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Evaluation of the Renal and Cardiovascular Effects of Long-Term Tolvaptan Treatment in Autosomal Dominant Polycystic Kidney Disease

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Keywords
Autosomal dominant polycystic kidney disease · Tolvaptan · Kidney progression · Cardiac effects · QTc interval

Abstract
Introduction: Cardiovascular diseases constitute a significant cause of morbidity and mortality in individuals with autosomal dominant polycystic kidney disease (ADPKD). This study aimed to assess the long-term effects of tolvaptan on the kidneys and heart in rapidly progressing ADPKD. ***Methods:*** Among 354 patients diagnosed with ADPKD, 58 meeting the eligibility criteria for tolvaptan were included in the study. The study comprised two groups with similar demographic and clinical characteristics: 29 patients receiving tolvaptan treatment and 29 in the control group. Several included genetic analysis, magnetic resonance imaging, and echocardiography. Clinical and cardiac changes were recorded in both groups after a 3-year follow-up. ***Results:*** Tolvaptan treatment demonstrated a significant reduction in the rate of eGFR decline compared to the control group. Furthermore, it was observed that tolvaptan could prevent the development of cardiac arrhythmias by inhibiting an increase in QTc interval and heart rate. ***Conclusion:*** These findings suggest that, in addition to slowing kidney progression in ADPKD management, tolvaptan may potentially benefit in preventing cardiac complications.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) follows a chronic, progressive course with multisystem involvement, ultimately leading to end-stage renal failure in advanced age [1]. It is a genetic kidney disorder responsible for approximately 1 in 1,000 cases within the population, contributing to 5–10% of all etiologies of chronic kidney disease [2]. In the majority of cases, mutations in the PKD1 gene, encoding polycystin-1 (85%), or the PKD2 gene, encoding polycystin-2 (15%), are responsible [2]. Patients carrying the PKD1 gene tend to have a worse prognosis than those carrying PKD2 [3]. While most ADPKD patients progress to end-stage renal failure, the primary

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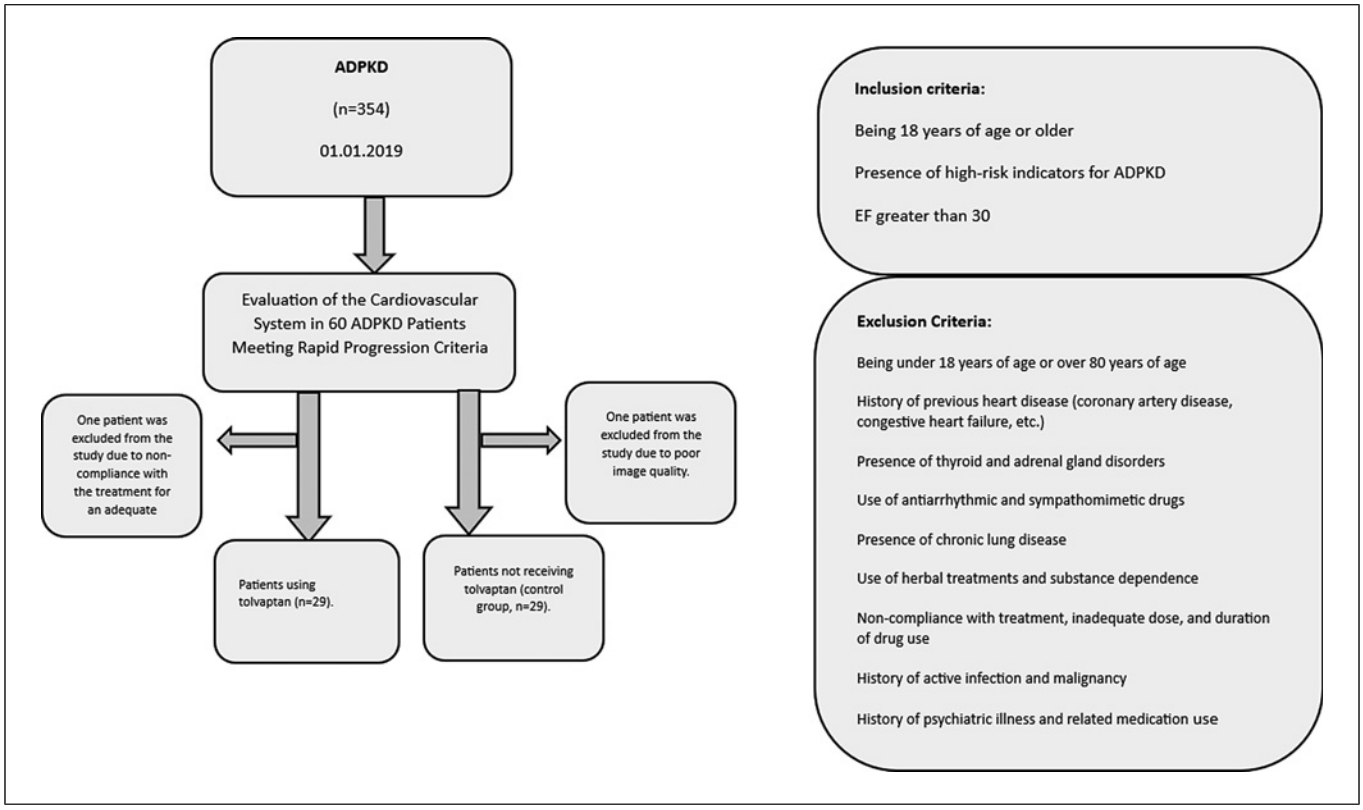

Fig. 1. Study design, inclusion criteria, and exclusion criteria for study participation.

causes of mortality and morbidity are complications related to the cardiovascular system [4]. In the majority of patients, hypertension develops before the onset of end-stage renal failure, and studies have demonstrated that hypertension occurs at an earlier age compared to the healthy population [5, 6]. The development of hypertension in ADPKD is thought to be significantly influenced by the pressure exerted by growing cysts on renal vascular structures, activating the renin-angiotensin-aldosterone system. Additionally, this, along with secondary increased systemic vascular resistance, sets the stage for the development of cardiovascular complications [7, 8]. Tolvaptan, a short-acting vasopressin V2 receptor inhibitör, recently introduced worldwide, has been shown to slow disease progression and reduce cyst development [9]. Despite sufficient data on the efficacy of high-dose and long-term tolvaptan use in preserving renal function in progressive ADPKD, there is currently limited information regarding its effects on the cardiovascular system. Therefore, we aimed to investigate the renal and cardiovascular effects of tolvaptan treatment in rapidly progressing ADPKD patients.

Materials and Methods

Study Population

Among 354 patients diagnosed with ADPKD through follow-up magnetic resonance imaging (MRI), ultrasonography, and genetic analysis at our center, 58 patients deemed suitable for tolvaptan use were randomized. These patients exhibited criteria for rapid progression in ADPKD according to the guidelines established by Chebib. et al. [10]. Patients were divided into two groups: those receiving medication (tolvaptan group) and those not using medication (control group). The control group consisted of patients with a confirmed diagnosis of ADPKD through genetic and MRI assessments, who either did not wish to undergo tolvaptan treatment or used the medication for less than 1 month (Fig. 1). Informed consent was obtained from all participants, and the study received approval from the Local Academic and Ethical Committee (project number: 2022–196). Tolvaptan was administered to 29 patients at doses of 90 mg/day or 120 mg/day, and their progress was monitored for 36 months from 2019 to 2022. Among them, 21 patients received 120 mg/day, while eight received 90 mg/day of tolvaptan. The control group underwent conservative follow-up for 36 months. In both groups, baseline assessments were conducted before starting tolvaptan and after the treatment period, following similar evaluation criteria for the control group. The inclusion and exclusion criteria for the study are depicted in Figure 1. Medical histories and physical examinations during outpatient controls for both the medication and

control groups were recorded in the electronic database system of the Erciyes University Faculty of Medicine Hospital. Blood pressure measurements were taken using a sphygmomanometer after 10 min of rest. Information on age, gender, height, weight, the presence of hypertension, duration of hypertension if present, history of cardiovascular disease, smoking, alcohol, and drug use were collected and recorded. Subsequently, 12-lead electrocardiogram (ECG) and echocardiography assessments were performed, and biochemical samples were collected for analysis at the Erciyes University Central Biochemistry Laboratory.

Biochemical Assessment

Blood samples were obtained from patients in the morning after a 12-h overnight fast. Plasma glucose, serum albumin, serum electrolytes (Na, K, Ca, Mg), kidney function tests (BUN, creatinine, proteinuria), and complete blood count parameters were determined using standard methods. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [11].

Genetic Analysis

All genes associated with nephropathy were sequenced using bead capture technology, and the entire gene sequences were analyzed with the Sophia Genetics Nephropathy Panel (Saint-Sulpice, Switzerland). DNA isolation from peripheral blood samples was performed using automated systems and standard protocols. Within the scope of the test, genes were sequenced using the Sophia Nephropathy kit. Next-generation sequencing was conducted on the Illumina MiSeq platform, and variant calling and bioinformatic analysis were performed using the Sophia DDM [12].

MRI Evaluation

MRI without gadolinium contrast agent was performed using a 1.5-T system (Magnetom Aera; Siemens Healthineers). Kidney volume measurement was conducted using the mid-slice technique on T1-weighted ultrafast gradient echo MRI series with post-processing workstations (Vitrea Workstation, Version 4.1.51, Canon Medical Systems).

Electrocardiographic Evaluation

Standard 12-lead electrocardiography was used to record ECGs for patients using and not using tolvaptan. ECG recordings were made with the Tepa EKG Master device at a speed of 25 mm/s and a voltage of 10 mm/mV. All ECG records were transferred to a computer and analyzed. P wave, heart rate, and QTc intervals were evaluated in the electrocardiographic assessment. The QTc interval was calculated using the Bazett formula, and in cases of interobserver differences, two experienced cardiologists recalculated measurements, and the average values were taken.

Echocardiographic Evaluation

All patients participating in the study underwent examination with transthoracic echocardiography by two experienced cardiologists. Examinations were conducted using the VIVID S70 with a 2.5-MHz probe, and patients were positioned in the left lateral decubitus position according to the guidelines of the American Society of Echocardiography. Imaging was performed from the parasternal long axis, parasternal short axis, apical 4-chamber, and apical 2-chamber windows. Simultaneous ECG monitoring was performed during echocardiography. Systolic functions of the heart, wall thickness, diameters of the left and right heart chambers, aortic root, and valve structures were examined. The left atrium volume was calculated using the dimensions obtained from the apical 4-chamber and apical 2-chamber windows. Finally, left ventricular mass indices were calculated using interventricular septal thickness (IVSD), posterior wall thickness, and left ventricular end-diastolic diameter (LVEDD).

Statistical Analysis

The normal distribution of data was evaluated using the Shapiro-Wilk test, histograms, and q-q plots. Dependent two-sample *t* test, Wilcoxon test, independent two-sample *t* test, Mann-Whitney U test, and Kruskal-Wallis *H* test were utilized to compare quantitative data before and after treatment and between groups. Multiple comparisons were performed using the Dunn-Bonferroni test. McNemar's, Fisher-Freeman-Halton exact, and Pearson χ^2 tests were used to compare categorical data before and after treatment and between groups. When the influence of eGFR variation was controlled for, a linear regression analysis (Enter method) was utilized to investigate potential differences in QTc interval changes between groups, distinguishing between those who were using medication and those who were not. In this analysis, the statistical impact of medication on QT changes was examined, with adjustments made for alterations in eGFR**.** A significance level of $p < 0.05$ was considered. The analyses were conducted using the SPSS 22.0 software package.

Results

A total of 60 ADPKD patients were included for evaluation based on inclusion and exclusion criteria from the initial pool of 354 patients. One patient who self-reported inadequate duration and dosage of tolvaptan treatment, and another with poor image quality, were not included in the study. Therefore, data from a total of 58 patients were analyzed. The baseline characteristics of patients, both those using tolvaptan and the control group, were analyzed and summarized in Table 1. The average age of the 29 patients using tolvaptan was 45.62 ± 6.27, with 18 (62.1%) males. In the control group, the average age was 44.83 ± 10.18, with 16 (53.3%) males. No significant differences were observed in the baseline characteristics of both groups, including BMI, office blood pressure, Mayo score, genetic factors, total kidney volume (hTKV), laboratory findings, electrocardiography, and echocardiography (Table 2) ($p > 0.05$). However, when analyzed after 36 months of follow-up, differences in clinical parameters were observed (Tables 1, 3). First, comparing electrocardiographic findings between the two groups after treatment, heart rate was significantly higher in the control group (80.00 ± 7.57 beats/minute) compared

Table 1. Changes in biochemical and radiological parameters before and after treatment in patient groups receiving and not receiving tolvaptan

Results	Patients using tolvaptan (n = 29)	Control group (n = 29)	p value
eGFR[a] baseline, mL/min/1.73 m^2	45.45±11.93	56.43±32.2	0.24
eGFR[a] post-treatment, mL/min/1.73 m^2	43.56±16.06	49.45±26.32	0.39
Δ eGFR, mL/min/1.73	−1.89±9.33	−6.99±13.83	0.10
p value	0.63	0.01*	
Sodium baseline, mmol/L	140.34±3.35	140.03±3.24	0.73
Sodium post-treatment, mmol/L	139.66±3.82	139.23±3.87	0.57
Δ Sodium, mmol/L	−0.69±3.65	−0.80±3.81	0.91
p value	0.83	0.87	
Potassium baseline, mmol/L	4.25±0.46	4.51±0.49	0.05
Potassium post-treatment, mmol/L	4.38±0.44	4.51±0.54	0.05
Δ Potassium, mmol/L	0.13±0.45	0.00±0.58	0.33
p value	0.74	0.99	
Calcium baseline, mmol/L	9.44±0.42	9.31±0.51	0.35
Calcium post-treatment, mmol/L	9.43±0.44	9.32±0.47	0.35
Δ Calcium, mmol/L	0.00±0.39	0.01±0.63	0.91
p value	0.92	0.93	
Magnesium baseline, mmol/L	0.82±0.03	0.83±0.03	0.22
Magnesium post-treatment, mmol/L	0.81±0.06	0.83±0.06	0.36
Δ Magnesium, mmol/L	0.00±0.06	0.00±0.0.60	0.76
p value	0.96	0.99	
Proteinuria baseline	0.23±0.16	0.23±0.56	0.66
Proteinuria post-treatment	0.27±0.42	0.38±0.39	0.29
Δ Proteinuria	0.15±0.29	0.04±0.09	0.30
p value	0.12	0.01*	
hTKV baseline, mL	1,216.03±616.35	1,126.57±677.99	0.59
hTKV post-treatment, mL	1,307.58±621.03	1,256.06±697.33	0.76
Δ hTKV, mL	98.44±56.13	126.26±66.98	0.09
p value	0.64	0.56	

[a]Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Δ: represents the difference between post-treatment and pretreatment. Data are expressed as mean and standard deviation for normally distributed variables. eGFR, estimated glomerular filtration rate; TKV, total kidney volume. Results with a p value less than 0.05 are deemed statistically significant.

to the tolvaptan-treated group (75.00 ± 12.01 beats/minute) (p = 0.04) (Fig. 2). QTc interval was significantly higher in the control group (420.83 ± 25.89 ms) compared to the tolvaptan-treated group (397.21 ± 37.37 ms) (p = 0.01). In the control group, the QTc interval, initially measured at 400.73 ± 34.39 ms, increased to 420.83 ± 25.89 ms at the 36-month follow-up, and this change was statistically significant (p = 0.01) (Table 3) (Fig. 2). Second, among the biochemical parameters, differences were observed in some parameters related to kidney function. eGFR decreased from 45.45 ± 11.93 mL/min/1.73 m^2 to 43.56 ± 16.06 mL/min/1.73 m^2 in the tolvaptan-treated group and from 56.43 ± 32.2 mL/min/1.73 m^2 to 49.45 ± 26.32 mL/min/1.73 m^2 in the control group, and these changes were statistically significant (p = 0.01). The regression analysis demonstrated a significant alteration in QTc interval under the fixed change condition of eGFR (p = 0.03, r = 0.43). Simultaneously, the correlation analysis within the same dataset revealed a statistically significant, albeit weak, negative correlation between medication usage and QTc interval (b = −0.323, p = 0.03) (Table 4). Similarly, while the amount of proteinuria did not change significantly in the tolvaptan-treated group (0.23 ± 0.16–0.27 ± 0.42, p = 0.12), an increase was observed in the control group (0.23 ± 0.56 to 0.38 ± 0.39, p = 0.01) (Table 1). There were no significant differences in systolic and diastolic blood pressure between the tolvaptan-treated and the control group (p > 0.05). Similarly, although there was an increase in systolic blood pressure in the control group over a similar period, it was

Table 2. Baseline characteristics of ADPKD patients planned for tolvaptan treatment and ADPKD patients not using tolvaptan (control group) before treatment

Basic characteristic features	Patients with ADPKD using tolvaptan (n = 29)	Control group (n = 29)	p value
Age, years	45.62±6.27	44.83±10.18	0.65
Gender, *n* (%)			
Male	18 (62.1)	16 (55.1)	0.08
Female	11 (37.9)	13 (44.8)	
BMI, kg/m^2	28.55±3.33	28.37±3.21	0.61
Smoking			
None, *n* (%)	7 (24.1)	6 (20.6)	0.89
Present, *n* (%)	22 (75.9)	23 (79.3)	
Drug distribution			
ACEi/ARB, *n* (%)	12 (44.4)	13 (50)	
Ca channel blocker, *n* (%)	5 (18.5)	4 (15.3)	0.53
Alfa blockers, *n* (%)	3 (11.1)	2 (7.6)	
Diuretic, *n* (%)	7 (25.9)	7 (15.3)	
B blocker	None	None	
Systolic blood pressure, mm Hg	140.86±9.83	136.83±14.05	0.23
Diastolic blood pressure, mm Hg	73.1±6.47	71.67±5.77	0.29
Pulse pressure, mm Hg	68.28±9.19	64.5±12.34	0.36
hTKV, mL	1,216.03±616.35	1,126.57±677.99	0.59
Mayo classification, *n* (%)			
1C	11 (41.3)	20 (68.9)	0.12
1D	15 (51.7)	4 (13.7)	
1E	2 (6.9)	5 (17.2)	
Hypertension			
None, *n* (%)	2 (6.9)	3 (10.3)	0.35
Present, *n* (%)	27 (93.1)	26 (89.6)	
Genetic			
PKD1, *n* (%)	16 (55.2)	14 (48.2)	0.42
PKD2, *n* (%)	1 (3.4)	3 (10.3)	
PKD3, *n* (%)	12 (41.4)	12 (41.3)	
Laboratory			
eGFR[a], mL/min/1.73 m^2	45.45±11.93	56.43±32.2	0.24
Creatinine, mg/dL	1.65±0.41	1.67±1	0.20
Calcium, mmol/L	9.44±0.42	9.31±0.51	0.35
Magnesium, mmol/L	0.82±0.03	0.83±0.03	0.22
Sodium, mmol/L	140.34±3.35	140.03±3.24	0.73
Potassium, mmol/L	4.38±0.44	4.51±0.49	0.05
Glucose, mg/dL	92.36±11.36	112.36±69.1	0.23
Spot urine protein-to-creatinine ratio	0.23±0.16	0.23±0.56	0.66
Hemoglobin, g/dL	13.97±1.51	13.49±1.40	0.29
Electrocardiography			
Heart rate (beat/minutes)	76.00±12.97	78.23±10.15	0.43
QTc interval, ms	405.66±36.82	400.73±34.39	0.56
P wave, ms	101.86±27.56	111.48±28.19	0.24
Echocardiography			
Ejection fraction, %	59.97±5.78	57.3±8.04	0.17
Pulmonary artery pressure, mm Hg	23.86±4.61	30.56±15.21	0.35
LVEDD, mm	47.24±5	48.47±5.04	0.42
LVESD, mm	35.27±7.53	35.59±7.26	0.79

Table 2 (continued)

Basic characteristic features	Patients with ADPKD using tolvaptan (n = 29)	Control group (n = 29)	p value
PWD, mm	11.69±2.29	10.59±1.96	0.06
IVSD, mm	11.59±1.78	10.46±2.25	0.06
Aortic root diameter, mm	32.62±2.81	31.82±3.09	0.11
Left atrium diameter, mm	35.24±3.92	36.93±7.39	0.47

[a]Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. QTc interval was calculated using the Bazett formula. Data are expressed as the mean and standard deviation for normally distributed variables. BMI, body mass index; TKV, total kidney volume; eGFR, estimated glomerular filtration rate; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; PWD, posterior wall diameter; IVSD, interventricular septal diameter.

not statistically significant ($p > 0.05$). However, there was no significant difference in pulse pressure between pre- and posttreatment in the tolvaptan-treated group In contrast, in the control group, pulse pressure increased from 64.5 ± 12.34 mm Hg to 68.83 ± 12.15 mm Hg. This change was significant ($p = 0.01$) (Table 3). Echocardiographic findings, including ejection fraction, pulmonary artery pressure, left ventricular end-systolic diameter, left ventricular end-diastolic diameter (LVEDD), IVSD, and aortic root diameter, did not show significant differences during the treatment period in both the tolvaptan-treated and control groups ($p > 0.05$) (Table 3).

Discussion

This study evaluated the long-term renal and cardiac effects of tolvaptan in a group of rapidly progressing ADPKD patients. First, when patients receiving treatment and the control group were assessed at 36 months of posttreatment, it was observed that the decrease in eGFR in the tolvaptan-treated group was significantly less than that in the control group, and proteinuria was significantly higher in the control group compared to the tolvaptan-treated group. These findings are as consistent with studies such as TEMPO 4:4 and REPRISE, suggesting that tolvaptan treatment slows the progression to end-stage renal failure in ADPKD [9, 13, 14]. Second, after 36 months of treatment, it was found that the QTc interval from electrocardiographic findings did not increase in the tolvaptan-treated group, and in fact, it slightly decreased compared to the baseline. In contrast, the control group significantly increased the QTc interval. Similarly, the heart rate was lower in the tolvaptan-treated group than in the control group. Studies have shown that a lower heart rate is beneficial in prolonging lifespan and predicting cardiovascular diseases [15, 16]. These results could be attributed to the secondary effects of tolvaptan; however, there is insufficient literature on the pathophysiological processes related to these findings. An increase in QTc interval as chronic kidney disease progresses, independently of other risk factors, has been shown in studies [17]. The QT interval consists of the distance from the beginning of ventricular depolarization to the end of ventricular repolarization. It can vary in conditions such as medications, electrolyte imbalances, ischemic conditions, congenital diseases, cerebrovascular diseases, and diabetic neuropathy. Studies have demonstrated the clinical and prognostic significance of an increased QT interval in diseases other than cardiac diseases, such as type 1 and type 2 diabetes mellitus, nutritional disorders, rheumatological diseases, patients undergoing renal replacement therapy, patients with electrolyte imbalances, severe burns, and individuals who have undergone renal transplantation [18, 19]. In patients with prolonged QTc intervals, ventricular premature beats and sudden death are more common than in those with a normal QTc range. ADPKD, known to be associated with arrhythmic risk and autonomic imbalance, is among the secondary causes of hypertension and chronic kidney disease [20]. The literature has shown a significant delay in cardiac repolarization as chronic kidney disease progresses, independently of other risk factors, suggesting a relationship between the worsening of kidney functions and cardiac repolarization in chronic kidney patients. This situation may also increase the risk of sudden cardiac death and drug-related arrhythmia sensitivity [21, 22]. Additionally, both prolonged QTc

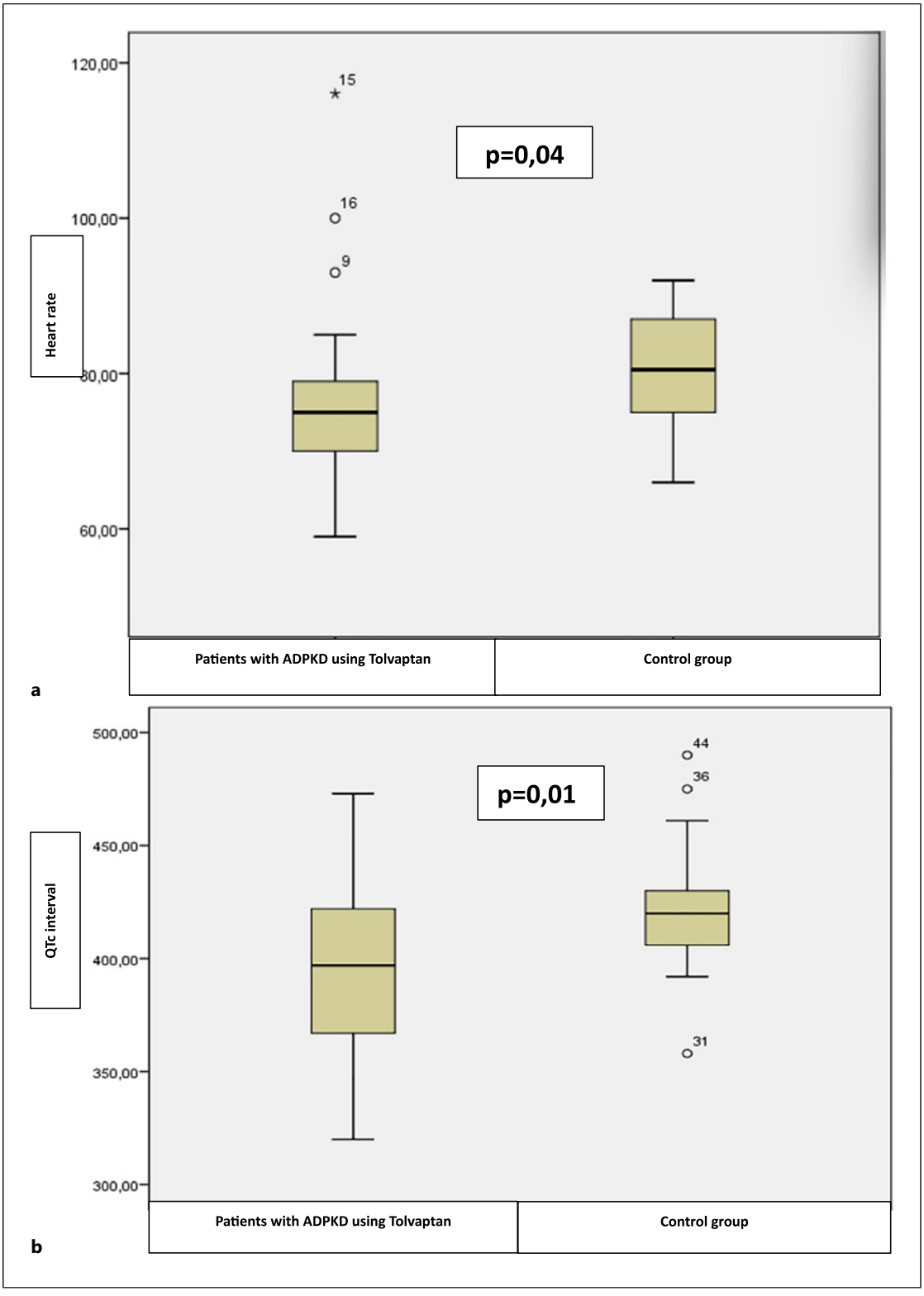

Fig. 2. a Comparison of heart rates between the control group and patients receiving tolvaptan after follow-up. **b** Comparison of QTc intervals between the group receiving tolvaptan and the control group after follow-up.

Table 3. Changes in cardiovascular findings before and after treatment in patient groups receiving and not receiving tolvaptan

Results	Patients using tolvaptan (n = 29)	Control group (n = 29)	p value
Systolic blood pressure, mm Hg baseline	140.86±9.83	136.83±14.05	0.23
Systolic blood pressure, mm Hg post-treatment	139.14±9.73	139.33±16.39	0.83
Δ Systolic blood pressure, mm Hg	−1.72±11.12	2.50±8.98	0.11
p value	0.46	0.16	
Diastolic blood pressure, mm Hg baseline	73.10±6.47	71.67±5.77	0.29
Diastolic blood pressure, mm Hg post-treatment	71.21±7.03	71.33±6.01	0.91
Δ Diastolic blood pressure, mm Hg	−1.90±7.49	−0.33±6.81	0.40
p value	0.16	0.59	
Pulse pressure, mm Hg baseline	68.28±9.19	64.5±12.34	0.36
Pulse pressure, mm Hg post-treatment	68.79±8.09	68.83±12.15	0.80
Δ Pulse pressure, mm Hg	0.52±13.39	4.33±8.48	0.19
p value	0.54	**0.01***	
QTc interval baseline	405.66±36.82	400.73±34.39	0.56
QTc interval post-treatment	397.21±37.37	420.83±25.89	**0.01***
Δ QTc interval	−8.45±43.90	20.10±41.25	**0.01***
p value	0.73	**0.01***	
Heart rate baseline	76.1±12.97	78.23±10.15	0.43
Heart rate post-treatment	75±12.01	80±7.57	**0.04***
Δ Heart rate	−0.10±14.43	1.77±13.27	0.60
p value	0.62	0.80	
Ejection fraction baseline	59.97±5.78	57.30±8.04	0.17
Ejection fraction post-treatment	58.34±9.74	55.47±12.13	0.48
Δ Ejection fraction	−1.62±7.75	−1.83±8.39	0.92
p value	041	044	
Pulmonary artery pressure, mm Hg baseline	23.86±4.61	30.56±15.21	0.35
Pulmonary artery pressure, mm Hg post-treatment	25.73±7.07	29.07±12.33	0.50
Δ Pulmonary artery pressure, mm Hg	1.58±6.98	−1.48±7.94	0.13
p value	0.28	0.26	
LVEDD baseline, mm	47.24±5.00	48.47±5.04	0.42
LVEDD post-treatment, mm	46.62±4.43	47.76±5.23	0.51
Δ LVEDD, mm	−0.62±6.29	−0.28±7.73	0.85
p value	0.92	0.80	
LVESD baseline, mm	35.27±7.53	35.59±7.26	00.79
LVESD post-treatment, mm	36.35±8.34	35.05±6.94	0.63
Δ LVESD, mm	0.05±10.43	−1.47±7.21	0.59
p value	0.74	0.29	
IVSD, mm baseline	11.59±1.78	10.46±2.25	0.06
IVSD mm post-treatment	11.59±1.82	10.93±2.28	0.06
Δ IVSD, mm	0.00±2.24	0.38±3.38	0.62
p value	0.53	0.59	
Aortic root diameter, mm, baseline	32.62±2.81	31.82±3.09	0.11
Aortic root diameter post-treatment, mm	32.04±3.23	32.62±2.82	0.53
Δ Aortic root diameter, mm	0.00±3.90	−0.07±4.45	0.94
p value	0.96	0.96	

Δ: indicates the difference between post-treatment and pretreatment. QTc interval was calculated using the Bazett formula. Data are expressed as the mean and standard deviation for normally distributed variables. Results with a p value less than 0.05 are deemed statistically significant. LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; IVSD, interventricular septal diameter.

Table 4. Results of multiple linear regression analysis on QTC interval using the Enter method

Variables	Coefficient (B)	Standard error (SE)	*t* value	*p* value
Tolvaptan therapy	−34.065	−0.385	−3.119	0.003
eGFR changes	1.082	0.291	2.360	0.022
Constant	27.657		3.400	0.001

F-statistic: $F(x, y) = 6.367$, $p = 0.003$ (significance of the model). R^2: 0.185 (percentage of variance explained by the model). Multiple linear regression analysis was conducted to examine the effects of independent variables on QTC distance, with all independent variables included in the model simultaneously using the "Enter" method. According to the analysis results, the effects of independent variables on QTC distance are statistically significant ($p < 0.05$). The overall significance of the model is indicated by the F-statistic. The R^2 value represents the percentage of variance explained by the independent variables in the model.

and chronic kidney disease are independently associated with an increased risk of mortality. When combined, there is a higher mortality risk than those with typical values [23, 24]. Upon evaluating the data obtained from our study, it can be interpreted that the increase in QTc interval in the control group and the faster progression toward end-stage renal failure compared to those receiving tolvaptan suggest that tolvaptan treatment may stabilize both risk factors more effectively, potentially providing cardiovascular benefits. Both groups had similar demographic findings, genetic findings, comorbidity conditions, biochemical tests, and echocardiographic findings influencing QTc interval. The similarity of these findings reduces the possibility that the mentioned results are due to other causes in our study. Cardiovascular system assessment in our study was evaluated in terms of electrocardiographic and echocardiographic findings, and it was observed that tolvaptan treatment did not cause a significant difference in measurements of echocardiographic findings (ejection fraction (%), pulmonary artery pressure, LVEDD, left ventricular end-systolic diameter, IVSD, aortic root diameter) before and after treatment in both groups (Table 3). The results suggest a significant potential for tolvaptan to slow down renal progression in ADPKD patients and prevent arrhythmic complications associated with the elongation of QTc interval. This study has some significant limitations: standard dosage could not be applied to all patients; they were followed with tolvaptan treatment at a tolerable level. This limits the generalizability of the results for the overall population. Also, 24-hour Holter recording could not be performed, preventing a more comprehensive analysis of the cardiovascular condition. Moreover, the number of randomized ADPKD patients is limited due to patients who do not meet rapid progression criteria and are not candidates for tolvaptan treatment. Furthermore, longer term studies are needed to assess this effectiveness. The patients in the study represent a rapidly progressing ADPKD patient group that meets specific criteria. Therefore, caution should be exercised when generalizing the findings to the general ADPKD population.

Conclusion

The findings from our study indicate that the use of tolvaptan in ADPKD patients has the potential to slow down renal progression and prevent arrhythmic complications associated with the elongation of QTc interval. The study's results suggest a promising role for tolvaptan in managing ADPKD, but further data and long-term follow-ups are needed to clarify this potential.

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Statement of Ethics

Informed consent was obtained from all participants, and the study received approval from the Local Academic and Ethical Committee (project number: 2022–196).

Conflict of Interest Statement

The authors declare no conflicts of interest related to this research.

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Author Contributions

This article, authored by Alparslan Demiray (AD), encompasses the study's design, data management, and manuscript composition. Ramazan Ozan (RO) contributed to data collection and analysis processes, providing valuable assistance in manuscript editing. Salih Güntuğ Özaytürk (SGÖ), with substantial contributions to literature review and methodology, meticulously reviewed the manuscript. Hakan İmamoğlu (HI) played a crucial role in analysis processes and oversaw statistical evaluations. Gökmen Zararsız (GZ) contributed to the study's design and data collection processes, actively participating in the manuscript review. Murat Hayri Sipahioğlu (MHS) made contributions to the literature review and methodology, aiding in the manuscript editing process. Bülent Tokgöz (BT), through significant contributions to data analysis and interpretation, provided substantial support throughout the writing process. Deniz Elçik (DE) actively participated in the data collection process and assisted in the creation of graphics and tables for the manuscript. İsmail Koçyiğit (IK) contributed to the study's design, managed the literature review, and meticulously reviewed the manuscript.

Data Availability Statement

The data supporting the findings of this study are available upon request.

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