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Per-Treatment Post-Hoc Analysis of Clinical Trial Outcomes With Tolvaptan in Autosomal Dominant Polycystic Kidney Disease

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Per-Treatment Post-Hoc Analysis of Clinical Trial Outcomes With Tolvaptan in Autosomal Dominant Polycystic Kidney Disease

Running head: **Impact of Tolvaptan Completion on ADPKD Outcomes**

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ABSTRACT Word count: 250 (limit 250)

Introduction: In pivotal trials of patients with autosomal dominant polycystic kidney disease at risk of rapid progression, tolvaptan slowed estimated glomerular filtration rate (eGFR) decline in early-to-moderate (TEMPO 3:4 [NCT00428948]) and moderate-to-late stage (REPRISE [NCT02160145]) chronic kidney disease (CKD). Discontinuation was less frequent in REPRISE (15.0%) than TEMPO 3:4 (23.0%), given that in REPRISE, only subjects who tolerated tolvaptan 60/30 mg daily initiated the double-blind phase. We evaluated whether the greater treatment effect in REPRISE was attributable to different completion rates.

Methods: We conducted *post hoc* analyses of TEMPO 3:4 and REPRISE completers, defined as subjects who took trial drug to the end of the treatment period in TEMPO 3:4 (3 years) or REPRISE (1 year). Efficacy (rate of change in eGFR for tolvaptan versus placebo) was analyzed as in each trial. Subjects from TEMPO 3:4 and REPRISE were also matched by propensity score for age, gender, and baseline eGFR to explore potential additional determinants of treatment effect.

Results: The annualized tolvaptan treatment effect in TEMPO 3:4 completers (difference versus placebo of 0.98 mL/min/1.73 m^2/year) and REPRISE completers (difference of 1.23) was similar to that of the respective total trial populations (TEMPO 3:4: 0.94; REPRISE: 1.27). The treatment effect of tolvaptan was also similar between matched subjects.

Conclusion: Greater treatment completion rate did not drive greater treatment effect in REPRISE. The more advanced CKD of REPRISE subjects may be more relevant. More rapid decline in kidney function in later-stage CKD enabled the effects of tolvaptan to be more easily discerned.

Keywords: autosomal dominant polycystic kidney disease, clinical trial, tolvaptan, chronic kidney disease, persistence, treatment effect

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney condition and a leading cause of end-stage kidney disease (ESKD) globally.[1–4] Tolvaptan, a vasopressin receptor antagonist, is the first drug to be approved for the treatment of ADPKD and has been licensed in a number of regions including the United States, Europe, Japan, Korea, and Australia.[5–7] The drug exerts its therapeutic effects by targeting V2 receptors in renal epithelial cells, resulting in downregulation of the intracellular cyclic adenosine monophosphate (cAMP) signaling pathway. Cystic growth has been linked to upregulation of the cAMP pathway in ADPKD, as reviewed elsewhere.[5,8–11] The evidence for tolvaptan effectiveness is based on results from the 3-year TEMPO 3:4 (NCT00428948) and the 1-year REPRISE (NCT02160145) clinical trials. The trials demonstrated that tolvaptan slows estimated glomerular filtration rate (eGFR) decline and total kidney volume (TKV) growth compared to placebo in ADPKD subjects at risk of rapid progression.[12,13]

Inhibition of vasopressin activity also decreases urine concentrating activity and is associated with aquaretic adverse events (AAEs; e.g., polyuria, thirst, nocturia, pollakiuria), which can negatively impact adherence to treatment.[14] In TEMPO 3:4, 23.0% of tolvaptan-treated subjects discontinued from the trial early; the most common reason for discontinuation was adverse events (15.4% of subjects), and those most frequently leading to discontinuation were AAEs (8.3% of subjects).[12] The double-blind treatment phase of REPRISE included only subjects who tolerated tolvaptan at a split dose of at least 60/30 mg during a preceding single-blind tolvaptan treatment phase. Compared to TEMPO 3:4, discontinuations were, therefore, less frequent during the double-blind phase of REPRISE: 15.0% of subjects in the tolvaptan arm discontinued treatment; 9.5% discontinued due to adverse events, and 2.1% discontinued due to AAEs.[13]

Both trials were analyzed in accordance with the intention-to-treat (ITT) principle, which mandates that outcome analyses are based on all subjects randomized to a treatment, without

regard for noncompliance, protocol deviations, or early withdrawal.[15,16] Intention-to-treat is an established feature of interventional clinical trial design intended to minimize bias in the estimation of treatment effect that would arise from the exclusion of subjects nonadherent to study treatment. The approach is mandated by many regulatory bodies, even if studies go on to also include additional per-protocol or as-treated analyses.[17,18] However, it is widely recognized that in scenarios where there are high levels of nonadherence to a trial treatment, ITT analysis may substantially underestimate the effect of a therapy.[16]

To evaluate the possibility that subjects who completed their respective trials on treatment would show a larger effect size than those who terminated treatment early, we conducted a *post hoc* analysis. The primary objective of this analysis was to assess the effects of tolvaptan on eGFR in subgroups of TEMPO 3:4 and REPRISE trial subjects who completed the follow-up period on treatment. A secondary objective was to explore the potential effects of treatment completion on the magnitude of treatment responses observed in TEMPO 3:4 and REPRISE.

METHODS

TEMPO 3:4 and REPRISE Trial Design and Population

TEMPO 3:4 and REPRISE trial design and enrollment criteria have been described previously.[12,13] Both were randomized, double-blind, placebo-controlled trials. In TEMPO 3:4, tolvaptan was initiated at a daily split dose of 45/15 mg, which was increased weekly to 60/30 mg and then to 90/30 mg, based on subject-reported tolerability. Subjects took the highest tolerable dose for the 36-month treatment period.

In REPRISE, all subjects received tolvaptan during a single-blind, 5-week titration and run-in phase. Those who tolerated a 60/30 mg or 90/30 mg dose were then randomized to 12 months of double-blind tolvaptan or placebo. Tolvaptan was taken at the highest dose tolerated (with a maximum dose of 90/30 mg).

Both studies targeted ADPKD populations with a high likelihood of rapid disease progression. TEMPO 3:4 enrolled subjects with preserved renal function: 18-50 years old with estimated creatinine clearance ≥60 mL/min and TKV ≥750 mL. REPRISE enrolled an older population with more advanced disease: ages 18−55 years with eGFR ≥25 and ≤65 mL/min/1.73 m^2, or ages 56−65 years with eGFR ≥25 and ≤44 mL/min/1.73 m^2 and evidence of ADPKD progression (an eGFR decline of >2.0 mL/min/1.73 m^2/year based on historical eGFR data). Based on the above enrollment criteria, TEMPO 3:4 had a trial population in CKD stages 1-3, >80% in stage 1 or 2 CKD. In REPRISE, 75% of subjects were in stage 3 and 20% were in stage 4 CKD. A *post hoc* analysis of the TEMPO 3:4 trial population indicated a population enriched for high risk of rapid progression, with 89.5% of the population in Mayo risk classes 1C-1E versus 60.5% in an unselected ADPKD population of Mayo Clinic patients.[19]

Outcomes Evaluated in the Post-Hoc Analyses

The effect of tolvaptan on rate of change in eGFR in each trial was evaluated for the subgroup of completers, i.e., subjects who continued to take the trial drug to the end of the treatment period in TEMPO 3:4 (3 years) or REPRISE (1 year). Similarly, the effect of tolvaptan on annualized rate of TKV growth was calculated for the completer subpopulation in TEMPO 3:4 (TKV was not assessed in REPRISE).

To further explore determinants of tolvaptan treatment effects on kidney function in ADPKD, subgroup analyses of change in eGFR over time by baseline demographic and clinical variables were performed. Finally, subject characteristics by completer/non-completer status were compared to identify variables associated with completion/non-completion.

Statistical Methods

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Analysis of efficacy endpoints was based on the methods used in each trial and using the full trial datasets. For TEMPO 3:4, comparisons between tolvaptan completers and placebo completers were derived by testing the time treatment interaction with a linear mixed model in which both intercept and slope are fixed and random effects. For REPRISE, the comparison was derived from a weighted analysis of covariance with effects of treatment and randomization stratification factors and covariate baseline.

In an analysis of the effects of baseline variables, we compared eGFR slope between subjects from TEMPO 3:4 and REPRISE who were matched by propensity score for gender, age, and baseline eGFR. Propensity score-based matching was used to exclude the effects of differences in trial populations (for example, in the proportions of subjects with early versus late-stage CKD) and assess the treatment effects of tolvaptan in subjects with similar clinical profiles. For the propensity analysis, the SAS procedure PROC PSMATCH was utilized in three steps with the local optimal algorithm, caliper=0.03, and the sex as exact match. In Step 1, TEMPO 3:4 placebo subjects were matched to TEMPO 3:4 tolvaptan subjects. The total absolute difference in the logit of the propensity score for all matches was 0.692729. In Step 2, REPRISE tolvaptan subjects were matched to the TEMPO 3:4 tolvaptan subjects found in Step 1. The total absolute difference in the logit of the propensity score for all matches was 1.722285. In Step 3, REPRISE placebo subjects were matched to TEMPO 3:4 placebo subjects found in Step 1. The total absolute difference in the logit of the propensity score for all matches was 0.78467.

In a comparison of subject characteristics by completer/non-completer status, *P*-values were derived by Fisher's Exact Test for binary characteristics and by T-test/Wilcoxon Test for continuous characteristics.

RESULTS

Subject Disposition

In TEMPO 3:4, 740/961 (77.0%) subjects randomized to the tolvaptan arm and 417/484 (86.2%) randomized to the placebo arm completed the trial on treatment.[12] In REPRISE, the number of completers was 578/683 (84.6%) for tolvaptan and 637/687 (92.7%) for placebo.[13] Several completers in each trial had missing or unusable eGFR data, yielding an efficacy analysis population of 713 tolvaptan and 410 placebo completers for TEMPO 3:4 and 576 tolvaptan and 634 placebo completers for REPRISE (Figure 1). Testing of the potential interaction between completer status and treatment found no treatment difference between completers and non-completers in either TEMPO 3:4 (P=0.4846) or REPRISE (P=0.0924).

Efficacy in the Completer Subpopulation

In both TEMPO 3:4 and REPRISE, rates of change in eGFR with tolvaptan and placebo were very similar between the total trial population and the subgroup of treatment completers (Figure 2). Accordingly, the treatment effect of tolvaptan versus placebo was also similar between the total population and the subgroup of treatment completers. Annualized TKV growth rate was 2.8% for subjects in the tolvaptan group and 5.5% for those in the placebo group in the total TEMPO 3:4 population (P<0.001).[12] Among the subgroup of TEMPO 3:4 completers, annualized TKV growth rate was 2.7% for subjects in the tolvaptan group and 5.5% for those in the placebo group (P<0.001). As with rates of change in kidney function, rates of TKV growth in the subpopulation of completers were similar to those in the total trial population.

Impact of Baseline Characteristics

Subgroup analyses of completers by baseline characteristics showed that tolvaptan was efficacious versus placebo in slowing renal function decline regardless of age, sex, or race in both trials (Supplementary Tables S1 and S2). The few non-significant differences between tolvaptan

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and placebo were in subgroups with low subject numbers: non-Caucasian subjects in TEMPO 3:4 and REPRISE and subjects aged >55 years in REPRISE.

Propensity score matching for gender, age, and baseline eGFR generated an analysis set of 108 subjects for each trial (54 subjects in each of the tolvaptan and placebo treatment arms). Gender composition was 23 females (43%) and 31 males (57%) in each matched tolvaptan and placebo group, and mean age was 42–44 years (Figure 3A). The mean eGFR (~53 mL/min/1.73 m^2) in the matched population fell within CKD stage 3a, indicating the area of overlap in the two trial populations between subjects with early to moderate stage CKD (TEMPO 3:4) and subjects with moderate to late stage CKD (REPRISE) (Figure 3B). The baseline characteristics of the matched population are provided in Supplementary Table S3 and the age and CKD stage distributions are shown in Supplementary Figure S1. In the matched population, the treatment effect of tolvaptan in TEMPO 3:4 (1.44 mL/min/1.73 m^2/year) was similar to that in REPRISE (1.89 mL/min/1.73 m^2/year), with a nonsignificant difference of -0.45 (P = 0.71) (Figure 4).

Analyses of baseline demographic and clinical characteristics revealed potential associations of age, body mass index, use of blood pressure lowering drugs, history of hematuria, and history of kidney pain with treatment completion in TEMPO 3:4 but not REPRISE (Table).

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DISCUSSION

Tolvaptan has demonstrated statistically and clinically significant efficacy in reducing the rate of kidney function decline in ADPKD patients with both early-stage and later-stage CKD, with slight differences observed in the tolvaptan effect sizes between the total TEMPO 3:4 and REPRISE populations. In TEMPO 3:4, the annualized mean change in eGFR was reduced by 1.20 mL/min/1.73 m^2/year with tolvaptan vs. placebo.[13] In REPRISE, tolvaptan reduced the annualized mean change in eGFR by 1.27 mL/min/1.73 m^2/year.[13] In TEMPO 3:4, the annualized eGFR slope was −2.72 mL/min/1.73 m^2/year in the tolvaptan group versus −3.70 mL/min/1.73 m^2/year in the

placebo group (a difference of 0.98 mL/min/1.73 m^2/year; 95% CI, 0.60 to 1.36; P<0.001).[12] In REPRISE, annualized eGFR slope was −3.16 mL/min/1.73 m^2/year with tolvaptan and −4.17 mL/min/1.73 m^2/year with placebo, a significant difference of 1.01 mL/min/1.73 m^2/year (95% CI, 0.62 to 1.40; P<0.001).[13]

The slightly greater tolvaptan treatment effects in REPRISE might plausibly be ascribed to the higher frequency of tolvaptan discontinuation during double-blind treatment in TEMPO 3:4 (23.0%) compared to REPRISE (15.0%). In this post hoc analysis, we evaluated the hypothesis that subjects completed their respective trials on treatment would show a larger effect size than those who discontinued treatment early. No difference in effect size, however, was found between the total trial population and the subgroup of completers. Tolvaptan was generally effective versus placebo in subgroups of completers defined by baseline age, sex, and race. The treatment difference between tolvaptan and placebo was not significant in non-Caucasian subjects in both trials and in subjects aged >55 years in REPRISE, observations that may have been due to the small sample sizes of these subgroups. Given the lack of impact of treatment completion and demographic characteristics on outcomes, the small differences in tolvaptan treatment effect between TEMPO 3:4 and REPRISE therefore appear to be due to differences in disease stage between the trial populations, namely, earlier-stage CKD in TEMPO 3:4 and later-stage CKD in REPRISE. Deterioration in kidney function accelerates over the course of ADPKD, enabling the easier detection of inhibitory effects on eGFR decline in patients with later-stage disease.[20,21]

The importance of CKD stage at baseline is supported by the observation that when differences in subject baseline characteristics were accounted for via propensity matching, the treatment effect was not significantly different between TEMPO 3:4 and REPRISE. The lack of a significant treatment difference observed between tolvaptan and placebo within the matched REPRISE population may be due to the small size of the propensity matched subgroup relative to the total REPRISE cohort, which represents a limitation of the analysis. An analysis of changes in

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TKV in TEMPO 3:4 completers versus the total trial population showed similar results to the eGFR analyses, with little evident effect of completion on outcomes.

Tolvaptan was consistently associated with a slowing of eGFR decline by approximately 1 mL/min/1.73 m^2/year relative to placebo in TEMPO 3:4 and REPRISE across completers and the overall trial populations. Although evaluating the efficacy of treatment for ADPKD remains an under-researched topic and there are no generally agreed on standards for the clinic,[22] a slowing of eGFR loss of 1 mL/min/1.73 m^2/year is clinically meaningful and can be expected to substantially slow progression to ESKD.[23] Similarly, tolvaptan slowed the annual increase in TKV by approximately half, which can be expected to make an impact on patient outcomes and quality of life over the long-term.

We found associations between baseline characteristics and treatment completion in TEMPO 3:4. Subjects who were older or took blood pressure medication were more likely to be completers, possibly because they were already accustomed to daily pharmacotherapy. Mean baseline blood pressure itself did not significantly differ by completer/non-completer status. A history of hematuria or kidney pain was negatively associated with treatment completion. Previous research on predictors of medication utilization supports a positive association between older age and better adherence, whereas data on the impact of comorbidity or the use of multiple medications on adherence are equivocal.[24–26] Lower body mass index was also positively associated with treatment completion in TEMPO 3:4. The finding of correlations between subject characteristics and completer/non-completer status in TEMPO 3:4 but not REPRISE may be due to the longer treatment period in TEMPO 3:4 (three years vs. one year). Differences in trial design and trial populations between TEMPO 3:4 and REPRISE must also be borne in mind. The double-blind treatment phase of REPRISE included only subjects who tolerated tolvaptan during a preceding single-blind phase. Subjects enrolled in REPRISE may also have been aware of the earlier TEMPO 3:4 findings demonstrating efficacy of tolvaptan in ADPKD and thus have been more willing to

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tolerate aquaretic adverse events. Given the established association of decreased drug compliance with negative health outcomes in chronic conditions, more research on predictors of medication persistence is needed in the context of treatment for ADPKD.[27,28]

Limitations of the analysis are the *post hoc* nature of the analyses and the relatively small proportion of non-completers in each trial arm (ranging from 7.7% to 23.0%). The small number of non-completers may have decreased the power to detect differential effects of completer versus non-completer status. When REPRISE was conducted, more was understood about the short-term hemodynamic effects of tolvaptan, with the timing of eGFR assessments designed to take these effects into account in evaluating long-term efficacy. The assessment of treatment effect was therefore not identical between TEMPO 3:4 and REPRISE. Additionally, outcomes after drug discontinuation were monitored differently in each trial. In REPRISE, eGFR data after discontinuation were included in the dataset for the overall population only for subjects who underwent the Month 12 visit and at least 1 follow-up serum creatinine assessment. In TEMPO 3:4, there was no requirement for follow-up after discontinuation to extend to end of study. Accordingly, the TEMPO 3:4 data may provide a less robust pool of data on non-completers.

Within the context of the demonstrated efficacy of tolvaptan in ADPKD subjects with early- to late-stage CKD, the most important factor in determining tolvaptan effect size in inhibiting eGFR decline appears to be stage of kidney disease at treatment commencement. This conclusion is consistent with earlier findings.[20] Given that kidney function decline accelerates with the progression of ADPKD, the effects of tolvaptan in slowing kidney function loss are most easily discernible in later-stage patients. In clinical practice, monitoring kidney function to assess the effects of tolvaptan therapy therefore may be particularly useful for patients with later-stage disease.

DISCLOSURES

Dr. Mallett reports being a Medical Advisory Board member for Otsuka; and receiving grants from Sanofi-Genzyme, PKD Australia, Queensland Health and NHMRC for studies outside the submitted work. Dr. Perrone reports grants from Otsuka and Otsuka Steering Committee Membership during the conduct of the study; grants from Department of Defense, grants from Sanofi-Genzyme, personal fees from Sanofi-Genzyme, Palladio Biosciences, and Reata, grants from Kadmon, grants from Reata, other from UpToDate, outside the submitted work. Dr. Rangan is a member of the Scientific Advisory Board of PKD Australia; received grants from the National Health and Medical Research Council of Australia; investigator-initiated grants from PKD Australia, Danone Nutricia (manufacturer of bottled water), Otsuka Australia, and been a member of an Advisory Board for Sanofi-Genzyme. Dr. Hawley reports receiving personal fees from GlaxoSmithKline, Johnson & Johnson, and Otsuka; and grants from Baxter Healthcare, Fresenius Medical Care, PKD Australia, Queensland Health, and NHMRC Australia for studies outside the submitted work. Dr. El-Damanawi has nothing to disclose. Dr. Hiemstra reports having received research funding from AstraZeneca and GlaxoSmithKline, and having served as an advisor to AstraZeneca and Vifor Pharma. Ms. Townsend Arellano has nothing to disclose. Dr. Lee is an employee of Otsuka. Dr. Torres reports grants and/or other fees from Acceleron Pharma Inc., Blueprint Medicines, Mironid, Otsuka Pharmaceuticals, Palladio Biosciences, Sanofi Genzyme, Regulus Therapeutics, and Vertex Pharmaceuticals, all outside the submitted work.

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SUPPLEMENTARY MATERIAL

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Supplementary information is available at *KI Report's* website:

- CONSORT Statement (PDF)
- Supplementary Table S1. TEMPO 3:4 completers, annual rate of change in renal function, estimated by CKD-EPI formula (mL/min/1.73 m^2/year) (PDF)
- Supplementary Table S2. REPRISE completers, annualized change in eGFR (mL/min/1.73 m^2/year) from pretreatment baseline to posttreatment follow-up (PDF)
- Supplementary Table S3. Baseline characteristics of matched subjects from TEMPO 3:4 and REPRISE (PDF)
- Supplementary Figure S1. The age (A) and chronic kidney disease stage (B) distributions of the matched analysis population (PDF)

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Table. Baseline characteristics of TEMPO 3:4 and REPRISE participants by completer status

Parameter	TEMPO 3:4			REPRISE		
	Completers (n=1157)	Non-completers (n=288)	*P*-value	Completers (n=1215)	Non-completers (n=155)	*P*-value
Male, n (%)	605 (52)	141 (49)	0.32	612 (50)	68 (44)	0.15
Age (yr), mean (SD)	39.03 (6.97)	37.15 (7.47)	<.001	47.38 (8.05)	46.33 (8.99)	0.13
Age ≤55 yr, n (%)	1157 (100)	288 (100)		1041 (86)	132 (85)	0.90
Caucasian, n (%)	972 (84)	246 (85)	0.59	1117 (92)	141 (91)	0.64
BMI (kg/m^2), mean (SD)	25.95 (4.79)	26.88 (5.93)	0.005	27.87 (5.71)	27.71 (5.77)	0.75
SBP (mmHg), mean (SD)	128.4 (13.59)	129.0 (13.21)	0.51	129.5 (14.09)	131.1 (14.23)	0.19
DBP (mmHg), mean (SD)	82.44 (9.63)	82.59 (10.08)	0.81	82.18 (9.62)	83.52 (10.17)	0.10
BPLD use, n (%)	856 (74)	191 (66)	0.01	1060 (87)	129 (83)	0.17
RAASi use, n (%)	848 (73)	191 (66)	0.02	1049 (86)	127 (82)	0.14
Cholesterol (mmol/L), mean (SD)	5.00 (0.91)	5.03 (0.97)	0.71	5.04 (1.01)	4.99 (0.95)	0.55
Hypercholesterolemia, n (%)	287 (25)	68 (24)	0.70	546 (45)	60 (39)	0.15
LLD use, n (%)	149 (13)	30 (10)	0.27	396 (33)	45 (29)	0.41
Glucose (mmol/L), mean (SD)	5.19 (0.80)	5.22 (0.90)	0.63	5.15 (0.83)	5.04 (0.69)	0.13
Diabetes mellitus, n (%)	1 (0)	0 (0)	1.00	28 (2)	4 (3)	0.78
GLD use, n (%)	0 (0)	0 (0)		28 (2)	4 (3)	0.78
Hematuria, n (%)	388 (34)	115 (40)	0.05	333 (27)	44 (28)	0.78
Kidney pain, n (%)	567 (49)	168 (58)	0.005	607 (50)	75 (48)	0.73
Kidney stone, n (%)	225 (19)	71 (25)	0.06	247 (20)	33 (21)	0.75
Upper UTI (kidney/bladder), n (%)	355 (31)	99 (34)	0.23	292 (24)	38 (25)	0.92
eGFR (CKD-EPI), mean (SD)	81.13 (21.47)	83.53 (22.05)	0.09	41.13 (10.99)	39.92 (11.52)	0.25
Total kidney volume (mL), median (IQR)	1470 (1072, 2024)	1454 (1066, 1976)	0.34			

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Total kidney volume ≤2000 mL, n (%)[a]				131 (11)	18 (12)	0.78
Urine osmolality (mOsm/kg), mean (SD)[b]	498.4 (180.0)	515.3 (173.4)	0.15	168.8 (61.12)	169.1 (66.36)	0.95

P-values were derived by Fisher's Exact test for binary characteristics. *P*-values were derived by T-test/Wilcoxon test for continuous characteristics.

[a]Total kidney volume was not assessed in REPRISE. During the screening period for REPRISE, the subject's eligibility for the trial was confirmed using historical imaging data and recorded total kidney volume, if available. Randomization was stratified in REPRISE by total kidney volume ≤2000 mL, >2000 mL, or unknown. Baseline total kidney volume was unknown for 80% of subjects.

[b]Urine osmolality in TEMPO3:4 was collected on the day of randomization prior to participant exposure to tolvaptan. Urine osmolality in REPRISE was also collected on the day of randomization however this was at the completion of active tolvaptan run-in and therefore whilst participants were exposed to fully titrated tolvaptan.

BMI, body mass index; BPLD, blood pressure-lowering drugs; CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GLD, glucose-lowering drugs; IQR, interquartile range; LLD, lipid-lowering drugs; RAASi, renin-angiotensin-aldosterone system inhibitors; SBP, systolic blood pressure; SD, standard deviation; UTI, urinary tract infection; yr, years.

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FIGURE LEGENDS

Figure 1. Subject flow

Figure 2. Effect of tolvaptan on eGFR change (mL/min/1.73 m^2/year) in the total trial population and treatment completer subset of TEMPO 3:4 (A) and REPRISE (B). [a]Comparison of tolvaptan vs placebo within each analysis population. Data are ± 95% confidence interval for TEMPO 3:4 and ± standard error for REPRISE. eGFR, estimated glomerular filtration rate; PBO, placebo; TOL, tolvaptan.

Figure 3. (A) Eligible ages for trial enrollment and mean age of subjects matched by propensity score. (B) Eligible eGFR for trial enrollment and mean eGFR of subjects matched by propensity score. eGFR, estimated glomerular filtration rate; PBO, placebo; TOL, tolvaptan.

Figure 4. Tolvaptan effect on eGFR slope (mL/min/1.73 m^2/year) in TEMPO 3:4 and REPRISE in subjects matched by propensity score (A). Comparison of tolvaptan effect on eGFR slope (mL/min/1.73 m^2/year) between TEMPO 3:4 and REPRISE in subjects matched by propensity score (B). [a]Comparison of TOL vs PBO in the subset of propensity-matched subjects within TEMPO 3:4 and REPRISE. [b]Comparison of TOL effect between TEMPO 3:4 and REPRISE. eGFR data are ± standard error. eGFR, estimated glomerular filtration rate; PBO, placebo; TOL, tolvaptan.

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Per-Treatment Post-Hoc Analysis of Clinical Trial Outcomes With Tolvaptan in Autosomal Dominant Polycystic Kidney Disease

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Trials included

TEMPO 3:4

Randomization
961 Tolvaptan
484 Placebo

REPRISE

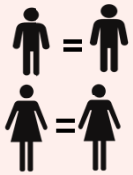
Randomization
683 Tolvaptan
687 Placebo

Methods

Treatment completers

TEMPO 3:4 (3 years)	713 Tolvaptan 410 Placebo
REPRISE (1 year)	576 Tolvaptan 634 Placebo

Matched subjects



Age
Gender
eGFR

54 matched subjects in each treatment group in each study

Findings: Tolvaptan vs placebo

Treatment effect on eGFR* (difference vs placebo)

	All randomized	Completers Only
TEMPO 3:4	0.98	0.94
REPRISE	1.27	1.23

*mL/min/1.73m²/year

Statistically similar treatment effect of Tolvaptan in matched subjects

	Difference*	*P*-value
TEMPO 3:4 vs REPRISE	-0.446	0.7068

*mL/min/1.73m²/year

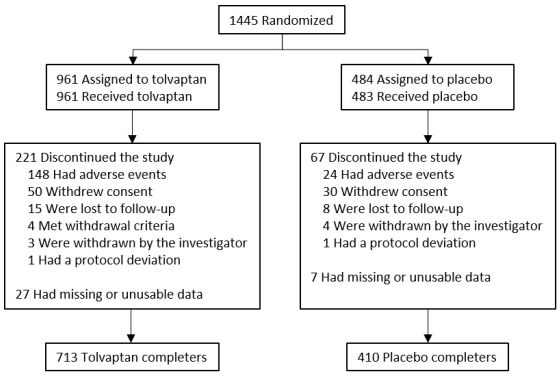
KI REPORTS
Kidney International Reports

Mallett et al, 2021.

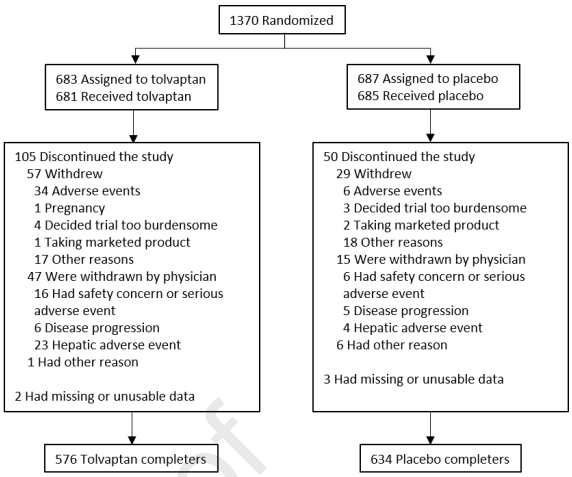
Visual abstract by:
Augusto Santos Jr, MD PhD

Conclusion Treatment completion had little impact on eGFR outcome. More rapid decline in kidney function in later-stage CKD enabled the effects of tolvaptan to be more easily discerned. Similar results between trials in subjects matched for baseline eGFR suggest that baseline eGFR is more relevant to effect size.

TEMPO 3:4



REPRISE



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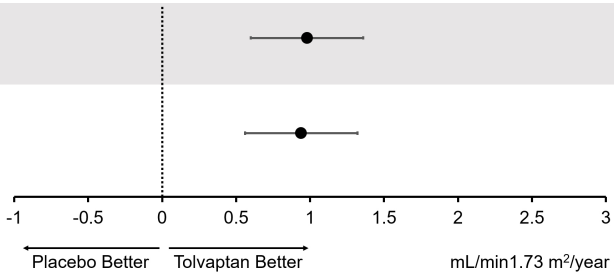
A) TEMPO 3:4

Analysis Population	TOL	PBO	Effect of TOL vs PBO on Annual eGFR Slope	TOL	PBO	Difference	*P*-value[a]
	Number of subjects			mL/min1.73 m^2/year			
Total trial population	842	464		-2.72	-3.70	0.98	<.0001
Completers	713	410		-2.74	-3.68	0.94	<.0001



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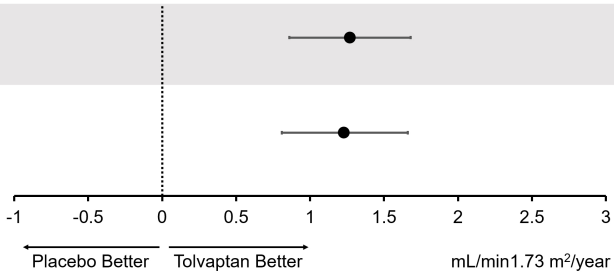
B) REPRISE

Analysis Population	TOL	PBO	Effect of TOL vs PBO on Annualized Change in eGFR	TOL	PBO	Difference	*P*-value[a]
	Number of subjects			mL/min1.73 m^2/year			
Total trial population	668	663		-2.34	-3.61	1.27	<.0001
Completers	576	634		-2.38	-3.61	1.23	<.0001



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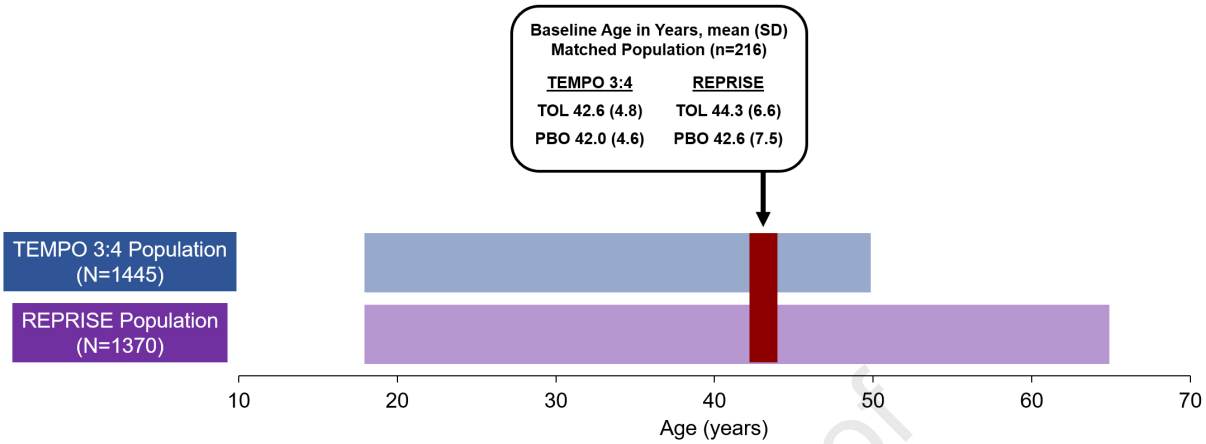

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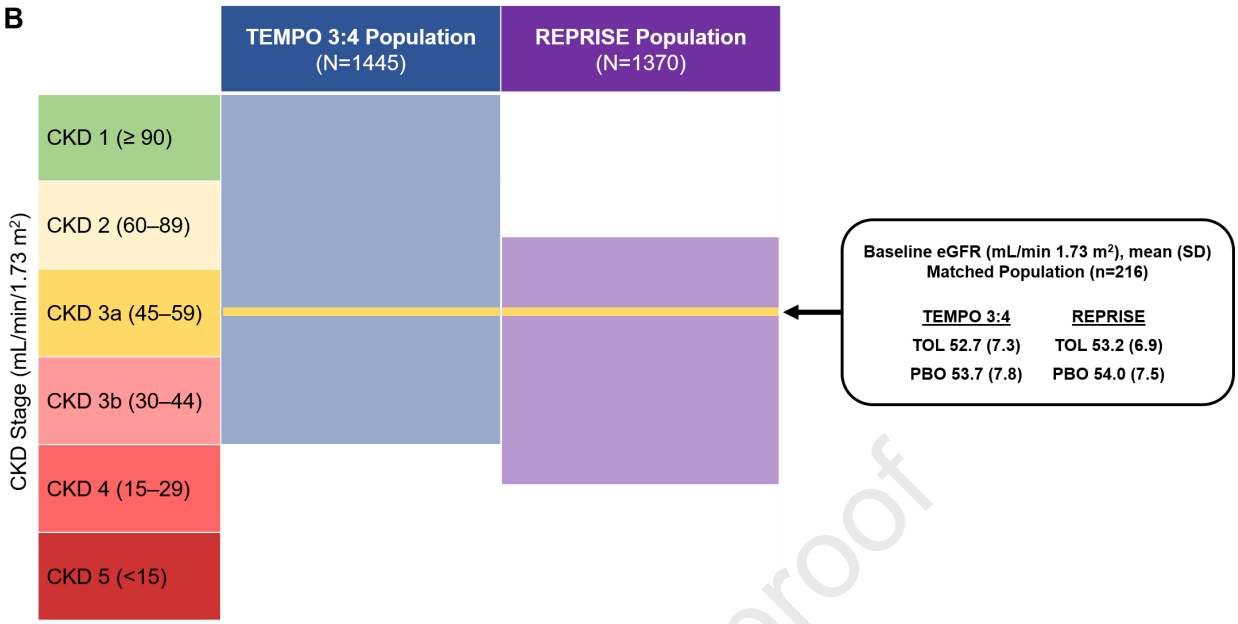

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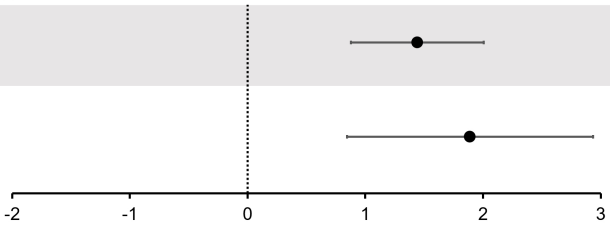
A

Analysis Population	TOL	PBO	Effect of TOL vs PBO on eGFR Slope	TOL	PBO	Difference	*P*-value[a]
	Number of subjects			mL/min1.73 m^2/year			
Matched TEMPO 3:4	54	54		-3.209	-4.651	1.442	0.0106
Matched REPRISE	54	54		-2.470	-4.359	1.889	0.0707



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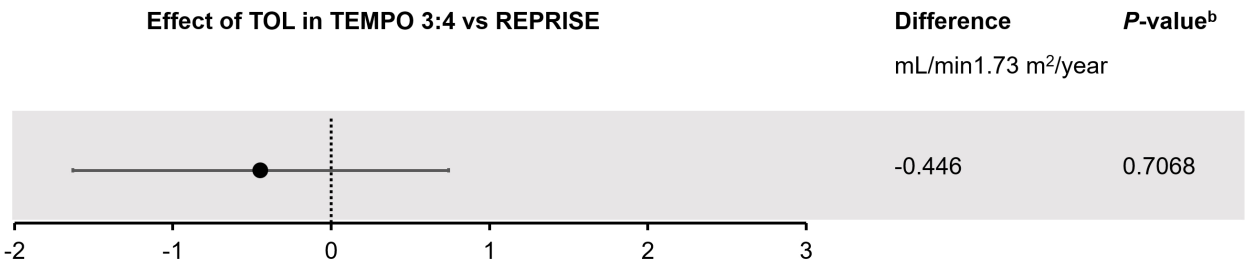

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