

## ORIGINAL ARTICLE

# Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease

Vicente E. Torres, M.D., Ph.D., Arlene B. Chapman, M.D.,  
Olivier Devuyst, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D.,  
Ronald D. Perrone, M.D., Gary Koch, Ph.D., John Ouyang, Ph.D.,  
Robert D. McQuade, Ph.D., Jaime D. Blais, Ph.D., Frank S. Czerwiec, M.D., Ph.D.,  
and Olga Sergejeva, M.D., M.P.H., for the REPRISÉ Trial Investigators\*

## ABSTRACT

**BACKGROUND**

In a previous trial involving patients with early autosomal dominant polycystic kidney disease (ADPKD; estimated creatinine clearance,  $\geq 60$  ml per minute), the vasopressin  $V_2$ -receptor antagonist tolvaptan slowed the growth in total kidney volume and the decline in the estimated glomerular filtration rate (GFR) but also caused more elevations in aminotransferase and bilirubin levels. The efficacy and safety of tolvaptan in patients with later-stage ADPKD are unknown.

**METHODS**

We conducted a phase 3, randomized withdrawal, multicenter, placebo-controlled, double-blind trial. After an 8-week prerandomization period that included sequential placebo and tolvaptan run-in phases, during which each patient's ability to take tolvaptan without dose-limiting side effects was assessed, 1370 patients with ADPKD who were either 18 to 55 years of age with an estimated GFR of 25 to 65 ml per minute per  $1.73 \text{ m}^2$  of body-surface area or 56 to 65 years of age with an estimated GFR of 25 to 44 ml per minute per  $1.73 \text{ m}^2$  were randomly assigned in a 1:1 ratio to receive tolvaptan or placebo for 12 months. The primary end point was the change in the estimated GFR from baseline to follow-up, with adjustment for the exact duration that each patient participated (interpolated to 1 year). Safety assessments were conducted monthly.

**RESULTS**

The change from baseline in the estimated GFR was  $-2.34$  ml per minute per  $1.73 \text{ m}^2$  (95% confidence interval [CI],  $-2.81$  to  $-1.87$ ) in the tolvaptan group, as compared with  $-3.61$  ml per minute per  $1.73 \text{ m}^2$  (95% CI,  $-4.08$  to  $-3.14$ ) in the placebo group (difference,  $1.27$  ml per minute per  $1.73 \text{ m}^2$ ; 95% CI,  $0.86$  to  $1.68$ ;  $P < 0.001$ ). Elevations in the alanine aminotransferase level (to  $> 3$  times the upper limit of the normal range) occurred in 38 of 681 patients (5.6%) in the tolvaptan group and in 8 of 685 (1.2%) in the placebo group. Elevations in the aminotransferase level were reversible after stopping tolvaptan. No elevations in the bilirubin level of more than twice the upper limit of the normal range were detected.

**CONCLUSIONS**

Tolvaptan resulted in a slower decline than placebo in the estimated GFR over a 1-year period in patients with later-stage ADPKD. (Funded by Otsuka Pharmaceuticals and Otsuka Pharmaceutical Development and Commercialization; REPRISÉ ClinicalTrials.gov number, NCT02160145.)

From the Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN (V.E.T.); the Section of Nephrology, University of Chicago, Chicago (A.B.C.); the Institute of Physiology, University of Zurich, Zurich, Switzerland (O.D.); the Division of Nephrology, Université Catholique de Louvain Medical School, Brussels (O.D.); the Division of Nephrology, University Medical Center Groningen, Groningen, the Netherlands (R.T.G.); the Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston (R.D.P.); the Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill (G.K.); and Otsuka Pharmaceutical Development and Commercialization, Rockville, MD (J.O., R.D.M., J.D.B., F.S.C., O.S.). Address reprint requests to Dr. Torres at the Division of Nephrology and Hypertension, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, or at [torres.vicente@mayo.edu](mailto:torres.vicente@mayo.edu).

\*A complete list of the investigators and the members of the committees of the Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISÉ) trial is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

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**A**UTOSOMAL DOMINANT POLYCYSTIC KIDNEY disease (ADPKD) is the fourth leading cause of end-stage kidney disease in adults.<sup>1,3</sup> When the genes encoding polycystin 1 (PKD1) and polycystin 2 (PKD2) are disrupted, tubular epithelial cells in vasopressin-sensitive distal nephrons and collecting ducts show enhanced proliferation, chloride-driven fluid secretion, and expression of proinflammatory cytokines, resulting in cyst development and the destruction of renal parenchyma.<sup>4</sup>

Vasopressin promotes kidney-cyst cell proliferation and fluid secretion by means of up-regulation of adenosine-3',5'-cyclic monophosphate (cAMP).<sup>5,6</sup> The suppression of vasopressin production, release, or action by means of hydration,<sup>7,8</sup> V<sub>2</sub>-receptor blockade,<sup>9-14</sup> or genetic mutation<sup>15</sup> has been shown to reduce cyst burden, protect kidney function, and prolong survival in rodent models.

In the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 trial, which involved patients with early ADPKD (estimated creatinine clearance,  $\geq 60$  ml per minute), tolvaptan reduced kidney growth and the decline in the estimated glomerular filtration rate (GFR).<sup>16</sup> The benefit with regard to the estimated GFR was maintained after 2 additional years of open-label treatment (TEMPO 4:4 study).<sup>17</sup> Idiosyncratic hepatocellular toxic effects were unanticipated.<sup>18</sup> With monitoring occurring once every 4 months, two patients in the TEMPO 3:4 trial and one in the TEMPO 4:4 study had evidence of potentially serious drug-induced liver injury. We conducted the Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trial, a phase 3, randomized withdrawal, multicenter, placebo-controlled, double-blind trial involving patients with ADPKD who had late chronic kidney disease of stage 2 to early stage 4, in order to ascertain the efficacy and safety of tolvaptan in patients with more advanced ADPKD with the use of more frequent monitoring for toxic effects in the liver.<sup>19</sup>

## METHODS

### TRIAL DESIGN AND OVERSIGHT

The institutional review board at each site approved the protocol and the informed-consent form. A steering committee that comprised investigators and representatives of the sponsor (Otsuka Pharmaceuticals and Otsuka Pharma-

ceutical Development and Commercialization) oversaw the trial design and conduct with the assistance of an independent data and safety monitoring committee and a hepatic adjudication committee. The sponsor collected and analyzed the data. The first author wrote the manuscript with substantial contributions from the coauthors (including authors who are employees of the sponsor) and assumes responsibility for its content and integrity. The sponsor had no other role in writing or reviewing the manuscript. All the authors had access to the analyzed data, jointly decided to submit the manuscript for publication, and vouch for the accuracy and completeness of the reported data and for fidelity of the trial to the protocol. The trial protocol, which is available with the full text of this article at NEJM.org, has been published previously.<sup>19</sup>

From May 2014 through March 2016, patients were enrolled at 213 sites globally. Eligible persons were either 18 to 55 years of age with an estimated GFR of 25 to 65 ml per minute per 1.73 m<sup>2</sup> of body-surface area or 56 to 65 years of age with an estimated GFR of 25 to 44 ml per minute per 1.73 m<sup>2</sup>. Patients in the older age group also had to have historical evidence of a decline in the estimated GFR of more than 2.0 ml per minute per 1.73 m<sup>2</sup> per year.<sup>20</sup>

The trial consisted of an 8-week prerandomization period that was divided into a screening phase, a single-blind placebo run-in phase, and a single-blind tolvaptan period that comprised a dose-adjustment phase and a run-in phase (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Patients who could take tolvaptan at daily morning and afternoon doses of 60 mg and 30 mg, respectively, or 90 mg and 30 mg, respectively, were randomly assigned in a 1:1 ratio, in a double-blind fashion, to receive tolvaptan or matching placebo for 12 months. Randomization was stratified according to the baseline estimated GFR ( $\leq 45$  or  $>45$  ml per minute per 1.73 m<sup>2</sup>), age of the patient ( $\leq 55$  or  $>55$  years), and total kidney volume ( $\leq 2000$  ml,  $>2000$  ml, or unknown).<sup>21</sup> The maximal dose of tolvaptan that could be taken without an unacceptable level of side effects during the run-in period, or the equivalent as matching placebo, was dispensed according to the randomization assignment. Adjustment of the dose down to morning and afternoon doses of 45 mg and 15 mg, respectively, or of 30 mg and 15 mg, respectively, was permitted during the trial period.

Serum creatinine levels were measured cen-

trally with the use of the isotope dilution mass spectrometry–traceable enzymatic method and were reported to two decimal points.<sup>19,22</sup> Determinations of the estimated GFR were made with the use of the Chronic Kidney Disease Epidemiology Collaboration equation.<sup>23</sup>

#### TRIAL ASSESSMENTS

Evaluations were performed at baseline (during the screening and placebo run-in phases) and during the single-blind tolvaptan period (Fig. S1 in the Supplementary Appendix). Patients underwent monthly laboratory testing and reported to the trial sites every 3 months. Three follow-up laboratory visits occurred between days 7 and 40 after the receipt of the last dose of the assigned trial regimen. For patients who did not complete the trial, the follow-up period started after the discontinuation of the trial regimen and included a final follow-up at the originally scheduled 12-month visit.

#### OUTCOME MEASURES

##### *Primary End Point*

The primary end point was the change in the estimated GFR from baseline (before the receipt of any placebo or tolvaptan) to follow-up (after the 1-year trial period had been completed), with adjustment for the time each patient was in the trial and with interpolation to 1 year. Without this adjustment, the trial group that had more withdrawals or earlier withdrawals would have had an advantage because patients who withdrew early would have had less time for renal-function deterioration. The GFR values that were obtained before and after the receipt of any placebo or tolvaptan were estimated from the mean of three baseline serum creatinine values (two obtained during screening and one during the placebo run-in phase) and from the mean of three follow-up values that were obtained after the 1-year trial period was completed. The trial duration for each patient was defined as the interval between the median timings of the baseline observations and the follow-up observations. These estimated GFR measurements were not affected by the acute hemodynamic effect of tolvaptan, which is rapidly reversible when the drug is not being taken.<sup>24-26</sup> Vasopressin acting on V<sub>2</sub>-receptors increases the glomerular filtration rate by means of the activation of tubuloglomerular feedback and afferent vasodilation and by means of renin release and efferent vasoconstriction<sup>27,28</sup>; tolvaptan counteracts these effects.

##### *Key Secondary End Point*

The key secondary end point was the slope of the change in the estimated GFR that was derived from the individual slopes for each patient, with adjustment for the duration of the observations and with interpolation to 1 year. This analysis included data for each participant in each group and used all the serum creatinine values that were obtained during the placebo run-in phase, the tolvaptan run-in period (not including the tolvaptan dose-adjustment phase), the 12-month double-blind period, and the follow-up phase in a linear model that included a factor to account for the hemodynamic effect on the estimated GFR during the tolvaptan run-in period and the 1-year trial period.

##### *Hepatic Safety Monitoring*

All the cases of elevations in the hepatic aminotransferase level to more than three times the upper limit of the normal range, elevations in the total bilirubin level to more than two times the upper limit of the normal range, and hepatic-related adverse events (that were serious or that led to the discontinuation of the trial regimen) were adjudicated by the hepatic adjudication committee. The members of this committee, who were unaware of the trial-group assignments, rated the likelihood that the trial regimen caused the event on a scale from “unlikely” to “definite.”<sup>18</sup>

#### STATISTICAL ANALYSIS

On the basis of a mixed-model, repeated-measurement analysis involving the non-Japanese patients with chronic kidney disease of stage 3 who were included in the TEMPO 3:4 trial, we calculated that it would be necessary for the present trial to include 1300 patients in order to test the primary hypothesis, assuming a between-group difference at 1 year in the decline in the estimated GFR of 1.07 ml per minute per 1.73 m<sup>2</sup>, with a standard deviation of 5.73, 90% power, a two-sided alpha level of 0.05, and a 10% rate of withdrawal.<sup>19,26</sup> (Data from the Japanese patients in the TEMPO 3:4 trial were not included in the power calculations because the present trial [REPRISE] was not planned to include Japanese patients.) The analyses of all the efficacy end points were performed according to the intention-to-treat principle. Details of the prespecified sensitivity and subgroup analyses are provided in the protocol.<sup>19</sup> The end points of the trial were

ordered hierarchically and tested sequentially with gatekeeping procedures; if the primary end point was found to be significant, analysis of the secondary end point would be justified.

A modified intention-to-treat population or full analysis set, in accordance with the intention-to-treat principle and the E9 regulation (regarding statistical principles for clinical trials) of the International Conference on Harmonisation, was used for the analysis of the primary end point. All patients with any data to inform the primary or secondary end points or safety were included in the modified intention-to-treat and safety populations. The primary end point was analyzed by means of a weighted analysis of covariance with trial group and randomization stratification factors as factor and baseline covariates, as described in the Supplementary Appendix and the statistical analysis plan (see the protocol). The key secondary end point was also assessed in the modified intention-to-treat population and was analyzed with the use of a linear mixed-effect model with effects of time (as a continuous variable), trial group, interaction of time and trial group, acute hemodynamic effect, stratification factors at randomization, and baseline covariate (of the primary end point) to fit the estimated GFR data (see the statistical analysis plan).

## RESULTS

### PATIENTS

A total of 2292 patients underwent screening and provided informed consent; 1496 patients entered the single-blind tolvaptan period, of whom 126 withdrew before randomization (owing to aquaretic events [polyuria, nocturia, thirst, dry mouth, and polydipsia] in 68 patients). The remaining 1370 patients (91.6%) who entered the single-blind tolvaptan period and did not have adverse effects that prevented their continuation in the trial were randomly assigned to receive tolvaptan (683 patients) or placebo (687 patients). A total of 95.8% of the patients in the tolvaptan group and 95.9% of those in the placebo group completed the month 12 visit. Details are provided in Figure 1, and in Tables S1 and S2 in the Supplementary Appendix.

Of the 1370 patients who underwent randomization, 1331 (97.2%) were included in the primary efficacy analysis, 1362 (99.4%) in the key secondary efficacy analysis, and 1366 (99.7%) in the safety analysis. The demographic and clinical

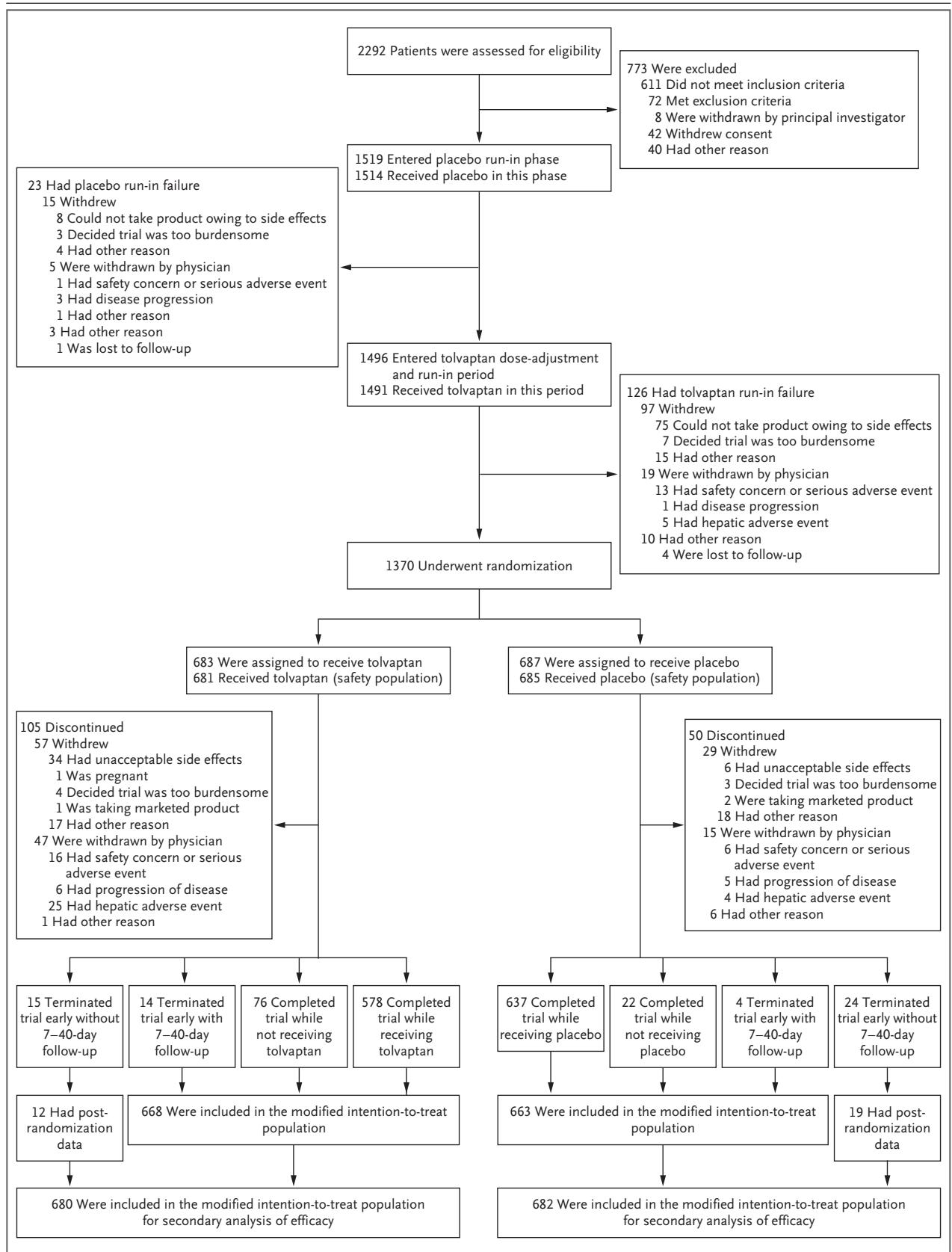
### Figure 1 (facing page). Patient Enrollment and Outcomes.

A total of 2292 patients were screened; 1519 patients entered the placebo run-in period and 1496 entered the tolvaptan dose-adjustment and run-in period. A total of 126 patients (8.4%) discontinued before randomization. The remaining 1370 patients (91.6%) were randomly assigned to receive tolvaptan (683 patients) or placebo (687). A total of 1313 patients (95.8%) completed the visit at month 12 (95.8% of the patients in the tolvaptan group and 95.9% of those in the placebo group), 1215 (88.7%) of whom were still taking the trial regimen (84.6% of the patients in the tolvaptan group and 92.7% of those in the placebo group) and 98 (7.2%) of whom had discontinued the regimen (11.1% of the patients in the tolvaptan group and 3.2% of those in the placebo group). A total of 29 patients (4.2%) assigned to receive tolvaptan and 28 (4.1%) assigned to receive placebo discontinued the trial. Patients who discontinued early with measurements of the serum creatinine level within the prespecified follow-up period of 7 to 40 days after the discontinuation of the trial regimen (14 patients in the tolvaptan group and 4 in the placebo group) were included in the modified intention-to-treat population for the primary efficacy end point. Of the remaining patients who discontinued early, 12 in the tolvaptan group and 19 in the placebo group had some post-randomization data that allowed them to be included in the modified intention-to-treat population for the key secondary efficacy end point. Reasons for exclusion from the primary efficacy analysis are provided in Table S1 in the Supplementary Appendix.

characteristics of the patients at baseline were balanced between the two groups. Most patients had chronic kidney disease of stage 3a (30.1%), stage 3b (45.2%), or stage 4 (19.5%) (Table 1).

### TOLVAPTAN DOSE

At the end of the single-blind tolvaptan period, 1128 of 1370 patients (82.3%) were receiving daily morning and afternoon doses of 90 mg and 30 mg, respectively, and 242 (17.7%) were receiving 60 mg and 30 mg, respectively (Table 1). Patients who were randomly assigned to the tolvaptan group and who completed the trial (578 patients) were taking daily morning and afternoon doses of 90 mg and 30 mg, respectively (350 patients [60.6%]); 60 mg and 30 mg, respectively (173 [29.9%]); or 45 mg and 15 mg, respectively, or less (55 [9.5%]). Patients who were randomly assigned to the placebo group and who completed the trial (637 patients) were taking mock morning and afternoon doses of 90 mg and 30 mg, respectively (447 patients [70.2%]); 60 mg and 30 mg, respectively (171 [26.8%]); or 45 mg and 15 mg, respectively, or less (19 [3.0%]).



**Table 1. Demographic and Clinical Characteristics at Baseline and Safety Profile during the Single-Blind Tolvaptan Period.\***

Characteristic	Tolvaptan Group (N = 683)	Placebo Group (N = 687)
Age — yr	47.3±8.2	47.2±8.2
Male sex — no. (%)	347 (50.8)	333 (48.5)
Height — cm	174±10	173±10
Weight — kg	84.6±19.9	81.6±19.3
Body-mass index	28.0±5.8	27.7±5.6
Race — no. (%)†		
White	626 (91.7)	632 (92.0)
Asian	22 (3.2)	19 (2.8)
Black	25 (3.7)	23 (3.3)
Other	10 (1.5)	13 (1.9)
Family history of polycystic kidney disease — no./total no. (%)	514/679 (75.7)	529/687 (77.0)
Blood pressure — mm Hg		
Systolic	129.3±13.8	129.9±14.5
Diastolic	82.1±9.6	82.6±9.7
Estimated GFR — ml/min/1.73 m <sup>2</sup> ‡	40.7±10.9	41.4±11.2
Chronic kidney disease stage — no./total no. (%)		
2	32/683 (4.7)	39/684 (5.7)
3a	209/683 (30.6)	202/684 (29.5)
3b	303/683 (44.4)	315/684 (46.1)
4	139/683 (20.4)	128/684 (18.7)
Hypertension — no. (%)§	634 (92.8)	640 (93.2)
Current use of RAAS inhibitor — no. (%)	595 (87.1)	581 (84.6)
History of kidney pain — no. (%)	338/675 (50.1)	344/679 (50.7)
Dose at end of single-blind tolvaptan period — no. (%)		
60 mg in morning and 30 mg in afternoon	118 (17.3)	124 (18.0)
90 mg in morning and 30 mg in afternoon	565 (82.7)	563 (82.0)

\* Plus–minus values are means ±SD. The demographic and clinical characteristics of the patients at baseline were balanced between the two groups. Data were missing on the following characteristics: on height, for four patients in the tolvaptan group and for two in the placebo group; on weight, for four in the tolvaptan group; on body-mass index (the weight in kilograms divided by the square of the height in meters), for six in the tolvaptan group; on blood pressure, for two in the tolvaptan group and two in the placebo group; on the estimated glomerular filtration rate (GFR), for three in the placebo group; and on urine osmolality, for two in the tolvaptan group and two in the placebo group. RAAS denotes renin–angiotensin–aldosterone system.

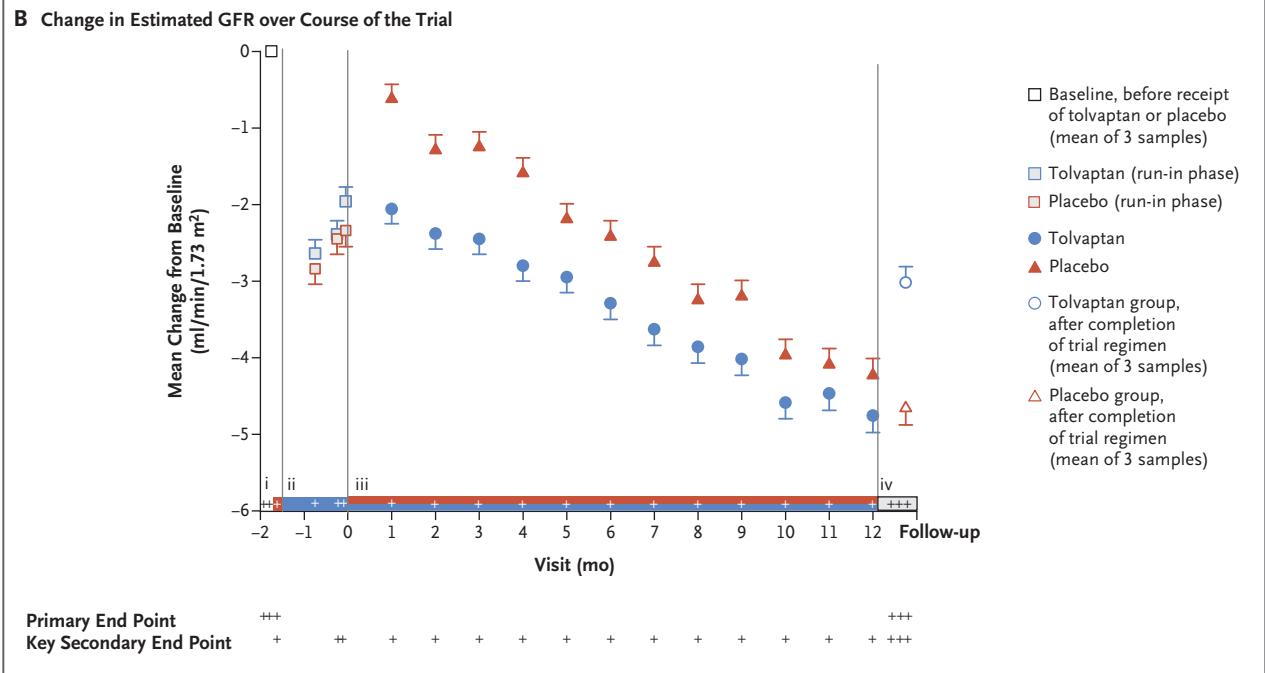
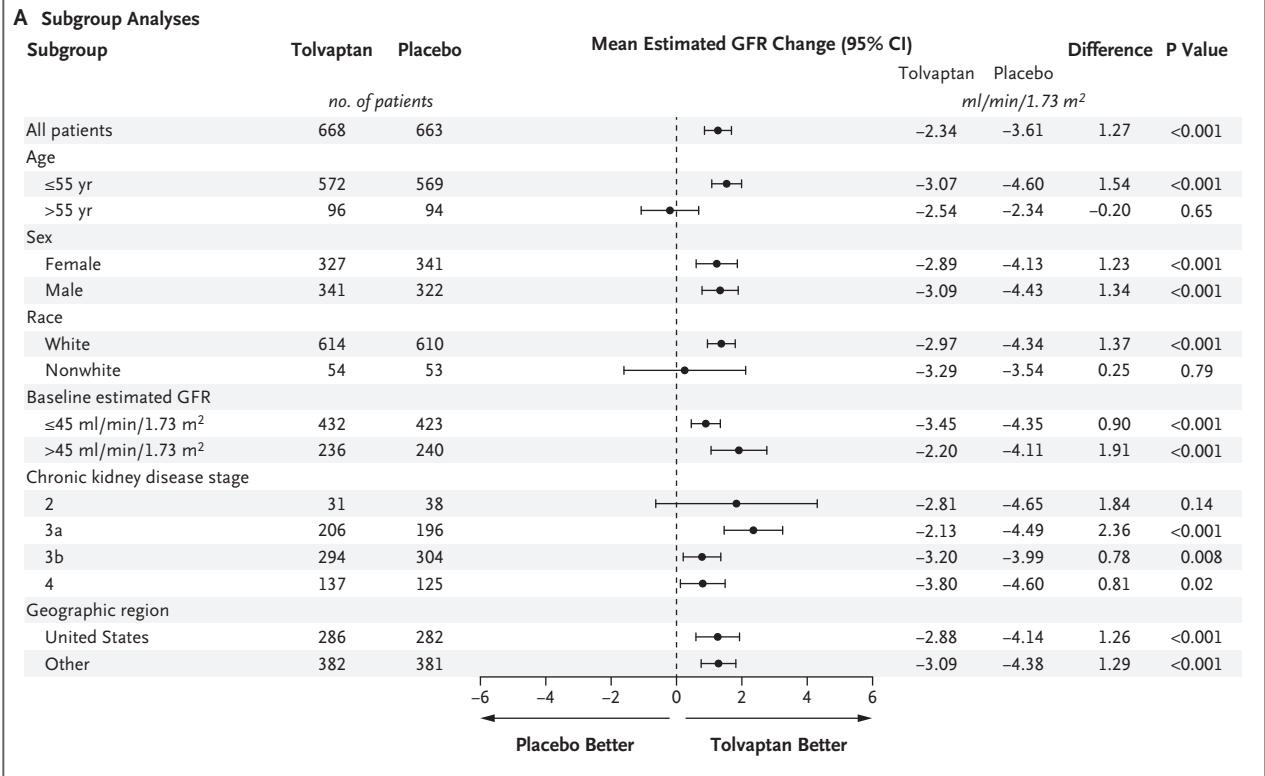
† Race was reported by the patients.

‡ The estimated GFR was determined with the use of the Chronic Kidney Disease Epidemiology Collaboration equation.

§ Hypertension was defined as a blood pressure of 140/90 mm Hg or more.

### Figure 2 (facing page). Effect of Tolvaptan on the Estimated Glomerular Filtration Rate (GFR).

Panel A shows a forest plot of the effect of tolvaptan versus placebo, overall and according to baseline subgroups. The overall annualized mean (±SE) change was  $-2.34 \pm 0.24$  ml per minute per 1.73 m<sup>2</sup> of body-surface area in the tolvaptan group, as compared with  $-3.61 \pm 0.24$  ml per minute per 1.73 m<sup>2</sup> in the placebo group (difference, 1.27 ml per minute per 1.73 m<sup>2</sup>; 95% CI, 0.86 to 1.68; P<0.001). The primary efficacy analysis included patients who completed the trial or who discontinued early with follow-up within the prespecified period of 7 to 40 days; some additional patients who discontinued but had postrandomization data were included in the analysis of the key secondary end point. Panel B shows the changes from baseline (i) in the estimated GFR that were due to the renal hemodynamic effect of tolvaptan during the single-blind tolvaptan period (ii) and the rapid reversal of these changes after randomization into the placebo group (iii) and after discontinuation of the drug in the tolvaptan group (iv); the vertical lines indicate these four time periods ([i] through [iv]). The red bar along the x axis indicates the period during which patients received placebo, and the blue bar the period during which patients received tolvaptan. Plus signs on the x axis indicate trial visits at which the estimated GFR was assessed and visits that were used in the analyses of the primary and secondary end points. Numerical values are provided in Table S4 in the Supplementary Appendix. A prespecified sensitivity analysis of the slopes of change in the estimated GFR during the double-blind period is shown in Figure S3 in the Supplementary Appendix.



**PRIMARY END POINT**

The mean (±SE) change in the estimated GFR at 1 year, with adjustment for the duration of the trial for each patient, was  $-2.34 \pm 0.24$  ml per minute per  $1.73 \text{ m}^2$  (95% confidence interval [CI],  $-2.81$  to  $-1.87$ ) in the tolvaptan group, as

compared with  $-3.61 \pm 0.24$  ml per minute per  $1.73 \text{ m}^2$  (95% CI,  $-4.08$  to  $-3.14$ ) in the placebo group. Tolvaptan resulted in a slower decline than placebo in the estimated GFR at 1 year (difference,  $1.27$  ml per minute per  $1.73 \text{ m}^2$ ; 95% CI,  $0.86$  to  $1.68$ ;  $P < 0.001$ ) (Fig. 2A).

Prespecified sensitivity analyses confirmed the robustness of the primary analysis (Table S3 in the Supplementary Appendix). Prespecified subgroup analyses showed a beneficial effect of tolvaptan across subgroups that were defined according to sex, baseline estimated GFR, stage of chronic kidney disease (except for stage 2), and geographic region (Fig. 2A), as well as in subgroups of patients who were 55 years of age or younger and patients who were white, but not in the smaller subgroups of patients who were older than 55 years of age, who were nonwhite, or who had chronic kidney disease of stage 2.

**KEY SECONDARY END POINT**

The mean slopes of the change in the estimated GFR at 1 year, with adjustment for the duration of the trial and the acute effect of tolvaptan, were  $-3.16 \pm 0.14$  ml per minute per  $1.73 \text{ m}^2$  (95% CI,  $-3.43$  to  $-2.89$ ) in the tolvaptan group, as compared with  $-4.17 \pm 0.14$  ml per minute per  $1.73 \text{ m}^2$  (95% CI,  $-4.45$  to  $-3.89$ ) in the placebo group (difference, 1.01 ml per minute per  $1.73 \text{ m}^2$ ; 95% CI, 0.62 to 1.40;  $P < 0.001$ ). Subgroup analyses of the secondary end point showed a beneficial effect of tolvaptan in the subgroups that were defined according to sex, baseline estimated

**Table 2. Most Common Adverse Events, Adverse Events during the Trial Period, and Serious Adverse Events.\***

Event	5-Wk Single-Blind Tolvaptan Period (N=1491)	1-Yr Double-Blind Period	
		Tolvaptan Group (N=681)	Placebo Group (N=685)
<i>number of patients with event (percent)</i>			
Any adverse event during the trial	1051 (70.5)	581 (85.3)	564 (82.3)
Serious adverse event	43 (2.9)	85 (12.5)	60 (8.8)
Discontinuation of trial regimen due to adverse event			
Any	101 (6.8)	65 (9.5)	15 (2.2)
Due to event in one of five liver-related SMQs†	4 (0.3)	11 (1.6)	1 (0.1)
Due to aquaretic adverse event‡	68 (4.6)	14 (2.1)	1 (0.1)
Death§	1 (0.1)	0	1 (0.1)
Most common adverse events during the trial¶			
Polyuria	472 (31.7)	36 (5.3)	11 (1.6)
Nocturia	305 (20.5)	32 (4.7)	12 (1.8)
Thirst	428 (28.7)	27 (4.0)	13 (1.9)
Polydipsia	145 (9.7)	12 (1.8)	3 (0.4)
Dry mouth	132 (8.9)	13 (1.9)	6 (0.9)
Diarrhea	29 (1.9)	47 (6.9)	23 (3.4)
Fatigue	64 (4.3)	46 (6.8)	24 (3.5)
Kidney pain	39 (2.6)	113 (16.6)	130 (19.0)
Back pain	22 (1.5)	34 (5.0)	41 (6.0)
Urinary tract infection	8 (0.5)	39 (5.7)	55 (8.0)
Peripheral edema	13 (0.9)	30 (4.4)	45 (6.6)
Headache	63 (4.2)	55 (8.1)	59 (8.6)
Hematuria	11 (0.7)	37 (5.4)	35 (5.1)
Hypertension	31 (2.1)	73 (10.7)	79 (11.5)
Blood creatinine level increased	40 (2.7)	46 (6.8)	46 (6.7)
Upper respiratory tract infection			
Any	21 (1.4)	59 (8.7)	58 (8.5)
Viral	47 (3.2)	72 (10.6)	84 (12.3)

**Table 2. (Continued.)**

Event	5-Wk Single-Blind Tolvaptan Period (N=1491)	1-Yr Double-Blind Period	
		Tolvaptan Group (N=681)	Placebo Group (N=685)
<i>number of patients with event (percent)</i>			
Clinically significant elevations in hepatic laboratory values and events in one of five liver-related SMQs†			
Specified liver-related event			
Any	23 (1.5)	74 (10.9)	36 (5.3)
Serious adverse event	8 (0.5)	31 (4.6)	4 (0.6)
Elevation in alanine aminotransferase level			
To >3× ULN	3 (0.2)	38 (5.6)	8 (1.2)
To >5× ULN	1 (0.1)	23 (3.4)	5 (0.7)
To >10× ULN	0	8 (1.2)	4 (0.6)

\* Adverse events that occurred during the trial and serious adverse events were categorized according to the *Medical Dictionary for Regulatory Activities* (MedDRA), version 20. Adverse events during the trial were defined as adverse events that were reported as starting or worsening (i.e., developing greater severity, becoming serious, or leading to discontinuation of the trial regimen or to death) after the initiation of the trial regimen. An event that started in one period and resolved completely may have been reported if it restarted at any severity in a subsequent period after resolution. An ongoing adverse event that was first reported in one trial period and continued into another period without fully resolving was not reported for subsequent trial periods if it continued with similar or lesser severity. An adverse event may also have been reported in a later period if it increased in severity, became serious, or led to discontinuation or death. Serious adverse events were defined as adverse events that were life-threatening or that resulted in inpatient hospitalization or prolongation of existing hospitalization, persistent or clinically significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect. ULN denotes upper limit of the normal range.

† The five liver-related standardized MedDRA queries (SMQs) included adverse events related to cholestasis and jaundice of hepatic origin; hepatic failure, fibrosis, cirrhosis, and other liver damage–related conditions; noninfectious hepatitis; liver-related investigations, signs, and symptoms; and liver-related coagulation and bleeding disturbances.

‡ Aquaretic adverse events included polyuria, nocturia, thirst, dry mouth, and polydipsia.

§ One patient died during the tolvaptan dose-adjustment phase before randomization owing to complications of a clinically silent infection that was unknown to the investigators at the time of enrollment. This death was deemed by the investigators not to be related to tolvaptan. One patient in the placebo group died during the 1-year, double-blind period of the trial owing to a motor vehicle accident.

¶ The most common adverse events during the trial were defined as adverse events that occurred in more than 5% of patients during the single-blind tolvaptan period or in more than 5% of the patients in either group during the double-blind period.

GFR, stage of chronic kidney disease (except for stage 2), and geographic region, as well as in subgroups of patients who were 55 years of age or younger and patients who were white, but not in the smaller subgroups of patients who were older than 55 years of age, who were nonwhite, or who had chronic kidney disease of stage 2. Details are provided in Figure S2 in the Supplementary Appendix.

The changes from baseline in the estimated GFR during the single-blind tolvaptan period and their rapid reversal after patients were randomly assigned to the placebo group and after the discontinuation of the trial regimen in the tolvaptan group, as well as the treatment effect of tolvaptan at the end of the trial, are shown in Figure 2B, and in Table S4 in the Supplementary Appendix. A prespecified sensitivity analysis of

the slopes of the change in the estimated GFR during the double-blind period showed a slower decline with tolvaptan than with placebo ( $-3.24 \pm 0.17$  vs.  $-4.08 \pm 0.17$  ml per minute per  $1.73 \text{ m}^2$ ) (Fig. S3 in the Supplementary Appendix).

**ADVERSE EVENTS**

During the double-blind period, the rates of new or worsening adverse events did not differ substantially between the tolvaptan group and the placebo group (85.3% and 82.3%, respectively) (Table 2). The rates of new or worsening adverse events (occurring in >5% of the patients) during the single-blind tolvaptan period were higher than the rates among the patients who received tolvaptan during the double-blind period. After randomization, patients who received tolvaptan had higher rates of polyuria, nocturia, thirst,

polydipsia, dry mouth, diarrhea, and fatigue, whereas those who received placebo had higher rates of peripheral edema, kidney pain, and urinary tract infection. Most adverse events during the trial were mild or moderate in severity.

During the single-blind tolvaptan period, adverse events led to the discontinuation of tolvaptan in 101 of 1491 patients (6.8%). Most of the events in these patients (in 68 of 1491 [4.6%]) were related to aquaresis (Table 2).

During the double-blind period, adverse events led to the discontinuation of the trial regimen in 65 of 681 patients (9.5%) receiving tolvaptan, as compared with 15 of 685 (2.2%) receiving placebo, including adverse events related to aquaresis in 14 patients in the tolvaptan group (2.1%), as compared with 1 (0.1%) in the placebo group, and hepatic enzyme abnormalities in 11 patients (1.6%) in the tolvaptan group, as compared with 1 (0.1%) in the placebo group. One patient in the placebo group died during the trial owing to a motor vehicle accident. One patient died during the single-blind tolvaptan dose-adjustment and run-in period from complications of a clinically silent infection that was unknown to the investigators at the time of enrollment; this death was deemed by the investigators not to be related to tolvaptan. Laboratory values of potential clinical significance are listed in Table S5 in the Supplementary Appendix.

#### HEPATIC ENZYME ELEVATIONS

A total of 74 of 681 patients (10.9%) receiving tolvaptan had hepatic adverse events, as compared with 36 of 685 (5.3%) receiving placebo (Table 2). A total of 31 patients (4.6%) receiving tolvaptan had serious hepatic adverse events, as compared with 4 (0.6%) receiving placebo. Elevations in the alanine aminotransferase level that exceeded three times the upper limit of the normal range occurred in 38 patients (5.6%) receiving tolvaptan, as compared with 8 (1.2%) receiving placebo (Fig. 3). In all cases, the elevated liver-enzyme levels returned to normal after the interruption or discontinuation of treatment. No reports of persistent sequelae have been received, and no patients had concurrent elevations in the bilirubin level to more than two times the upper limit of the normal range. Details are provided in Figures S4 and S5 in the Supplementary Appendix.

#### DISCUSSION

The results of the present trial indicate that the administration of tolvaptan in patients with later-stage ADPKD (mean [ $\pm$ SD] estimated GFR, 41.0 $\pm$ 11.1 ml per minute per 1.73 m<sup>2</sup> at a mean [ $\pm$ SD] 47 $\pm$ 8 years of age) who could take the treatment without an unacceptable level of side effects resulted in a slower decline than placebo in the estimated GFR from baseline to follow-up (net difference in the change in the estimated GFR at 1 year, 1.27 ml per minute per 1.73 m<sup>2</sup>; 95% CI, 0.86 to 1.68). The treatment effect on the secondary end point, the evaluation of which depended on modeling assumptions to adjust for the estimated hemodynamic on-treatment effect of tolvaptan<sup>24,25</sup> and is therefore less accurate, overlapped with that of the primary end point (net difference in the change in the slope of the estimated GFR at 1 year, 1.01 ml per minute per 1.73 m<sup>2</sup>; 95% CI, 0.62 to 1.40). These treatment effects are similar to the 1.20 ml per minute per 1.73 m<sup>2</sup> per year that was seen in the TEMPO 3:4 trial (annualized difference from baseline to follow-up; data on file), which involved patients with early-stage ADPKD (mean [ $\pm$ SD] estimated GFR, 81.6 $\pm$ 29.6 ml per minute per 1.73 m<sup>2</sup> at 39 $\pm$ 7 years of age).<sup>16</sup> Furthermore, the estimated GFR benefit that was accumulated in the tolvaptan group, as compared with the placebo group, in the 3 years of the TEMPO 3:4 trial (3.34 ml per minute per 1.73 m<sup>2</sup>,  $P < 0.001$ ) was maintained 2 years later (3.15 ml per minute per 1.73 m<sup>2</sup>,  $P < 0.001$ ) in the TEMPO 4:4 open-label extension study, in which all patients were treated with tolvaptan.<sup>17</sup>

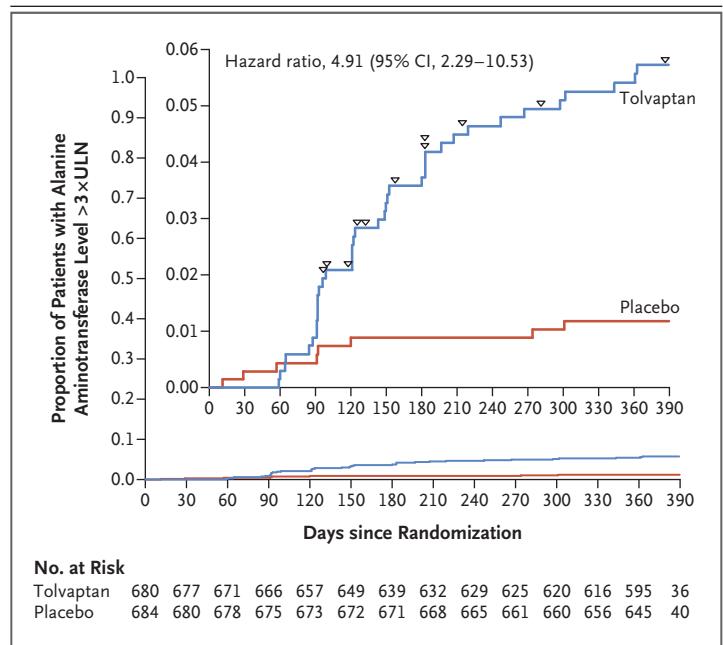
The investigation of whether the treatment effect in the present 1-year trial would also occur in subsequent years is needed in order to ascertain the potential long-term benefit. Although that information cannot be determined from the present trial, a post hoc analysis of data from patients with chronic kidney disease of stage 3 in the TEMPO 3:4 trial showed a treatment effect of 1.67 ml per minute per 1.73 m<sup>2</sup> per year, which was incremental over the 3 years of that trial.<sup>26</sup> In the present trial, the baseline estimated GFR was 41.1 ml per minute per 1.73 m<sup>2</sup> and declined over a 1-year period by 4.17 ml per minute per 1.73 m<sup>2</sup> with placebo. If one assumes that tolvaptan treatment would continue to slow

the decrement in the estimated GFR by 1.27 ml per minute per 1.73 m<sup>2</sup> per year, the time to chronic kidney disease of stage 5 would be extended from 6.2 years to 9.0 years. A larger benefit might be expected if treatment were started earlier, assuming that patients would be able to take the agent over time without an unacceptable level of adverse events.

The design of the present trial benefited from the experience in the TEMPO 3:4 trial,<sup>19</sup> in which 72 of 961 patients (7.5%) who had been randomly assigned to receive tolvaptan discontinued the drug because of aquaretic adverse events.<sup>16,29</sup> To limit early withdrawals, a randomized withdrawal design was successfully used to enrich the trial for patients who were able to take tolvaptan without an unacceptable level of adverse effects.<sup>21</sup> However, this design limits the broad applicability of our results, because a group of patients who had side effects with tolvaptan were removed from consideration.

Despite the more advanced stage of disease in the patients involved in the present trial, the safety profile of tolvaptan did not differ from that observed in the TEMPO 3:4 trial. In these two trials, elevations in the liver-enzyme levels occurred between 60 days and 240 days after the initiation of tolvaptan and became less frequent thereafter. Two patients in the TEMPO 3:4 trial and one in the TEMPO 4:4 study, which used monitoring once every 4 months, had laboratory and clinical evidence of potentially serious drug-induced liver injury, meeting Hy's law criteria (serum alanine aminotransferase level of >3 times the upper limit of the normal range and bilirubin level of >2 times the upper limit of the normal range).<sup>18</sup> In the present trial, in which monthly monitoring was used, no cases of elevations in the liver-enzyme and bilirubin levels met Hy's law criteria; this finding is possibly due to more frequent monitoring and earlier interruption of therapy.

A prespecified subgroup analysis suggested that tolvaptan had less of an effect in patients older than 55 years of age. These patients, who because of their age were expected to have more advanced disease,<sup>30,31</sup> were required to have an estimated GFR of 25 to 44 ml per minute per 1.73 m<sup>2</sup> and historical evidence of a decline in the estimated GFR that exceeded 2.0 ml per minute per 1.73 m<sup>2</sup> per year. Despite these pre-



**Figure 3. Time to First Elevation of Alanine Aminotransferase Level to More Than Three Times the Upper Limit of the Normal Range (ULN).**

Shown is the first elevation of the alanine aminotransferase level to more than three times the ULN during the double-blind period in a time-to-event analysis. Elevations started approximately 2 to 3 months after the initiation of the trial regimen and continued for the 12-month trial period. The hepatic adjudication committee deemed that elevations in 11 patients were probably related to tolvaptan; the time to the first elevation to more than three times the ULN is indicated by an arrowhead for each patient. The inset shows the same data on an enlarged y axis. By day 390, most patients had already completed the follow-up period with three blood samples for measurement of the serum creatinine level. The hepatic adjudication committee deemed two additional hepatic events with alanine aminotransferase elevations of less than three times the ULN (data not shown) to be probably related to tolvaptan. Three patients had an increase in the alanine aminotransferase level to more than three times the ULN during the single-blind period (data not shown).

requisites, the decline in the estimated GFR in these patients was faster than the expected age-related decline of 0.50 to 0.75 ml per minute per 1.73 m<sup>2</sup> per year in the general population of patients older than 40 years of age<sup>32</sup> but was much slower than the decline in patients 55 years of age or younger who had similar stages of chronic kidney disease in the present trial. Thus, this older population in our trial appeared to be enriched for slowly progressive disease, in which case it may be more difficult to show a treatment benefit.

The present trial has certain limitations. The selection of participants mainly on the basis of

the estimated GFR was justified by the fact that the estimated GFR is an excellent predictor of disease progression when the rate is already declining.<sup>33,34</sup> Nevertheless, it remains possible that additional selection criteria regarding genotype or age-adjusted total kidney volume could have further enriched the trial population for patients who would have rapid disease progression.<sup>30,31</sup> We did not study whether the effect of tolvaptan on the estimated GFR was mediated or paralleled by an effect on kidney volume; renal hemodynamic or other mechanisms could have also played a role.<sup>27,28,35</sup> The patients in the trial were asked to maintain good hydration. By increasing hydration and suppressing vasopressin release in the patients in the placebo group, the benefit that was associated with the administration of tolvaptan may have been underestimated. The conclusions regarding treatment benefit were not based on a hard end point such as a 50% decline in the estimated GFR or end-stage renal disease. The short duration of the trial limited the ability to assess adverse events over the medium or long term.

In conclusion, the results of the present trial

showed that tolvaptan slowed the progressive loss of renal function in patients with ADPKD at stages that were more advanced than those of the patients who were included in the TEMPO 3:4 trial. Monthly monitoring of liver-enzyme levels probably reduced the frequency of drug-induced liver injury. The long-term effectiveness of treatment with tolvaptan remains to be determined.

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