±44.6 |
| Serum Cr, mg/dL | 0.8±0.2 | 0.8±0.2 | 0.8±0.2 | 0.8±0.2 | 0.8±0.2 | 0.8±0.2 |
| CCr, mL/min | 93.1±22.7 | 94.7±22.5 | 100.9±37.0 | 93.7±29.0 | 92.6±25.7 | 95.6±23.4 |
| Total cholesterol, mg/dL | 196±30.7 | 192±28.5 | 196±37.5 | 199±32.6 | 193±34.8 | 198±30.4 |
| LDL, mg/dL | 118±27.3 | 116±26.3 | 117±31.3 | 121±32.0 | 114±31.0 | 118±27.7 |
| HDL, mg/dL | 55±15.8 | 52±12.7 | 49±14.4 | 52±14.6 | 52±13.9 | 52±14.3 |
| Complications, % | | | | | | |
| Retinopathy | 57.4 | 53.4 | 43.1 | 49.2 | 49.1 | 52.1 |
| Neuropathy | 29.6 | 39.7 | 33.3 | 30.8 | 28.9 | 29.9 |
| Hyperlipidemia | 57.4 | 46.6 | 62.7 | 55.0 | 58.8 | 58.1 |
| Pattern of drug usage, % | | | | | | |
| Insulin | 40.7 | 31.0 | 43.1 | 33.3 | 28.1 | 29.9 |
| Diet therapy | 42.6 | 34.5 | 49.0 | 37.5 | 44.7 | 39.3 |
| Hypoglycemic agents | 72.2 | 84.5 | 74.5 | 75.8 | 78.9 | 69.2 |
| Lipid lowering agents | 31.5 | 34.5 | 41.2 | 36.7 | 37.7 | 40.2 |

BMI, body mass index; DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; UACR, urinary albumin-to-creatinine ratio; Cr, creatinine; CCr, creatinine clearance; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol.

### Assessment

Overt nephropathy was defined as UACR >300 mg/g creatinine in the first morning voided urine sample and at least 30% higher than the baseline on two consecutive 4-week–interval visits after the treatment. Blood pressure was measured by either a mercury sphygmomanometer or a validated electronic device manometer in the sitting position after a 5 min rest at each site. Blood pressure was always measured after daily drug intake at each visit. Safety was assessed by the frequency and severity of adverse events that were possibly related to the study drug, and changes from baseline in laboratory parameters (standard hematology, biochemistry, and urinalysis).

### Statistical Analyses

The values are presented as means±SD. The transition rate to overt nephropathy and the regression rate from incipient nephropathy were compared by Fisher's exact test among the groups. Changes in SBP, DBP, and UACR from the baseline at each period were analyzed by using the paired *t*-test. Changes were compared by using ANCOVA. A significant change for all comparisons was defined as $p<0.05$ by a closed testing procedure. Correlations were determined by the Spearman rank correlation test. All statistical tests were two-sided.

## Results

### Patient Enrollment

A total of 1,855 patients were enrolled in the INNOVATION study (*22*, *23*). A total of 1,328 patients failed screening and were excluded. The main reasons for withdrawal were severe limitation of UACR in inclusion criteria (69.3%), protocol violation (27.7%), and withdrawal of consent (3.0%). Of the remaining 527 patients who were randomized to treatment groups, one patient was subsequently suspected of having type 1 diabetes and was excluded from the analysis set. Twelve patients were excluded from the primary analysis because their UACR measurements were missing during

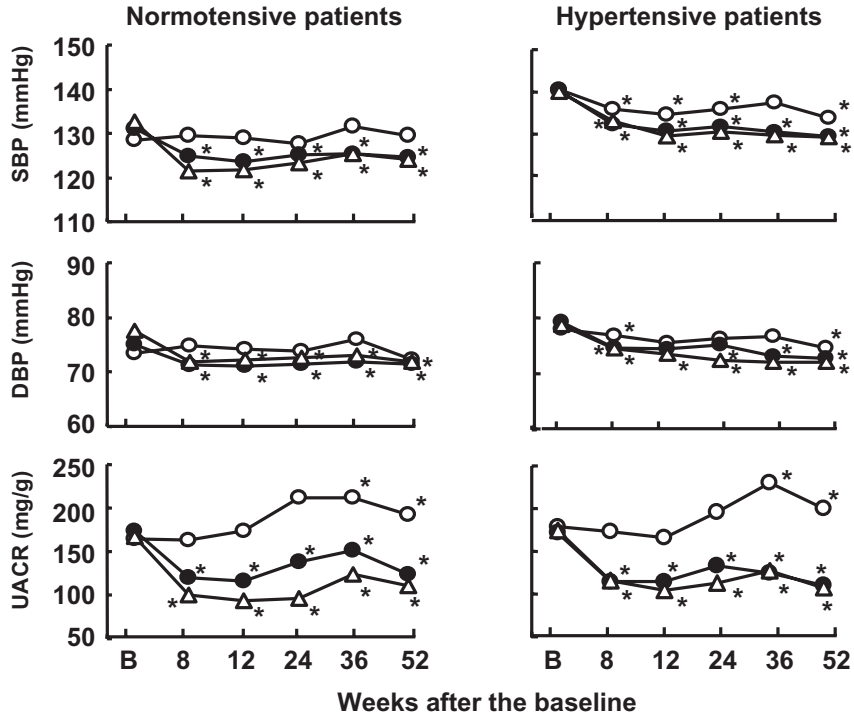


**Fig. 1.** *Time courses of SBP, DBP, and UACR from baseline to 52 weeks. Each data point indicates a mean value (SD). *Statistical difference from the baseline value at $p<0.05$. DBP, diastolic blood pressure; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio. Open circle: placebo group; closed circle: telmisartan 40 mg group; open triangle: telmisartan 80 mg group.*

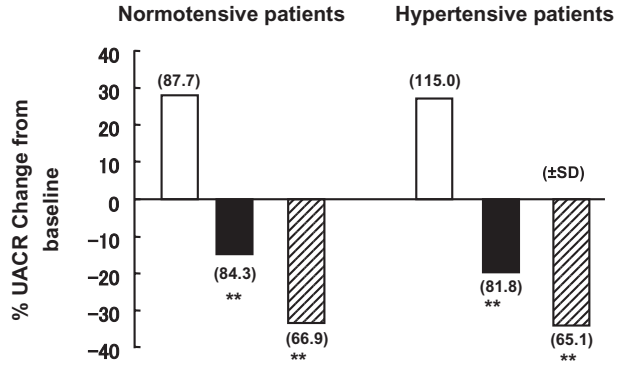


**Fig. 2.** *Effect of telmisartan on UACR at last observation from baseline. Each data point indicates a mean value (SD). **Statistical difference from placebo group at $p<0.001$. UACR, urinary albumin-to-creatinine ratio. Open column: placebo group; closed column: telmisartan 40 mg group; hatched column: telmisartan 80 mg group.*

treatment from the full analysis set (514 patients, 97.5%).

The mean follow-up period of the remaining 514 patients was approximately 1.3 years. These patients included 163 normotensive and 351 hypertensive patients. At baseline, the most commonly used antihypertensive medications in hypertensive patients were CCBs (73.8%), followed by diuretics (10.3%), α-blockers (12.0%), and β-blockers (10.3%). The rate of pretrial ARB or ACEI treatment was 21.1% or 14.2%, respectively. The average baseline SBP/DBP in each group is shown in Table 1. Other baseline characteristics did not significantly differ among the groups (Table 1).

## Blood Pressure Control

Temporal profiles of SBP and DBP from weeks 0 to 52 are depicted in Fig. 1. Changes in SBP and DBP were not observed in placebo-treated normotensive patients during the observation period. In hypertensive patients, placebo treatment significantly decreased SBP at weeks 8, 12, 24 and 52, and DBP at weeks 12 and 52. On the other hand, treatment with 40 or 80 mg telmisartan significantly decreased SBP and DBP in both normotensive and hypertensive patients throughout the treatment period. In normotensive patients, the averaged SBP/DBP at the last observation for the placebo-treated group was 128±14.3/75±10.0 *vs*. 122±15.1/73±9.0 mmHg for 40 mg telmisartan and 123±15.6/72±10.3 mmHg for 80 mg telmisartan) ($p<0.05$, respectively). Similarly, in hypertensive patients, the averaged SBP/DBP at the last observation for the placebo-treated group (134±14.8/73±9.6 mmHg) was significantly higher than that for 40 mg telmisartan (129±12.7/70±8.7 mmHg, $p<0.05$) or for 80 mg telmisartan

**Table 2. Effect of Telmisartan on Transition and Remission from Microalbuminuria at Last Observation**

| | Normotensive patients | | | Hypertensive patients | | |
|---|---|---|---|---|---|---|
| | Placebo | Telmisartan 40 mg | Telmisartan 80 mg | Placebo | Telmisartan 40 mg | Telmisartan 80 mg |
| *N* | 54 | 58 | 51 | 120 | 114 | 117 |
| Transitions, *n* (%) | 18 (33.3) | 7 (12.1)** | 5 (9.8)** | 41 (34.2) | 17 (14.9)** | 13 (11.1)** |
| Normalizations, *n* (%) | 1 (1.9) | 9 (15.5)** | 10 (19.6)** | 1 (0.8) | 14 (12.3)** | 25 (21.4)* |

Statistical difference from placebo group at *$p<0.05$ or **$p<0.01$, respectively.

(129±14.5/71±7.7 mmHg, $p<0.05$).

## Renal Outcomes

In each group, serum creatinine and creatinine clearance did not significantly change throughout the study (data not shown). Changes in UACR from weeks 0 to 52 are shown in Fig. 1, and percentage changes in UACR at the last observation from baseline are shown in Fig. 2. The baseline UACRs were similar among the treatment groups in both normotensive and hypertensive patients. In normotensive patients, treatment with 40 or 80 mg telmisartan significantly decreased UACR, whereas placebo treatment did not alter it (Figs. 1 and 2). The average UACR at the last observation for the placebo-treated group (204±140.3 mg/g) was significantly higher than those for 40 and 80 mg telmisartan (136±124.3 and 112±113.7 mg/g, $p<0.05$, respectively). Similarly, in hypertensive patients, the average UACR in this period for the placebo-treated group (219±180.2 mg/g) was significantly higher than those for 40 and 80 mg telmisartan (134±137.5 and 113±122.1 mg/g, $p<0.05$, respectively). At the last observation, placebo-treated normotensive and hypertensive patients showed each showed an approximately 30% increase in UACR from baseline. In contrast, treatment with 40 or 80 mg telmisartan significantly decreased UACR in both normotensive and hypertensive patients. However, dose-dependent effects of telmisartan at 40 or 80 mg on UACR were not observed in either the normotensive nor the hypertensive group (Fig. 2).

Table 2 shows the effects of telmisartan on transition and remission from microalbuminuria. Compared with those treated with placebo, patients treated with 40 or 80 mg telmisartan showed lower transition rates to overt nephropathy in both the normotensive and hypertensive groups. In addition, 40 or 80 mg telmisartan significantly increased the reversion rate to normoalbuminuria during the study period in both normotensive and hypertensive patients (Table 2). In both the normotensive and hypertensive groups, treatment with 80 mg telmisartan tended to elicit a lower transition rate to overt nephropathy and a higher reversion rate to normoalbuminuria compared to treatment with 40 mg telmisartan. However, these differences were not statistically significant.

Figure 3 shows the relationship between changes in UACR ($\Delta$UACR) and changes in SBP ($\Delta$SBP), as well as between changes in $\Delta$UACR and changes in DBP ($\Delta$DBP) at the last observation from baseline. In normotensive patients, there was no significant positive linear correlation between $\Delta$UACR and $\Delta$SBP in any group. In these patients, there was also no significant positive linear correlation between $\Delta$UACR and $\Delta$DBP in group (Fig. 3A). However, in each group of hypertensive patients, a significant positive linear correlation was observed between $\Delta$UACR and $\Delta$SBP or $\Delta$UACR and $\Delta$DBP, except for that between $\Delta$UACR and $\Delta$SBP in the 80 mg telmisartan-treated group (Fig. 3B).

## Safety

The safety set included 526 patients who received at least one dose of study drugs, and 485 patients experienced adverse events (92.2%): 163 patients (93.1%) in the 80 mg group; 158 patients (90.3%) in the 40 mg group; and 164 patients (93.2%) in the placebo group. There were no differences among the incidence rates of the telmisartan and placebo groups in both normotensive and hypertensive patients. MedDRA system organ classes with an incidence of 20% or greater in at least one of the telmisartan groups were eye disorders, gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, injury, poisoning and procedural complications, musculoskeletal and connective tissue disorders, and skin and subcutaneous tissue disorders. The events were generally mild or moderate in intensity; severe events occurred in 10.9%, 6.3%, and 7.4% in the telmisartan 80 mg, telmisartan 40 mg, and placebo groups, respectively.

As shown in Table 3, there were no significant differences among the groups in the frequency of discontinued patients with adverse events, suggesting that 40 or 80 mg telmisartan once daily was well tolerated not only in hypertensive patients but also normotensive Japanese type 2 diabetic patients with incipient nephropathy.

# Discussion

The effects of ARBs and ACEIs on the progression of microalbuminuria in type 2 diabetes have been demonstrated in several large clinical trials (*4–10*). In Japan, type 2 diabetic nephropathy is the main cause of chronic kidney disease (*1*, *13*). Furthermore, nephropathy accounts for a greater propor-

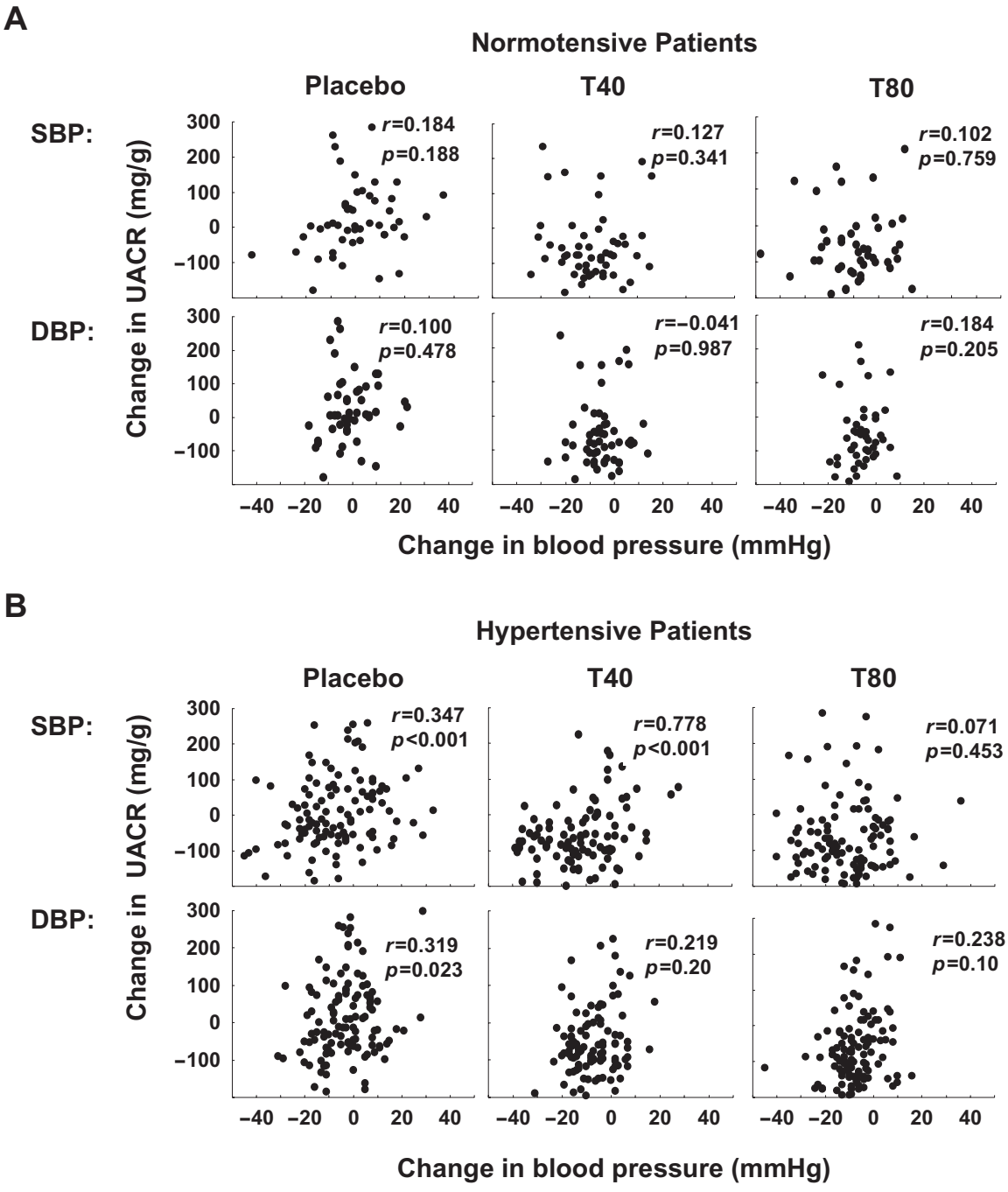


**Fig. 3.** *Relationship between ΔUACR and ΔSBP or ΔDBP at the last observation from the baseline. DBP, diastolic blood pressure; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio; T40, telmisartan 40 mg; T80, telmisartan 80 mg.*

**Table 3. Frequency of Discontinued Patients with Adverse Event**

| | Normotensive patients | | | Hypertensive patients | | |
|---|---|---|---|---|---|---|
| | Placebo | Telmisartan 40 mg | Telmisartan 80 mg | Placebo | Telmisartan 40 mg | Telmisartan 80 mg |
| Safety set, *n* | 54 | 58 | 51 | 120 | 116 | 121 |
| Discontinued by AE, *n* (%) | 7 (13.0) | 5 (8.6) | 9 (17.6) | 9 (7.5) | 13 (11.2) | 16 (13.2) |

AE, adverse event.

tion of deaths in Japanese patients with type 2 diabetes than in their Caucasian counterparts (*11–15*). In the present post-hoc analysis of the INNOVATION study, we investigated whether or not treatment with telmisartan elicits beneficial effects on the progression of microalbuminuria in Japanese normotensive patients with type 2 diabetes. Data show that renoprotective effects of telmisartan in normotensive patients from the INNOVATION study are consistent with those in the total subjects including both normotensive and hypertensive subjects (*22*, *23*); namely, treatment with telmisartan prevents the transition to overt nephropathy in Japanese normotensive type 2 diabetic patients with incipient nephropathy. In addition, more patients on telmisartan reverted from microalbuminuria to normoalbuminuria compared to those treated with placebo. Finally, these renoprotective effects and side effects of telmisartan were similar between normotensive and hypertensive patients. These data indicate that telmisartan is safe and well tolerated in Japanese normotensive patients with type 2 diabetes and incipient nephropathy.

A growing body of evidence indicates renoprotective effects of ARBs and ACEIs not only in hypertensive but also in normotensive diabetic patients. The ACE-Inhibitor Trial to Lower Albuminuria in Normotensive Insulin-Dependent Subjects (ATLANTIS) study demonstrated that treatment with ramipril had no effect on glomerular filtration rate, but significantly decreased microalbuminuria in normotensive type 1 diabetic patients (*20*). Similarly, captopril significantly decreased albuminuria in normotensive type 1 diabetic patients with albuminuria $>300$ mg/d (*21*). Further study showed that an ARB—losartan (*10*), irbesartan (*9*), or valsartan (*8*)—significantly decreased urinary albumin excretion in normotensive type 2 diabetes. Consistent with the data obtained by these studies performed in Western countries (*8*, *9*, *20*, *21*), the present study demonstrates that telmisartan treatment elicits renoprotective effects in Japanese normotensive type 2 diabetic patients with microalbuminuria. Since changes in UACR were not significantly correlated with changes in blood pressure in normotensive subjects (Fig. 3A), it seems that these renoprotective effects of telmisartan cannot be explained simply by its blood-pressure–lowering effect. In this regard, we observed that changes in UACR were positively correlated with changes in blood pressure in hypertensive subjects except the 80 mg telmisartan–treated group (Fig. 3B). Thus, it is possible that during angiotensin blockade with telmisartan, there is an important relationship between blood pressure reduction and reduction in albuminuria in hypertensive type 2 diabetic patients, as suggested by other clinical studies (*7*, *24*, *25*).

The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA2) study has shown that the effect of irbesartan, an ARB, at 300 mg once daily was superior to the effect of irbesartan at 150 mg once daily in reducing microalbuminuria and suppressing the progression to overt nephropathy in hypertensive type 2 diabetic patients (*6*). Further studies by Rossing *et al*. (*26*) demonstrated that the antiproteinuric effect of irbesartan at ultrahigh dosage (900 mg once daily) was superior to the usual recommended dose (300 mg) in hypertensive type 2 diabetic patients. Similar results were also reported by Ogawa *et al*. (*7*) who showed that candesartan's effects on albuminuria were dose-dependent in Japanese hypertensive type 2 diabetic patients. However, in the present study, the dose-dependent effects of telmisartan at 40 and 80 mg on UACR were not observed in hypertensive patients. Furthermore, although treatment with 80 mg telmisartan tended to elicit a lower transition rate to overt nephropathy and a higher reversion rate to normoalbuminuria compared with those of the 40 mg telmisartan in hypertensive patients, these differences were not statistically significant.

Dose-dependent effects of telmisartan were not observed in the present study, but this may be due to the differences in basal antihypertensive medications. In the present study, over 70% of hypertensive patients were treated with CCBs, whereas previous studies used a washout period of a few weeks to eliminate all antihypertensive medications, or their subjects were previously untreated moderate hypertensive patients (*6*, *7*, *26*). Other possibilities cannot be ruled out and need to be examined further.

In the present study, adverse events observed in telmisartan (40 or 80 mg)-treated normotensive and hypertensive patients were similar to those observed in placebo-treated patients in terms of their nature, frequency, and severity. However, telmisartan prevents the progression of microalbuminuria, and in some cases induces remission of albuminuria in normotensive type 2 diabetic patients. Since it now appears that microalbuminuria is a risk factor for cardiovascular morbidity and mortality (*2*, *27*), it is possible that sustained treatment with telmisartan has protective effects on cardiovascular events in normotensive patients with type 2 diabetes and microalbuminuria. However, our data failed to show this, because of the relatively small patient numbers, low incidences of serious adverse events, short duration of follow-up, and the inclusion of only early-stage diabetic nephropathy. The long-term benefit of telmisartan was demonstrated by Barnett *et al*. (*28*), who noted low incidences of cardiovascular events, all-cause mortality, and cardiovascular mortality in high-risk patients with type 2 diabetic nephropathy.

In conclusion, our data show that treatment with 40 or 80 mg telmisartan prevents the transition to overt nephropathy in Japanese normotensive type 2 diabetic patients with incipient nephropathy. In addition, more patients on telmisartan reverted to normoalbuminuria compared with those treated with placebo. Side effects did not differ among the groups. These data indicate that telmisartan is safe and well tolerated at both doses in Japanese normotensive type 2 diabetic patients with incipient nephropathy.

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