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# Kidney Function Decline in Patients With Autosomal Dominant Polycystic Kidney Disease: Assessment of Real-World Effectiveness of Tolvaptan

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## BACKGROUND

- Autosomal dominant polycystic kidney disease (ADPKD) is a progressive genetic disease that leads to loss of kidney function, ultimately resulting in kidney failure.
- Tolvaptan has been shown to slow decline in kidney function compared with placebo in clinical trials among patients with ADPKD who are at risk of rapid progression.[1-3]
- A recent postmarketing surveillance study of Japanese patients with ADPKD who were treated with tolvaptan in a real-world clinical setting (NCT02847624) demonstrated that tolvaptan was effective in reducing the rate of estimated glomerular filtration rate (eGFR) decline.[4]
- However, data evaluating the real-world effectiveness of tolvaptan in reducing the rate of kidney function decline among patients with ADPKD are limited by absence of a control group.
  - Accessing data sources that include both treated and comparable untreated patients with ADPKD in a real-world setting is challenging.

## OBJECTIVE

- To evaluate the real-world effectiveness of tolvaptan by comparing the annual rate of change in kidney function, as measured by eGFR, in adult patients (aged ≥ 18 years) with ADPKD treated with and without tolvaptan.

## METHODS

- The sample consisted of adult patients with ADPKD in the United States (US).
  - **Cases (patients treated with tolvaptan):** Information for this cohort was obtained from medical records of 57 US nephrologists who participated in a web-based survey between May 2019 and September 2022.[5]
  - **Historical controls (patients not treated with tolvaptan):** Patients were selected from the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) I and II, HALT Progression of Polycystic Kidney Disease (HALT-PKD) Study A, and OVERTURE studies in the pooled ADPKD database.[6]
- CRISP and OVERTURE are observational studies; HALT-PKD Study A is a randomized trial of angiotensin-converting enzyme inhibitors with or without angiotensin receptor blockers for blood pressure control.
  - These studies were conducted before tolvaptan was approved for ADPKD in the US.
- Inclusion and exclusion criteria for cases and controls are presented in Table 1.

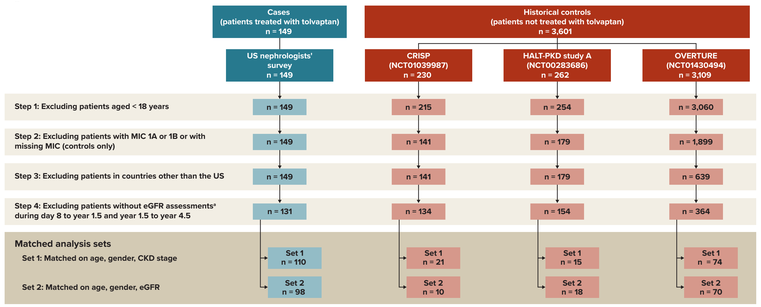
**Table 1. Summary of Inclusion and Exclusion Criteria**

| Cases | Historical controls |
|---|---|
| **Inclusion criteria** | |
| • Patients were required to have received tolvaptan continuously (i.e., interruptions no longer than 60 days) for ≥ 2 years beginning after April 2018 (when tolvaptan was approved for ADPKD in the US). | • Patients were required to be in MIC 1C to 1E. The intention was to include patients at risk of rapid progression in compliance with the recommendation for tolvaptan treatment. |
| **Exclusion criteria** | |
| • Patients who had previously participated in tolvaptan clinical trials; had a kidney transplant, dialysis, or renal malignancies before being treated with tolvaptan; or had ever been treated with tolvaptan for hyponatremia were excluded. | • Patients who used tolvaptan in CRISP, who were randomized to low-blood-pressure control arms in HALT-PKD study A, and who were enrolled in OVERTURE in Japan were excluded from the pooled ADPKD database. |

MIC = Mayo imaging classification.

- eGFR was calculated using the 2009 CKD-EPI equation[7] based on serum creatinine.
  - In the US nephrologists' survey, eGFR values reported in the patients' medical records were used when serum creatinine was missing (< 4%). Month 1 eGFR was considered as the baseline value because eGFR was not captured at tolvaptan initiation.
- Cases and controls were matched 1:1 on baseline age (± 2 years), gender (female, male), and chronic kidney disease (CKD) stage (1, 2, 3a, 3b, 4, 5) using a greedy algorithm.[8]
  - Kidney function decline was compared between cases and controls in the matched analysis set using a mixed model with eGFR as the response variable.
    - The model included treatment, time (as a continuous variable), and a treatment-by-time interaction as fixed effects and patient-specific intercepts and slopes (for time) as random effects, which were assumed to have an unstructured covariance matrix.
- Additional analyses were performed using a second matched analysis set, wherein cases and controls were matched on baseline age (± 2 years), gender (female, male), and eGFR (± 5 mL/min/1.73 m$^2$).

**Figure 1. Cohort Selection Flow Chart**




* In the historical controls cohort, eGFR assessments > 4.5 years, eGFR assessments from the HALT-PKD low-blood-pressure control group for patients initiating in CRISP, and eGFR assessments collected after surgical or invasive radiological procedures were excluded.

## RESULTS

- After applying the inclusion/exclusion criteria outlined in Table 1, the full set of patients consisted of 149 cases and 959 controls (Figure 1, Step 3).
- From the full set, 131 cases and 652 controls were eligible for matching (Figure 1, Step 4).
  - Of the patients receiving tolvaptan who were eligible for matching:
    - 84.0% (n = 110) were matched with a historical control in matched analysis set 1.
    - 74.8% (n = 98) were matched with a historical control in matched analysis set 2.

### Baseline Characteristics

- Baseline characteristics for the full set and 2 matched analysis sets are presented in Figure 2.
- Baseline characteristics of matched cases were generally similar to those of the full set of patients in the tolvaptan cohort from the US nephrologists' survey.
  - The matched analysis sets generally comprised a smaller proportion of patients in CKD stage 4 (7.3% and 7.2% in sets 1 and 2, respectively, vs. 13.5% in the full set).
- In the matched analysis sets:
  - Age, sex, and eGFR were well-balanced between the tolvaptan and control cohorts.
  - In matched analysis set 2, fewer patients in the control cohort were in CKD stage 3b even though their eGFR was matched within ± 5 mL/min/1.73 m$^2$.
  - Compared with historical controls, patients in the tolvaptan cohort comprised a smaller proportion who self-identified as White.

### Estimated Annual Rate of Change in eGFR From the Mixed Models

- Figure 3 displays eGFR values over time, estimated from the mixed model for each matched analysis set.
- The estimated annual rate of change in eGFR for each matched analysis set and cohort is displayed in Figure 4.
  - Matched analysis set 1: There was a statistically significant reduction in the estimated annual rate of change in eGFR of 1.40 mL/min/1.73 m$^2$ per year (95% confidence interval [CI], 0.05-2.74; $P$ = 0.042) for patients receiving tolvaptan compared with historical controls.
  - Matched analysis set 2: Tolvaptan was associated with a trend of reduction in decline rate by 1.18 mL/min/1.73 m$^2$ per year (95% CI, −0.22 to 2.58; $P$ = 0.097).

**Figure 3. Estimated eGFR From the Mixed Models Over Time by Treatment in the 2 Matched Analysis Sets**

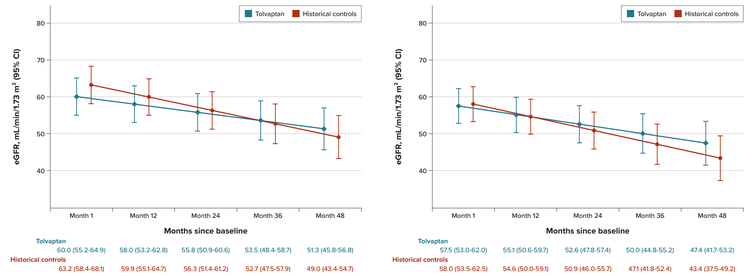



**Figure 4. Estimated Annual Rate of Change in eGFR by Treatment in the 2 Matched Analysis Sets**

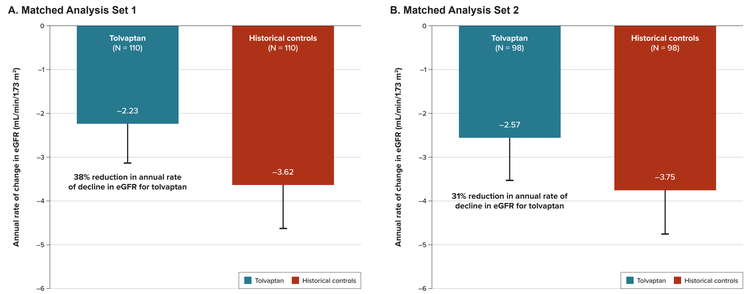
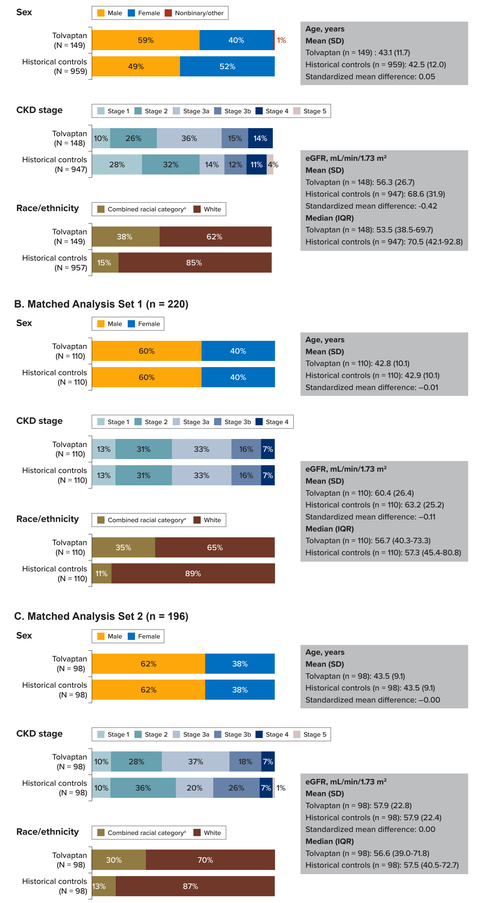



**Figure 2. Baseline Characteristics**




SD = standard deviation.

Note: This study included existing data from multiple studies. Therefore, previous data, which cannot be altered, may use terminology that is no longer in use or appropriate for certain racial and/or ethnic groups.

* Includes Asian, Black, Hispanic, other.

## LIMITATIONS

- Participating nephrologists were selected via convenience sampling, potentially limiting the generalizability of the results.
- The medical records chosen by participating nephrologists may be from memorable patients or patients seen more recently. As such, the selected patients may not be representative of the general population of US adults with ADPKD.
- Patient data such as diagnoses and laboratory measurements collected from medical records may contain inaccuracies.
- Although historical controls were matched to cases on key patient characteristics to control for confounding, the potential for residual confounding still exists.
- Some cases in the full set were not matched with a control. This may further limit generalizability and reduce statistical power. However, only the distribution of CKD stage was slightly different from that in the full set.
- Historical controls were selected because of confounding by indication bias. Using historical controls could introduce non-contemporaneous bias as clinical practice may have changed over time.

## CONCLUSIONS

- In this pooled analysis evaluating the real-world use of tolvaptan in adult patients with ADPKD in the US, tolvaptan was shown to be effective in slowing the annual rate of decline in eGFR compared with matched historical controls.
- These results are consistent with findings from clinical trials of tolvaptan and expand the body of evidence supporting tolvaptan's effect in preserving kidney function for patients with ADPKD.

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