Effect of Telmisartan on Renal Outcomes
A Randomized Trial

Johannes F.E. Mann, MD; Roland E. Schmieder, MD; Leanne Dyal, MSc; Matthew J. McQueen, MD; Helmut Schumacher, MD; Janice Pogue, PhD; Xingyu Wang, PhD; Jeffrey L. Probstfield, MD; Alvaro Avezum, MD, PhD; Ernesto Cardona-Munoz, PhD; Gilles R. Dagenais, MD; Rafael Diaz, MD; George Fodor, MD, PhD; Jean M. Maillon, MD; Lars Rydén, MD; Cheuk M. Yu, MD; Koon K. Teo, MD; and Salim Yusuf, DPh, MD, for the TRANSCEND (Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease) Investigators

Background: Angiotensin-receptor blockers (ARBs) blunt progression of advanced diabetic nephropathy, but their long-term renal effects in other patients are not clear.

Objective: To examine the long-term renal effects of telmisartan versus placebo in adults at high vascular risk.

Design: Randomized trial. Patients were randomly assigned by a central automated system between November 2001 and May 2004 and were followed until March 2008. Participants and investigators were blinded to intervention status.

Setting: Multicenter, multinational study.

Patients: 5927 adults with known cardiovascular disease or diabetes with end-organ damage but without macroalbuminuria or heart failure who cannot tolerate angiotensin-converting enzyme inhibitors.

Intervention: Telmisartan, 80 mg/d ($n = 2954$), or matching placebo ($n = 2972$) plus standard treatment for a mean of 56 months.

Measurements: Composite renal outcome of dialysis or doubling of serum creatinine, changes in estimated glomerular filtration rate (GFR), and changes in albuminuria.

Results: No important difference was found in the composite renal outcome with telmisartan (58 patients [1.96%]) versus placebo (46 patients [1.55%]) (hazard ratio, 1.29 [95% CI, 0.87 to 1.89]; $P = 0.20$). Among the telmisartan and placebo groups, 7 and 10 patients had dialysis and 56 and 36 patients had doubling of serum creatinine, respectively (hazard ratio, 1.59 [CI, 1.04 to 2.41]; $P = 0.031$). Albuminuria increased less with telmisartan than with placebo (32% [CI, 23% to 41%] vs. 63% [CI, 52% to 76%]; $P < 0.001$). Decreases in estimated GFR were greater with telmisartan than with placebo (mean change in estimated GFR, -3.2 mL/min per 1.73 m^2 [SD, 18.3] vs. -0.26 mL/min per 1.73 m^2 [SD, 18.0]; $P < 0.001$).

Limitation: Only 17 participants had dialysis.

Conclusion: In adults with vascular disease but without macroalbuminuria, the effects of telmisartan on major renal outcomes were similar to those of placebo.

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The TRANSCEND (Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease) study examined cardiovascular outcomes with telmisartan, an angiotensin-receptor blocker (ARB), compared with placebo in people at high vascular risk who were intolerant of angiotensin-converting enzyme (ACE) inhibitors. Telmisartan had no statistically significant effect on the primary cardiovascular outcome, but it reduced the risk for the secondary composite outcome of cardiovascular death, myocardial infarction, and stroke to a moderate extent and had no effect on cardiovascular or total mortality (1). Renal outcomes were prespecified, important secondary outcomes of the TRANSCEND study, because a growing number of patients with atherosclerotic vascular disease are starting renal replacement therapy (2). For example, in a German registry, the proportion of individuals with vascular causes of nephropathy leading to long-term dialysis increased from 12% in 1995 to 23% in 2005 (3). Drugs used to reduce vascular events may also affect the kidney, so the effects of such drugs on renal outcomes in people with vascular disease are relevant.

Angiotensin-receptor blockers reduce elevated blood pressure (4) and urinary protein excretion (5), which are both considered to be surrogate variables of renal benefit.

Large trials in patients with overt diabetic nephropathy have demonstrated that ARBs reduce the rate of dialysis and doubling of serum creatinine (6, 7). The impact of ARBs on renal outcomes in other patients is not reliably known.

This prespecified analysis of the TRANSCEND study (1) examined the effects of telmisartan on renal function in a large sample that was intolerant of ACE inhibitors and had vascular disease but not macroalbuminuria. The composite renal outcome was dialysis or doubling of serum

See also:

Print

Web-Only
Appendix Table
Appendix Figures
Conversion of graphics into slides

Context

Few trials have evaluated whether angiotensin-receptor blockers (ARBs) prevent renal disease in people without proteinuria.

Contribution

In this trial, patients with cardiovascular disease or diabetes, but without macroalbuminuria or heart failure, were randomly assigned to receive telmisartan or placebo. During 4 to 5 years of follow-up, telmisartan recipients had albuminuria less often but had doubling of serum creatinine and slight decreases in estimated glomerular filtration rate more often than placebo recipients. Few patients in either group required dialysis.

Implication

The effects of ARBs on renal variables are complicated, but no strong evidence indicates that they prevent clinically important renal disease in patients without proteinuria.

—The Editors

creatinine. We also report changes in estimated glomerular filtration rate (GFR) and albuminuria.

METHODS

Design Overview

We enrolled and randomly assigned participants age 55 years or older with documented cardiovascular disease or diabetes with end-organ damage who could not tolerate ACE inhibitors between November 2001 and May 2004 to receive telmisartan, 80 mg/d, or matching placebo along with standard treatment. Follow-up was completed by March 2008. The main trial primary outcome, reported elsewhere (1), was the composite of myocardial infarction, stroke, cardiovascular death, and hospitalization for heart failure. We report the prespecified renal outcomes in this article. The ethics committees at all participating institutions and the regulatory authorities in each country approved the study protocol, and each participant provided written informed consent.

Setting and Participants

In 630 centers in 40 countries, we enrolled 5926 patients age 55 years or older who were intolerant of ACE inhibitors if they had coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage (1, 8). We defined ACE inhibitor intolerance as discontinuation of an ACE inhibitor for a documented reason—most commonly cough (88.2%), symptomatic hypotension (4.1%), angioedema (1.3%), and renal dysfunction (1%) (1, 8). We excluded patients who, according to the clinical investigators, needed an ARB; were known to be hypersensitive or intolerant to ARBs; or had heart failure, significant valvular or cardiac outflow tract obstruction, constrictive pericarditis,

complex congenital heart disease, unexplained syncope, planned cardiac surgery, cardiac revascularization in the previous 3 months, systolic blood pressure of 160 mm Hg or greater, heart transplantation, subarachnoid hemorrhage, known significant renal artery stenosis (formal exclusion not required), serum creatinine levels greater than 265 μmol/L (>3.0 mg/dL), or hepatic dysfunction. The **Appendix Table** (available at www.annals.org) lists all exclusion criteria. Macroalbuminuria (urinary albumin–creatinine ratio [UACR] >33.9 mg/mmol) was an exclusion criterion, but it was detected at baseline in 78 participants (1.44%) when the urine was analyzed centrally. Before entering the study, 1773 participants (29.9%) were receiving or had received ARBs.

The study was coordinated by the Population Health Research Institute at McMaster University, Hamilton, Ontario, Canada. The steering committee designed and oversaw the trial and implemented an operations committee, an independent data safety and monitoring board, and an end point adjudication committee. Clinical sites in 40 countries, selected by the national coordinators, used a wide variety of recruitment strategies, including chart review, referral from other physicians, and mass mailing.

Randomization and Interventions

After a 3- to 4-week run-in phase, participants were randomly assigned to telmisartan, 80 mg/d, or placebo. During the run-in phase, all participants received single-blind placebo for 1 week followed by telmisartan, 80 mg/d, for 2 to 3 weeks. Of 6666 participants entering the run-in phase, 11 (0.2%) withdrew because of elevated serum creatinine levels and 26 (0.4%) withdrew because of elevated serum potassium levels. **Figure 1** shows the study flow diagram and reasons for exclusion; baseline characteristics of the participants are published elsewhere (1). Participants were randomly assigned by telephone through a central automated system. Randomization was stratified by hospital or clinic. All participants and trial investigators were blinded to randomized treatment. Tablets identical in color, shape, and taste were provided in blister packs. Unblinded data were made available exclusively to the independent data safety and monitoring board by a statistician who was independent of the trial.

Outcomes and Measurements

In August 2007, before completion of the TRANSCEND study, we developed a statistical analysis plan for the renal outcomes. As in other large renal trials, the primary composite outcome was defined as the first occurrence of dialysis, renal transplantation, doubling of serum creatinine, or death (6, 7, 9). No cases of renal transplantation were reported in this trial. The secondary renal outcome was the composite of dialysis or doubling of serum creatinine. After completion of the analysis, death—a nonspecific outcome—outnumbered the other components of the primary outcome by 4-fold. Therefore, we determined the secondary outcome as the composite outcome measure of this

analysis. Further outcomes were components of the composite outcome, changes in estimated GFR and UACR, and progression of proteinuria (defined as development of new micro- or macroalbuminuria), as well as the original primary composite outcome and the composite of dialysis; doubling of serum creatinine; or development of new microalbuminuria, macroalbuminuria, or both. Dialysis was categorized as short-term (≤2 months) or long-term (>2 months). Such information was missing in 1 patient. Urinary albumin and creatinine were measured centrally (10), and serum creatinine was measured locally at study sites. The estimated GFR was calculated from serum creatinine by using the 4-variable Modification of Diet in Renal Disease Study formula (11). Serum creatinine values below 35 μmol/L (<0.4 mg/dL) were considered implausible, and we excluded participants with such values from the analysis (10 patients at baseline and 15 patients at follow-up). Information about dialysis was recorded at each visit.

Follow-up Procedures and Monitoring

We followed participants after 6 weeks, 6 months, and every 6 months thereafter for a mean of 56 months. At each visit, we collected information about adverse events,

Figure 1. Study flow diagram.
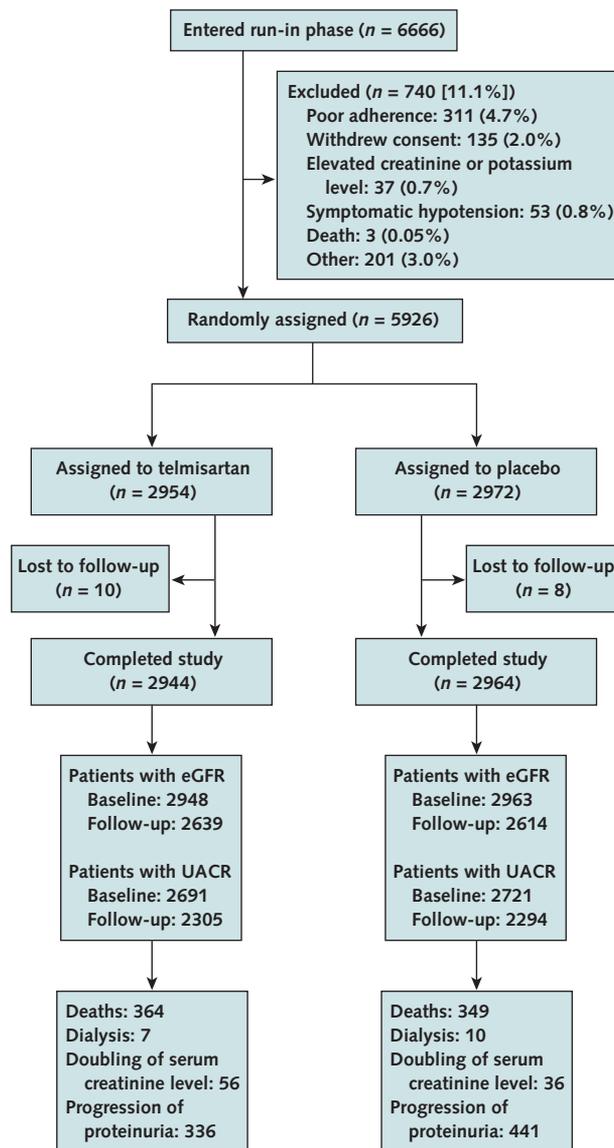
All participants received randomized therapy and were followed, except for 18 (0.3%) who were followed until the end of the study or until a primary event occurred. The number of patients considered for the trial who did not enter the run-in phase is unknown. A figure showing trial follow-up and cardiovascular outcomes is published elsewhere (1). Progression of proteinuria was defined as new microalbuminuria, macroalbuminuria, or both. eGFR = estimated glomerular filtration rate; UACR = urinary albumin–creatinine ratio.

Table 1. Baseline Patient Characteristics

Characteristic	Telmisartan Group (n = 2954)	Placebo Group (n = 2972)
Mean age (SD), y	66.9 (7.3)	66.9 (7.4)
Mean blood pressure (SD), mm Hg	140.7/81.8 (16.8/10.1)	141.3/82.0 (16.4/10.2)
Mean heart rate (SD), beats/min	68.8 (11.5)	68.8 (12.1)
Mean body mass index (SD), kg/m²	28.2 (4.6)	28.1 (4.6)
Mean glucose level (SD)		
mmol/L	6.51 (2.43)	6.49 (2.45)
mg/dL	117 (44)	117 (44)
Mean creatinine level (SD)		
μmol/L	91.9 (23.1)	91.9 (22.8)
mg/dL	1.0 (0.3)	1.0 (0.3)
Mean potassium level (SD), mmol/L	4.38 (0.44)	4.37 (0.45)
Female, n (%)	1280 (43.3)	1267 (42.6)
Ethnic group, n (%)		
Asian	637 (21.6)	624 (21.0)
Arab	37 (1.3)	40 (1.3)
African	51 (1.7)	55 (1.9)
European	1801 (61.0)	1820 (61.2)
Native or Aboriginal	390 (13.2)	393 (13.2)
Other	38 (1.3)	40 (1.3)
Condition, n (%)		
Coronary artery disease	2211 (74.8)	2207 (74.3)
Stroke or transient ischemic attack	648 (2l.9)	654 (22.0)
Peripheral artery disease	349 (11.8)	323 (10.9)
Hypertension	2259 (76.5)	2269 (76.3)
Diabetes	1059 (35.8)	1059 (35.6)
Left ventricular hypertrophy*	376 (12.7)	401 (13.5)
Microalbuminuria†	283 (10.6)	273 (10.1)
Smoking status, n (%)		
Current	293 (9.9)	289 (9.7)
Past	1273 (43.1)	1283 (43.2)
Medications, n (%)		
Statin	1645 (55.7)	1627 (54.7)
β-Blocker	1753 (59.3)	1700 (57.2)
Aspirin	2215 (75.0)	2210 (74.4)
Clopidogrel or ticlopidine	319 (10.8)	314 (10.6)
Antiplatelet agent	2356 (79.8)	2349 (79.0)
Diuretic	980 (33.2)	974 (32.8)
Calcium-channel blocker	1179 (39.9)	1202 (40.4)

* Based on the local investigators' electrocardiographic interpretations.
† Central measurements.

including dialysis; adherence to trial medication; and outcomes. We began data management as soon as data had been submitted, usually within 1 week of the patient visit. The data were sent through the datafax system and examined for ranges, plausibility, and missing data. Queries were sent to the investigator until responses were obtained. We measured serum creatinine before the run-in phase, 6 weeks after randomization, after 2 years, and at the end of the study, and we measured UACR before the run-in phase, at 2 years, and at the penultimate visit in a first morning urine sample. A UACR between 3.4 and 33.9 mg/mmol was defined as microalbuminuria and a value greater than 33.9 mg/mmol (approximately 300 mg/g creatinine) as macroalbuminuria. A blinded central committee, using standardized criteria, adjudicated all deaths and primary outcomes. After trial conclusion, a questionnaire was sent to all sites that reported dialysis to obtain information about duration of dialysis.

Statistical Analysis

The original sample size estimates for the trial were based on a composite cardiovascular outcome (1) and not on renal outcomes. Our primary analysis used a time-to-event approach and included all randomly assigned participants. Treatment comparisons with regard to time-to-event–related data (based on Cox regression of time to occurrence of first event) are displayed as hazard ratios (HRs) with 95% CIs. We performed analyses of prespecified subgroups by using the Cox regression model with factors for treatment, subgroup, and interactions. Adjustment for a center effect did not materially alter the analysis. Continuous data are presented as means (SDs) and categorical data as actual frequencies and percentages. All P values are 2-sided. We compared study groups for categorical data by using the chi-square test. For continuous variables, we compared study groups by using t tests. Urinary albumin levels and UACR were not normally distributed;

therefore, values were log-transformed before statistical analysis. For log-transformed data, the geometric means and 95% CIs are presented. We analyzed the relationships between changes in estimated GFR and blood pressure or changes in UACR by using least-squares linear regression. We analyzed the association of outcomes with changes in estimated GFR and UACR as continuous variables by using multivariate Cox regression adjusted for age, sex, baseline systolic blood pressure, and baseline estimated GFR. We also divided changes in estimated GFR into tertiles and analyzed the P value for trend for the outcomes. We used SAS, version 8.2 (SAS Institute, Cary, North Carolina), for all analyses.

Role of the Funding Source

Boehringer Ingelheim funded the study. The steering committee designed and oversaw the trial and had the final decision on the contents of the manuscript. All data were received, checked, and analyzed independently at the coordinating center at McMaster University. An operations committee, with representatives from McMaster University; its suboffices at the University of Oxford, Oxford, United Kingdom, and University of Auckland, Auckland, New Zealand, and the funding source met regularly. The decision for the present analysis was made by members of the steering committee. The funding source received the unblinded data after completion of the present analysis by the independent coordinating center.

RESULTS

Baseline Characteristics

Baseline patient characteristics were similar between the 2 groups, as reported elsewhere (1, 8). **Table 1** gives an overview of those characteristics. Mean estimated GFR was 71.7 mL/min per 1.73 m^2 (SD, 19.9); estimated GFR was less than 60 mL/min per 1.73 m^2 in 1629 participants (27.6%) and 60 mL/min per 1.73 m^2 or greater in 4282 participants (72.4%). Few participants (49 [0.8%]) had an estimated GFR less than 30 mL/min per 1.73 m^2. Microalbuminuria (UACR ≥3.4 to <33.9 mg/mmol) was present in 559 patients (10.3%) and macroalbuminuria in 78 patients (1.44%). Mean blood pressure at randomization was 141/82 mm Hg, which was significantly lower by about 3/1.5 to 5/2.5 mm Hg with telmisartan than with placebo throughout the study despite more intensive antihypertensive medication in the placebo group (details published elsewhere [1]). Among the telmisartan and placebo groups, 1.8% and 2.9% of patients at 1 year and 5.8% and 7.6% at the end of the study, respectively, were receiving an open-label ARB.

During the study, fewer participants in the telmisartan group (21.6%) than the placebo group (23.7%) (P = 0.055) permanently discontinued trial medication (1). Hypotensive symptoms leading to permanent discontinuation of trial medication were more frequent with telmisartan (0.98% vs. 0.54%). Hyperkalemia with potassium val-

ues greater than 5.5 mmol/L was also more frequent with telmisartan (3.8% vs. 1.4%), as were renal abnormalities reported on local clinical reports (10.4% vs. 8.1%) that rarely, however, led to trial medication discontinuation (0.81% vs. 0.44%) (1).

Main Outcomes

The incidence of the composite outcome of dialysis or doubling of serum creatinine was similar with telmisartan and placebo (58 patients [1.96%] vs. 46 patients [1.55%]; HR, 1.29 [95% CI, 0.87 to 1.89]; P = 0.20) (**Figure 2** and **Table 2**). Of 17 patients requiring dialysis, 6 cases were short-term, 10 were long-term, and 1 was unknown. In 4 of the 17 patients, dialysis occurred within the first year of participating in the trial. Dialysis cases did not significantly differ between groups (**Table 2**).

Doubling of serum creatinine was more frequent with telmisartan than with placebo (56 vs. 36 patients) (**Table 2**) and occurred mainly in patients with baseline serum creatinine levels less than 89 μmol/L (<1.0 mg/dL) (72 of 92 patients). Among the telmisartan and placebo groups, it occurred within 6 weeks in 15 of 56 patients and 6 of 36 patients, respectively, and was reversible in 14 of 56 patients and 9 of 36 patients, respectively. The composite outcome of dialysis, doubling of serum creatinine, or death did not significantly differ between the telmisartan and placebo groups (412 patients [14.0%] vs. 381 patients [12.8%]; HR, 1.10 [CI, 0.95 to 1.26]; P = 0.193) (**Table 2**). The timing of and reasons for death are published elsewhere (1). We categorized death as cardiovascular, due to cancer, or other, but we did not know the number of deaths due to renal disease.

Figure 2. **Kaplan–Meier curves for the composite renal outcome (dialysis or doubling of serum creatinine).**

HR, 1.29 (95% CI, 0.87–1.89); P = 0.20
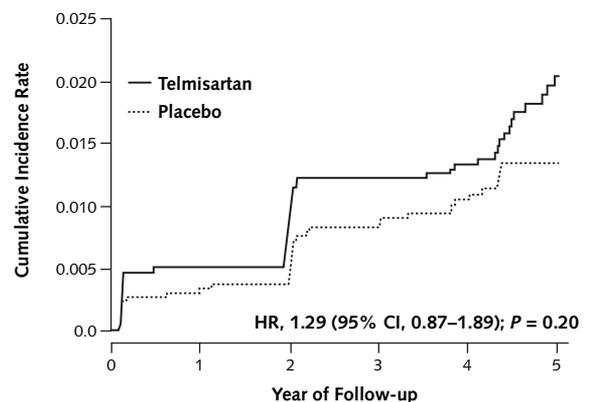
Patients at risk, *n*

Telmisartan	2954	2882	2807	2711	2433	1745
Placebo	2972	2908	2842	2746	2456	1763

There were no significant differences between groups (see **Table 1** for details). HR = hazard ratio.

Table 2. Incidence of the Main Outcomes*

Outcome	Telmisartan Group, n (%)	Placebo Group, n (%)	Hazard Ratio (95% CI)	P Value
Dialysis or doubling of serum creatinine	58 (1.96)	46 (1.55)	1.29 (0.87–1.89)	0.20
Dialysis†	7 (0.24)	10 (0.34)	0.71 (0.27–1.86)	0.49
Short-term	2 (0.07)	4 (0.14)	0.51 (0.09–2.76)	0.43
Long-term	4 (0.14)	6 (0.14)	0.67 (0.19–2.38)	0.54
Doubling of serum creatinine	56 (1.90)	36 (1.21)	1.59 (1.04–2.41)	0.031
Death	364 (12.3)	349 (11.7)	1.05 (0.91–1.22)	0.49
Dialysis, doubling of serum creatinine, or death	412 (14.0)	381 (12.8)	1.10 (0.95–1.26)	0.193

* Differences between groups were analyzed by time-to-event analysis. The number of participants with doubling of serum creatinine varies slightly from a previous report (1) because we excluded some implausible serum creatinine levels <35 μmol/L (<0.4 mg/dL) (see Methods section).
† Patients who had ≥1 dialysis treatment were considered to be having dialysis; long-term dialysis was >2 months, and short-term dialysis was ≤2 months. No information on duration of dialysis was available for 1 patient.

Changes in Albuminuria

Incident albuminuria increased less with telmisartan than with placebo (**Table 3**). The risk for new microalbuminuria, macroalbuminuria, or both during the trial was lower with telmisartan than with placebo (336 patients [11.4%] vs. 441 patients [14.8%]; relative risk [RR], 0.77 [CI, 0.67 to 0.88]; $P = 0.001$). Among patients with microalbuminuria at baseline (559 total [286 telmisartan recipients and 273 placebo recipients]), 28 patients (9.8%) in the telmisartan group and 49 (17.9%) in the placebo group progressed to macroalbuminuria (RR, 0.58 [CI, 0.36 to 0.92]; $P = 0.018$). The composite outcome of dialysis; doubling of serum creatinine; and new microalbuminuria, macroalbuminuria, or both occurred in 383 patients (13.0%) in the telmisartan group and 474 (16.0%) in the placebo group (HR, 0.81 [CI, 0.72 to 0.92]; $P = 0.001$).

We further analyzed the association of changes in estimated GFR with the increase in UACR from baseline to 2 years (**Table 3**). A greater decline in estimated GFR from baseline to 6 weeks (linear regression $P = 0.003$; 4255 patients) and from baseline to 2 years (linear regression $P = 0.005$; 4257 patients) was associated with less increase in UACR from baseline to 2 years. For these 2 correlations, there was a treatment interaction; the correlations were significant only in the telmisartan group. In that group, UACR increased 17.6% less for each 1–mL/min per 1.73

m^2 decrease in estimated GFR at 6 weeks ($P = 0.008$; 2134 patients) and increased 19.1% less for each 1–mL/min per 1.73 m^2 decrease in estimated GFR at 2 years ($P = 0.001$; 2138 patients).

Changes in Estimated GFR

During follow-up, estimated GFR decreased more with telmisartan than with placebo (**Table 4** and **Appendix Figure 1**, available at www.annals.org). The decrease in estimated GFR was mainly observed during the initial 6 weeks of the trial. After 6 weeks, a further significant but very slight decline in estimated GFR occurred in the telmisartan group (**Table 4**). Of participants in the placebo and telmisartan groups with a baseline estimated GFR of 30 mL/min per 1.73 m^2, 44 of 2897 (1.52%) and 74 of 2903 (2.55%), respectively, reached an estimated GFR less than 30 mL/min per 1.73 m^2 (RR, 1.71 [CI, 1.18 to 2.48]; $P = 0.005$). Of participants with a baseline estimated GFR of 60 mL/min per 1.73 m^2 or greater, 555 of 2128 (26.1%) and 729 of 2109 (34.6%), respectively, reached an estimated GFR less than 60 mL/min per 1.73 m^2 (RR, 1.40 [CI, 1.125 to 1.56]; $P < 0.001$).

The modest initial changes in estimated GFR were related to the change in systolic blood pressure during the same interval (**Figure 3**); a greater decrease in blood pressure was associated with a greater decrease in estimated GFR. **Figure 3** shows the relationship for all participants;

Table 3. Changes in Log-Transformed UACR*

Variable	Telmisartan Group		Placebo Group		P Value (Telmisartan vs. Placebo)
	Geometric Mean UACR (95% CI), mg/mmol	Patients, n	Geometric Mean UACR (95% CI), mg/mmol	Patients, n	
Baseline UACR	0.68 (0.65–0.72)	2691	0.66 (0.63–0.70)	2721	–
Ratio of 2-year vs. baseline UACR	1.17 (1.11–1.24)	2172	1.45 (1.37–1.53)	2163	<0.001
Ratio of final vs. baseline UACR	1.32 (1.23–1.41)	1565	1.63 (1.52–1.76)	1557	<0.001

UACR = urinary albumin–creatinine ratio.
* All UACRs were log-transformed before analyses; geometric mean values are back-transformed. Differences were calculated by using an analysis of variance model adjusted for baseline values. Only participants with baseline and follow-up values could be included in the analysis. Mean follow-up time for the final UACR was 50 months. Absolute values of UACR at 2 years and final values also significantly differed between groups, as did absolute values of changes from baseline between groups ($P < 0.001$ for all comparisons; data not shown).

Table 4. Estimated GFR at Baseline and Changes in Estimated GFR*

Variable	Telmisartan Group		Placebo Group		P Value (Telmisartan vs. Placebo)
	Mean Estimated GFR (SD), mL/min per 1.73 m²	Patients, n	Mean Estimated GFR (SD), mL/min per 1.73 m²	Patients, n	
Baseline estimated GFR	71.8 (19.9)	2948	71.7 (19.9)	2963	–
Change in estimated GFR					
Baseline to 6 weeks	−2.56 (14.4)	2862	−0.97 (13.5)	2864	<0.001
Baseline to 2 years	−3.02 (17.1)	2597	−0.05 (16.0)	2562	<0.001
Baseline to final	−3.20 (18.3)	2216	−0.26 (18.0)	2179	<0.001
6 weeks to final	−1.36 (17.6)	2190	0.47 (17.8)	2147	<0.001

GFR = glomerular filtration rate.
* Differences between groups were calculated by using the *t* test. Only participants with baseline and follow-up values could be included in the analysis. Mean follow-up time for the final estimated GFR value was 56 months.

the association was evident for both groups with no treatment interaction. Linear regression analysis indicated that a 10–mm Hg decrease in systolic blood pressure was associated with a decrease in estimated GFR of 2.05 mL/min per 1.73 m² from the run-in phase to 6 weeks. The change in estimated GFR from baseline to week 6, analyzed as a continuous variable by Cox regression for all participants and for the 2 groups separately, was not associated with subsequent death or the composite outcome of myocardial infarction, stroke, and cardiovascular death, adjusted for baseline estimated GFR, age, sex, and baseline systolic blood pressure. Similarly, we found no evidence that those cardiovascular outcomes differed by tertiles of change in estimated GFR from baseline to week 6.

Main Outcomes in Subgroups

For the composite renal outcome of dialysis or doubling of serum creatinine, the effects of telmisartan varied by the baseline UACR (*P* = 0.006 for interaction) and estimated GFR (*P* = 0.022) (**Figure 3**). Telmisartan increased the incidence of the composite renal outcome in patients with no microalbuminuria or an estimated GFR greater than 60 mL/min per 1.73 m². In contrast, telmisartan tended to reduce this outcome in those with microalbuminuria or an estimated GFR below 60 mL/min per 1.73 m² (**Appendix Figure 2**, available at www.annals.org).
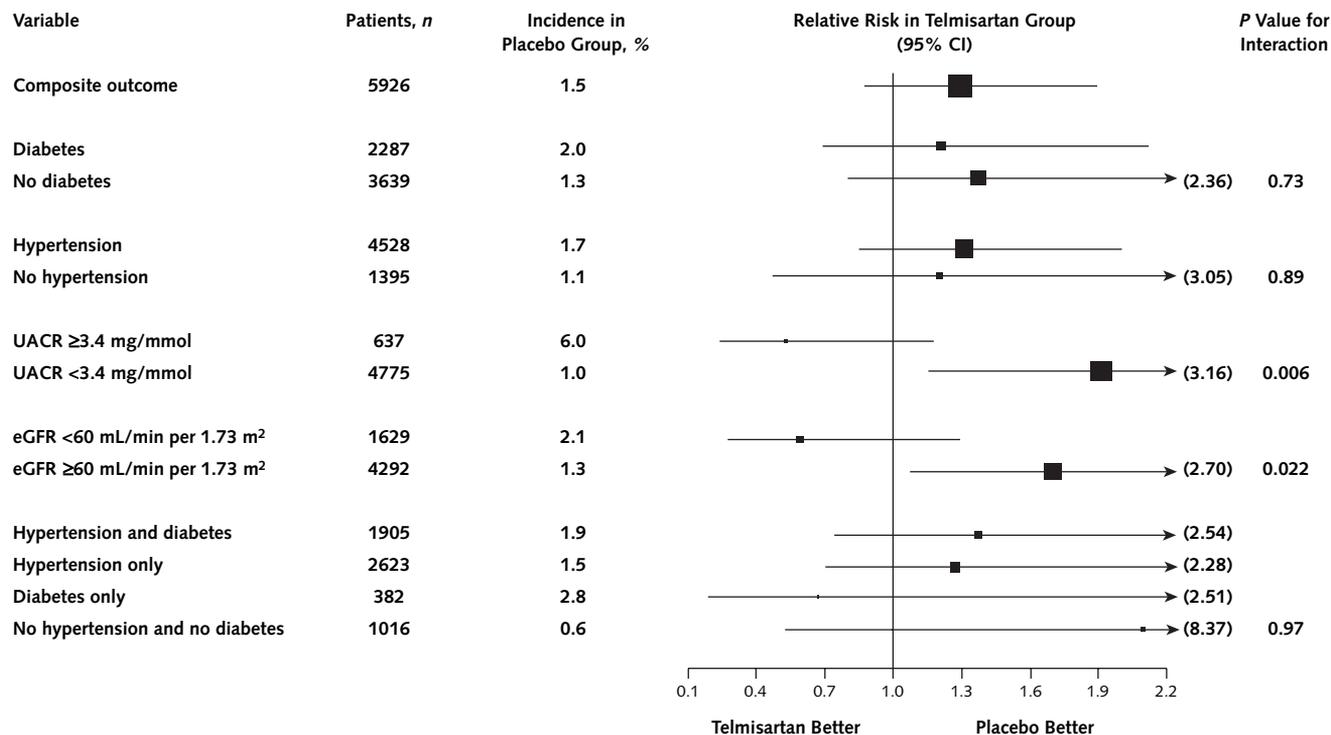
DISCUSSION

The TRANSCEND study was a large trial in adults intolerant of ACE inhibitors who had atherosclerotic vascular disease but not macroalbuminuria; it evaluated an ARB, telmisartan, versus placebo and measured 2 common markers of renal dysfunction—serum creatinine and urinary albumin—over 56 months. Telmisartan had no important effect on the composite outcome of dialysis or doubling of serum creatinine, decreased UACR, and decreased estimated GFR. Telmisartan increased 1 component of the composite renal outcome: doubling of serum creatinine. The prognostic implication of doubling of serum creatinine in this population is unclear. Because doubling of serum creatinine indicates an approximate halving of GFR

(12), the difference may suggest a potential disadvantage of telmisartan. However, the excess of 20 of these events must be balanced by the reduction in 56 major vascular events, including cardiovascular death, stroke, and myocardial infarction (1). The former outcome is a laboratory measure and is clinically less severe than the latter clinical outcome and may reverse after stopping treatment. Doubling of serum creatinine occurred mainly in participants with normal estimated GFR at baseline and was not associated with dialysis during the 5 years of the trial; only studies with a much longer follow-up can determine the clinical significance of doubling of serum creatinine from normal values.

Given the potential of inhibitors of the renin–angiotensin system, including ARBs, to induce acute renal failure (13), the results of the TRANSCEND study are informative. In this large sample of people with vascular disease and a follow-up of almost 5 years, only 6 cases of dialysis-dependent acute renal failure were documented: 4 with placebo and 2 with telmisartan. When telmisartan was combined with an ACE inhibitor in ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial), the incidence of acute renal failure was substantially higher (9, 14).

Estimated GFR was fairly stable in the study and changed less than the annual decrease in estimated GFR of about 1 mL/min that is expected (12) in people with vascular disease. Estimated GFR decreased slightly more with telmisartan than with placebo. An initial short-term decrease in estimated GFR after initiation of ARB therapy is expected as a consequence of decreasing intraglomerular hydraulic pressure. Decreasing the intraglomerular pressure has been shown to contribute to blunt progressive renal damage (12). The initial decrease in estimated GFR may even be associated with a long-term benefit on estimated GFR (15). Our findings do not support or refute the latter expectation, because estimated GFR remained stable with placebo. The latter is unexpected and is a new finding in people with vascular disease given intensive treatment with proven drugs. Longer-term follow-up would be necessary to evaluate substantial effects of telmisartan on estimated

Figure 3. Relative risk for the composite renal outcome (dialysis or doubling of serum creatinine) in subgroups.

Variable	Patients, n	Incidence in Placebo Group, %	Relative Risk in Telmisartan Group (95% CI)	P Value for Interaction
Composite outcome	5926	1.5		
Diabetes	2287	2.0		
No diabetes	3639	1.3	(2.36)	0.73
Hypertension	4528	1.7		
No hypertension	1395	1.1	(3.05)	0.89
UACR ≥3.4 mg/mmol	637	6.0		
UACR <3.4 mg/mmol	4775	1.0	(3.16)	0.006
eGFR <60 mL/min per 1.73 m^2	1629	2.1		
eGFR ≥60 mL/min per 1.73 m^2	4292	1.3	(2.70)	0.022
Hypertension and diabetes	1905	1.9	(2.54)	
Hypertension only	2623	1.5	(2.28)	
Diabetes only	382	2.8	(2.51)	
No hypertension and no diabetes	1016	0.6	(8.37)	0.97

Some 95% CIs exceed the scale of relative risk and are shown by the numbers in parentheses. *P* values for interaction test whether there is an interaction of the respective subgroup with the 2 treatment methods. Diabetes is defined as having a history of diabetes or a fasting glucose level >7 mmol/L (>126 mg/dL). eGFR = estimated glomerular filtration rate; UACR = urinary albumin–creatinine ratio.

GFR in a patient sample at low renal risk or during a washout period at study end. Other studies have shown that GFR may considerably increase during a washout period of ARB (15, 16).

We also demonstrate that an initial decrease in estimated GFR is closely related to an initial decrease in blood pressure that was greater with telmisartan than with placebo. The relative contribution of angiotensin-receptor blockade and blood pressure to estimated GFR can be examined only with more rigorous measurement of blood pressure. Changes in blood pressure occurred within the renal autoregulatory range, but autoregulation may be variously impaired in this study population. Furthermore, the difference in estimated GFR between the telmisartan and placebo groups is not necessarily a disadvantage, because the change in estimated GFR was not related to death or other cardiovascular outcomes.

Compared with placebo, telmisartan reduced urinary albumin excretion and the progression of micro- to macroalbuminuria. This reduction was associated with an initial decrease in estimated GFR and blood pressure. The decrease in UACR is generally considered to be beneficial for the kidney, but we observed directionally opposite long-term effects on estimated GFR with telmisartan. The lack of association of less albuminuria with decreased long-term

renal outcomes in patients with vascular disease and similar data from ONTARGET (10) suggest that reduction in urinary albumin excretion in people with a baseline level below the threshold of macroalbuminuria may not be a surrogate of other measures of renal function, at least over 5 years. In fact, a decrease in UACR was associated with a decrease in estimated GFR and may be nothing more than a consequence of the latter. Previous studies in patients with renal diseases and low levels of proteinuria reported varied results for the relationship of the early changes of UACR and long-term renal outcomes (17, 18).

Exploratory analyses of subgroups found a significant interaction of telmisartan's effect on the secondary renal outcome with baseline albuminuria and baseline estimated GFR. Telmisartan increased the incidence of the secondary renal outcome in subgroups without specific renal risk—namely, patients with normal albumin excretion and an estimated GFR greater than 60 mL/min per 1.73 m^2—but tended to be beneficial on the secondary renal outcome in subgroups at higher renal risk—namely, patients with elevated albuminuria and those with low estimated GFR. Even in such a large trial as TRANSCEND, subgroup results must be interpreted with great caution and should only be considered as hypothesis-generating. In proteinuric nephropathies above 1 g/g creatinine, inhibition of

the renin–angiotensin system is unequivocally beneficial (6, 7). In people with proteinuria below the macroalbuminuria threshold, several other studies reported no major detrimental or beneficial effects of ACE inhibitors or ARBs on GFR (19–22).

Our study has limitations. Our inclusion criteria were based on individuals at risk for cardiovascular outcomes. Nevertheless, the 104 more specific renal outcomes add to knowledge from other similar trials (6, 7), and the effect of ARBs on the kidney in the study sample is relevant, because this constitutes a large population eligible to receive ARBs. Serum creatinine was measured locally, and the local methods were not calibrated to a standard. However, variations among laboratories create random errors and do not systematically bias the results. When serum creatinine doubled, we did not require a confirmatory measurement; however, such information was available in 61% of events. Doubling of serum creatinine mainly occurred in patients with normal estimated GFR or low serum creatinine at baseline; thus, few participants reached end-stage renal disease. Whether individuals with doubling of serum creatinine would develop end-stage renal disease during longer follow-up or would die at a faster rate than those with more stable GFR is unknown and should be explored in trials of longer duration. Our study did not include a washout period at the end, which may have been important to assess whether the small decrease in estimated GFR with telmisartan was due to continuing blockade of the renin–angiotensin system and was therefore reversible (15, 16) or reflected a true structural damage to the kidney.

Our results suggest that ARBs offer no renal benefit in ACE-intolerant people at high vascular risk but without macroalbuminuria and are not associated with an excess of dialysis-dependent renal failure. Therefore, the effect on cardiovascular outcomes should dominate clinical decision making on whether to use telmisartan. Although telmisartan reduced proteinuria, the implications of this reduction as a surrogate marker for progression of renal disease are uncertain in patients with relatively stable estimated GFR.

From Schwabing General Hospital and KfH Kidney Center, Ludwig Maximilians University, Munich, Germany; Friedrich Alexander University, Erlangen, Germany; Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada; Boehringer Ingelheim, Ingelheim, Germany; Beijing Hypertension League Institute, Beijing, China; University of Washington, Seattle, Washington; Dante Pazzanese Institute of Cardiology, São Paulo, Brazil; University of Guadalajara, Guadalajara, Mexico; Institute of Cardiology and Pneumology, Laval University and Hospital, Quebec, Quebec, Canada; University of Buenos Aires, Buenos Aires, Argentina; Heart Institute, University of Ottawa, Ottawa, Ontario, Canada; University of Grenoble, Grenoble, France; Karolinska Institutet, Stockholm, Sweden; and Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Dr. Mann: Schwabing General Hospital, KfH Kidney Center, Ludwig Maximilians University, Kolner Platz 1, DE-80804 Munich, Germany.

Dr. Schmieder: Department of Nephrology and Hypertension, Friedrich Alexander University, DE-91054 Erlangen, Germany.

Ms. Dyal and Drs. Pogue, Teo, and Yusuf: Population Health Research Institute, McMaster University, 237 Barton Street East, Hamilton, Ontario L8L 2X2, Canada.

Dr. McQueen: Pathology and Molecular Medicine, McMaster University and Population Health Research Institute, 237 Barton Street East, Hamilton Ontario L8L 2X2, Canada.

Dr. Schumacher: Boehringer Ingelheim, DE-55091 Ingelheim, Germany.

Dr. Wang: Beijing Hypertension League Institute, Beijing, China.

Dr. Probstfield: Department of Medicine, University of Washington, Seattle, Washington.

Dr. Avezum: Dante Pazzanese Institute of Cardiology, São Paulo, Brazil.

Dr. Cardona-Munoz: Department of Physiology, University of Guadalajara, Guadalajara, Mexico.

Dr. Dagenais: Institute of Cardiology and Pneumology, Laval University and Hospital, Quebec, Quebec, Canada.

Dr. Diaz: Department of Medicine, University of Buenos Aires, Buenos Aires, Argentina.

Dr. Fodor: Heart Institute, University of Ottawa, Ottawa, Ontario, Canada.

Dr. Maillon: University of Grenoble, Grenoble, France.

Dr. Rydén: Cardiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.

Dr. Yu: Division of Cardiology, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China.

Appendix Table. Exclusion Criteria

Medication use*
  Inability to discontinue ACE inhibitor or ARB therapy
  Known hypersensitivity or intolerance to ARB or ACE inhibitors
Cardiovascular disease
  Symptomatic congestive heart failure
  Hemodynamically significant primary valvular or outflow tract obstruction (e.g., aortic or mitral valve stenosis, asymmetric septal hypertrophy, malfunctioning prosthetic valve)
  Constrictive pericarditis
  Complex congenital heart disease
  Syncope of unknown cause <3 months before informed consent
  Planned cardiac surgery or angioplasty within 3 months
  Uncontrolled hypertension with treatment (e.g., blood pressure >130/100 mm Hg)
 Heart transplant recipient
  Strokes due to subarachnoid hemorrhage
Other condition
  Significant renal disease, defined as:
    Documented significant renal artery stenosis
    Creatinine clearance <36 mL/min per 1.73 m² or serum creatinine level >265 μmol/L (>3.0 mg/dL)
    Hyperkalemia (potassium level >5.5 mmol/L)
    Proteinuria (for TRANSCEND only)
  Hepatic dysfunction, defined as:
    ALT or AST level greater than 4 times the upper limit of normal
    Additional criteria for hepatic impairment greater than the upper limit of normal
    Total bilirubin level >20 μmol/L (>8.2 mg/dL)
    Biliary obstructive disorders
  Uncorrected volume depletion or sodium depletion
  Primary aldosteronism
  Hereditary fructose intolerance
  Any other major noncardiac illness expected to reduce life expectancy or interfere with study participation
  Simultaneous use of another experimental drug
  Significant or sufficient disability or other incapacity that precludes regular attendance at clinic for follow-up
  Inability or unwillingness to provide written informed consent

ACE = angiotensin-converting enzyme; ALT = alanine aminotransferase; ARB = angiotensin-receptor blocker; AST = aspartate aminotransferase; TRANSCEND = Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease.
* Patients with known intolerance to ACE inhibitors should be enrolled in the TRANSCEND study.

Appendix Figure 1. **Change in estimated GFR from baseline to 6 weeks after randomization, by quartile of change in systolic blood pressure from baseline to 6 weeks.**
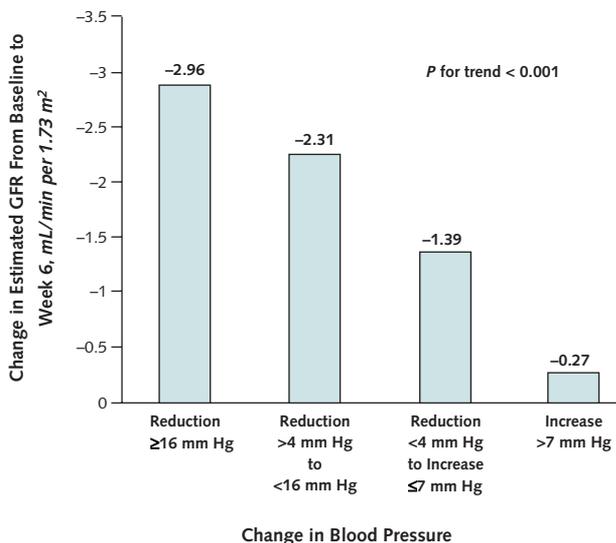
Regression analysis demonstrated that a change in systolic blood pressure of 10 mm Hg is associated with a change in estimated GFR of 2.05 mL/min per 1.73 m². GFR = glomerular filtration rate.

Appendix Figure 2. **Kaplan–Meier curves for the composite renal outcome (dialysis or doubling of serum creatinine), by baseline UACR.**
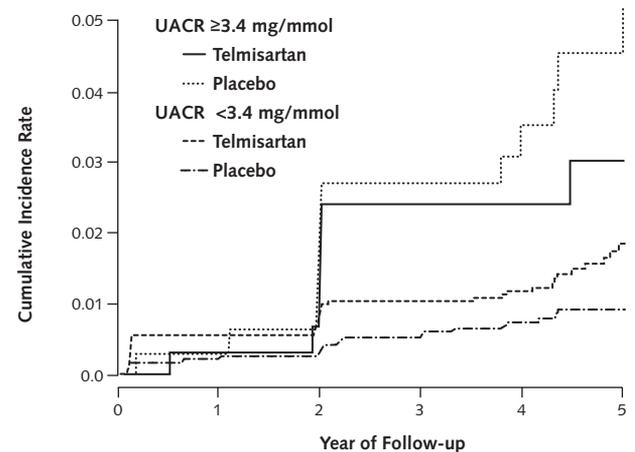
The treatment–subgroup interaction term was significant ($P = 0.006$). See **Appendix Figure 1**. UACR = urinary albumin–creatinine ratio.