Prevention of Transition From Incipient to Overt Nephropathy With Telmisartan in Patients With Type 2 Diabetes

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To date, evidence for long-term renoprotection with angiotensin receptor blockers (ARBs) has come almost exclusively from Caucasian patients (1–3), despite Japanese people being at high risk of diabetic nephropathy and very susceptible to end-stage renal disease (4–6). We conducted the INNOVATION Study (Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy) to evaluate the efficacy of an ARB in preventing transition from microalbuminuria to overt nephropathy in Japanese patients (7). This study is the first large-scale clinical study to investigate prevention of overt diabetic nephropathy using an ARB in normotensive and hypertensive Japanese patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— The randomized, multicenter, double-blind, placebo-controlled trial was performed in patients aged from 30 to 74 years with type 2 diabetes and urinary albumin-to-creatinine ratio (UACR) 100–300 mg/g and serum creatinine <1.5 mg/dl (men) and <1.3 mg/dl (women). Exclusion criteria included type 1 diabetes, age of diabetes onset <30 years, seated systolic blood pressure (SBP)/diastolic blood pressure (DBP) ≥180/100 mmHg, and definable chronic kidney disease other than diabetic nephropathy. A total of 527 patients out of 1,855 screened were randomized to 80 or 40 mg telmisartan or placebo; the starting dose was 20 mg, titrated to 40 mg after 2 weeks or to 80 mg after a further 2 weeks. Minimum treatment period was 1 year for each patient. Primary efficacy end point was the transition rate from incipient to overt nephropathy (UACR >300 mg/g and increase ≥30% from baseline at two consecutive 4-week visits). Secondary end point was microalbuminuria remission (UACR <30 mg/g). Frequency and severity of adverse events were also assessed. The Kaplan-Meier method was used to determine transition rates to overt nephropathy; log-rank test was used for pairwise comparison between treatment groups. Effect of blood pressure reduction on transition rate was estimated using Cox's proportional hazard model. The protocol conformed to the principles of the Declaration of Helsinki and was approved by the institutional review boards at the 142 study centers (7). Patients provided written informed consent before enrollment.

RESULTS

— Of the 527 randomized patients (mean age 61.7 years), 13 were excluded from primary analysis because of suspected type 1 diabetes or UACR measurements being missing during treatment. Mean duration of follow-up was 1.3 ± 0.5 years (maximum 2.3 years). Transition rates to overt nephropathy were 80 mg telmisartan (n = 168) 16.7%, 40 mg telmisartan (n = 172) 22.6%, and placebo (n = 174) 49.9% (both telmisartan doses vs. placebo, $P < 0.0001$) (Fig. 1*A*). In addition, 163 normotensive patients were included in the study. Transition rates in normotensive patients were 80 mg telmisartan (n = 51) 11.0%, 40 mg telmisartan (n = 58) 21.0%, and placebo (n = 54) 44.2% (both telmisartan doses vs. placebo, $P < 0.01$) (Fig. 1*B*). After adjustment for changes in SBP, telmisartan still decreased the transition rate to overt nephropathy. Telmisartan (80 and 40 mg) reduced mean UACR at final observation by 58.8 and 37.9 mg/g, respectively, and placebo increased UACR by 40.9 mg/g (both telmisartan doses vs. placebo, $P < 0.0001$). Microalbuminuria remission at final observation occurred in 21.2% with 80 mg telmisartan, 12.8% with 40 mg telmisartan, and 1.2% with placebo (both telmisartan doses vs. placebo, $P < 0.001$). One or more adverse event was recorded in >90% of patients in each treatment group; most events were mild or moderate in intensity. Regarding the decrease of blood pressure, SBP/DBP fell from 138/78 mmHg to 128/72 mmHg with 80 mg telmisartan, from 137/78 mmHg to 128/72 mmHg with 40 mg telmisartan, and from 137/77 mmHg to 132/74 mmHg with placebo (each blood pressure change at 1 year from baseline $P < 0.01$).

CONCLUSIONS

— Patients with type 2 diabetes and microalbuminuria receiving

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Abbreviations: ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

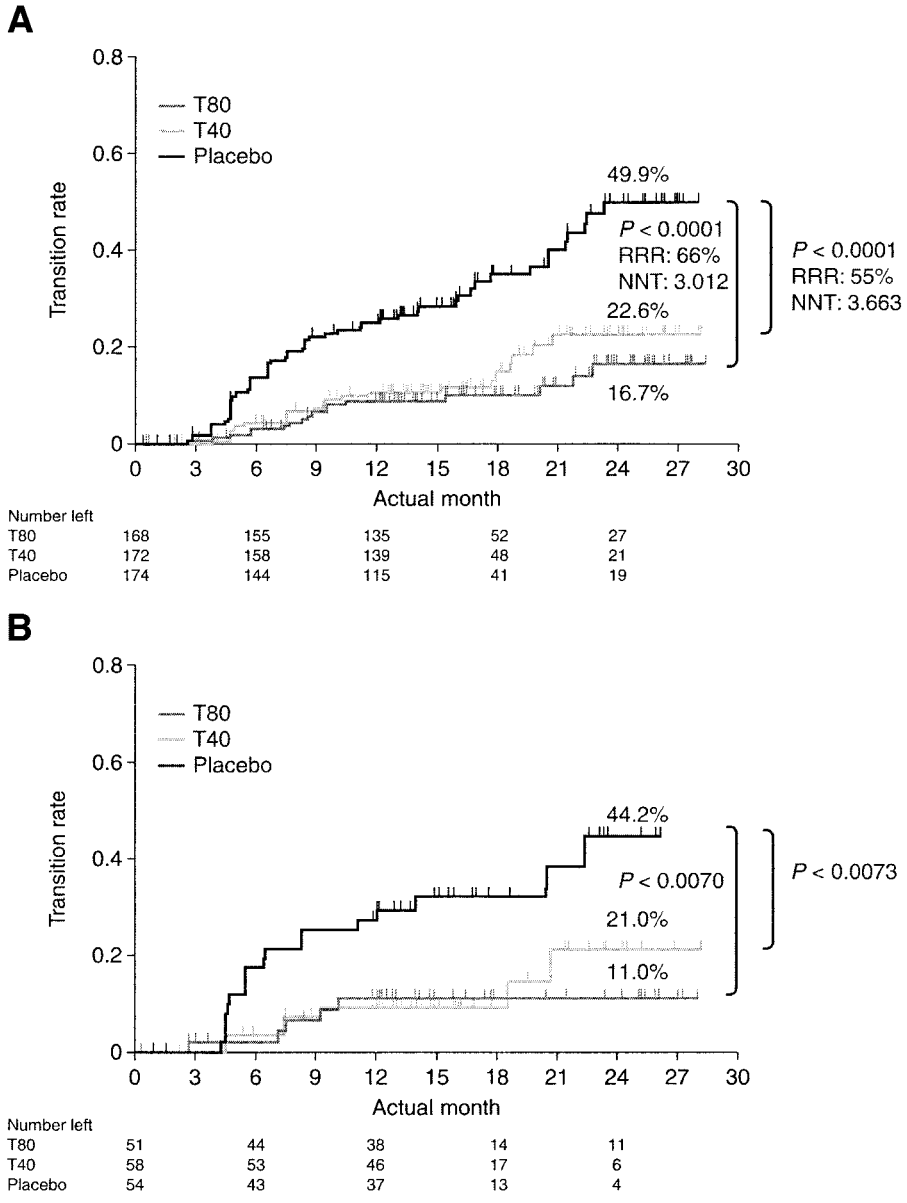

Figure 1—*Kaplan-Meier curves for transition from incipient to overt nephropathy in patients treated once daily with 80 mg telmisartan (T80), 40 mg telmisartan (T40), and placebo.*

80 or 40 mg telmisartan achieved superior renoprotection, demonstrated by lower transition rates to overt nephropathy, compared with placebo. Achievement of microalbuminuria remission was superior with 80 or 40 mg telmisartan than with placebo. Remission is a key goal for renoprotection, as well as cardiovascular protection (8). Remission rates compare very favorably with those reported in Caucasian hypertensive patients with type 2 diabetes and microalbuminuria treated with irbesartan (3). Telmisartan also reduced transition to overt nephropathy in normotensive patients, suggesting telmisartan had a blood pressure–independent effect. Further evidence for this is that differences in transition rates with respective treatments were maintained when adjustment was made for SBP reduction. The beneficial effects of telmisartan were dose dependent.

Overall, telmisartan reduced transition from incipient to overt nephropathy and induced remission of albuminuria in Japanese type 2 diabetic patients.

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