

EFFICACY OF TOLVAPTAN ON AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD) PATIENTS IN LATE-STAGE CKD

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Introduction

TEMPO 3:4 trial¹⁾ showed that tolvaptan decreased total kidney volume (TKV) growth and estimated glomerular filtration rate (eGFR) loss in ADPKD patients with creatinine clearance ≥ 60 mL/min, but did not reveal the efficacy and safety of tolvaptan on ADPKD patients in late-stage CKD.

1) Torres VE, et al. *N Engl J Med* 367: 2407-2418, 2012

Aim

The aim of our study is to evaluate the efficacy of tolvaptan for late-stage CKD in ADPKD patients.

Methods

17 ADPKD patients with CKD-Stage 3b ($30 \leq eGFR < 45$ ml/min/1.73m²) and CKD-Stage 4 ($15 \leq eGFR < 30$ ml/min/1.73m²) initiated tolvaptan and were evaluated at baseline and after 12 months. At the each time point, weight, blood pressure, kidney function and TKV, measured by CT or MRI scan, were investigated. Main outcomes were changes in TKV and eGFR (Retrospective, observational study).

CT: computed tomography, MRI: magnetic resonance imaging

Table 1 Baseline Characteristics of Study Participants, Stratified by eGFR

CKD stage	All (n=17)	Stage 3b (n=11)	Stage 4 (n=6)	P value
Age	53 [41 to 60]	46 [40 to 55]	62 [46 to 64]	0.08
Male	12/17 (71%)	9/11 (82%)	3/6 (50%)	0.28
Height(cm)	172.0 [164.1 to 177.3]	172.6 [168.0 to 177.6]	163.9 [156.3 to 172.1]	0.04
Weight(kg)	72.3 [66.2 to 80.3]	74.0 [67.4 to 88.8]	69.4 [53.7 to 74.1]	0.25
ACEIs/ARBs use	22.5 [22.5 to 60]	11/11 (100%)	3/6 (50%)	0.03**
Dose of tolvaptan(mg/day)	129 [118 to 144]	60 [22.5 to 60]	22.5 [22.5 to 22.5]	0.02*
SBP(mmHg)	86 [77 to 94]	135 [119 to 146]	124 [117 to 137]	0.39
DBP(mmHg)	0.24 [0.04 to 0.40]	86 [75 to 92]	85 [77 to 96]	0.96
Protein Urea (g/gCr)	2843 [2217 to 3924]	0.25 [0 to 0.41]	0.18 [0.07 to 0.32]	0.61
TKV(ml)	5.99 [2.93 to 10.7]	3450 [2384 to 4187]	2310 [1983 to 3111]	0.15
Δ TKV(%/year)	1.70 [1.43 to 1.99]	7.66 [3.86 to 10.6]	4.46 [2.32 to 11.3]	0.73
Serum Creatinine(mg/dl)	29.8 [26.0 to 36.9]	1.63 [1.37 to 1.77]	2.02 [1.74 to 2.29]	0.02*
eGFR(ml/min/1.73m ²)	-4.58 [-8.03 to -2.30]	35.6 [29.8 to 37.5]	24.1 [22.6 to 27.2]	<0.01*
Δ eGFR(ml/min/1.73m ² /year)	53 [41 to 60]	-6.89 [-8.07 to -2.25]	-3.50 [-11.4 to -1.34]	0.65

* Mann-Whitney's U test
** Fisher's exact test

Table 2 Changes from baseline 12 months after treatment of tolvaptan Treatment

	All patients (n=17)	Baseline	12 months after	Absolute Change	P value
Weight(kg)	72.3 [66.2 to 80.3]	70.0 [65.5 to 81.8]	-0.1 [-2.0 to 1.6]	0.59	
Dose of tolvaptan(mg/day)	22.5 [22.5 to 60]	45 [22.5 to 90]	15 [0 to 33.8]	<0.01*	
SBP(mmHg)	129 [118 to 144]	126 [120 to 130]	-5 [-13 to 7]	0.12	
DBP(mmHg)	86 [77 to 94]	84 [76 to 92]	-4 [-10 to 8]	0.57	
Protein Urea	0.24 [0.04 to 0.40]	0 [0 to 0.28]	-0.11 [-0.24 to 0.01]	0.04*	
Serum level of Sodium	142 [141 to 142]	143 [141 to 144]	0.5 [-3.1 to 3.0]	0.03*	
FENa	0.75 [0.41 to 1.17]	0.60 [0.30 to 0.96]	0.39 [-0.33 to 0.76]	0.21	
U-Osm(mOsm/kg)	338 [264 to 425]	172 [118 to 224]	-148 [-253 to -41]	<0.01*	
S-Osm(mOsm/L)	288 [288 to 292]	295 [291 to 298]	2.5 [2.0 to 9.0]	0.05	
TKV(ml)	2843 [2217 to 3924]	2865 [2360 to 4260]	65.4 [-114.5 to 376.4]	0.16	
Δ TKV(%/year)	5.99 [2.93 to 10.7]	1.56 [-4.31 to 9.14]	-4.0 [-10.9 to -0.69]	0.02*	
Serum Creatinine(mg/dl)	1.70 [1.43 to 1.99]	2.03 [1.62 to 2.43]	0.3 [0.21 to 0.51]	<0.01*	
eGFR(ml/min/1.73m ²)	29.8 [26.0 to 36.9]	27.1 [22.3 to 33.4]	-5.0 [-8.7 to -4.1]	<0.01*	
Δ eGFR(ml/min/1.73m ² /year)	-4.58 [-8.04 to -2.30]	-5.03 [-8.51 to -3.98]	-1.43 [-5.05 to 3.54]	0.37	

Values are median [interquartile range].
U-Osm: Urine osmolality, S-Osm: Serum-Osmolarity

*Wilcoxon signed rank test

Figure 1 Change in TKV from baseline at 12 months

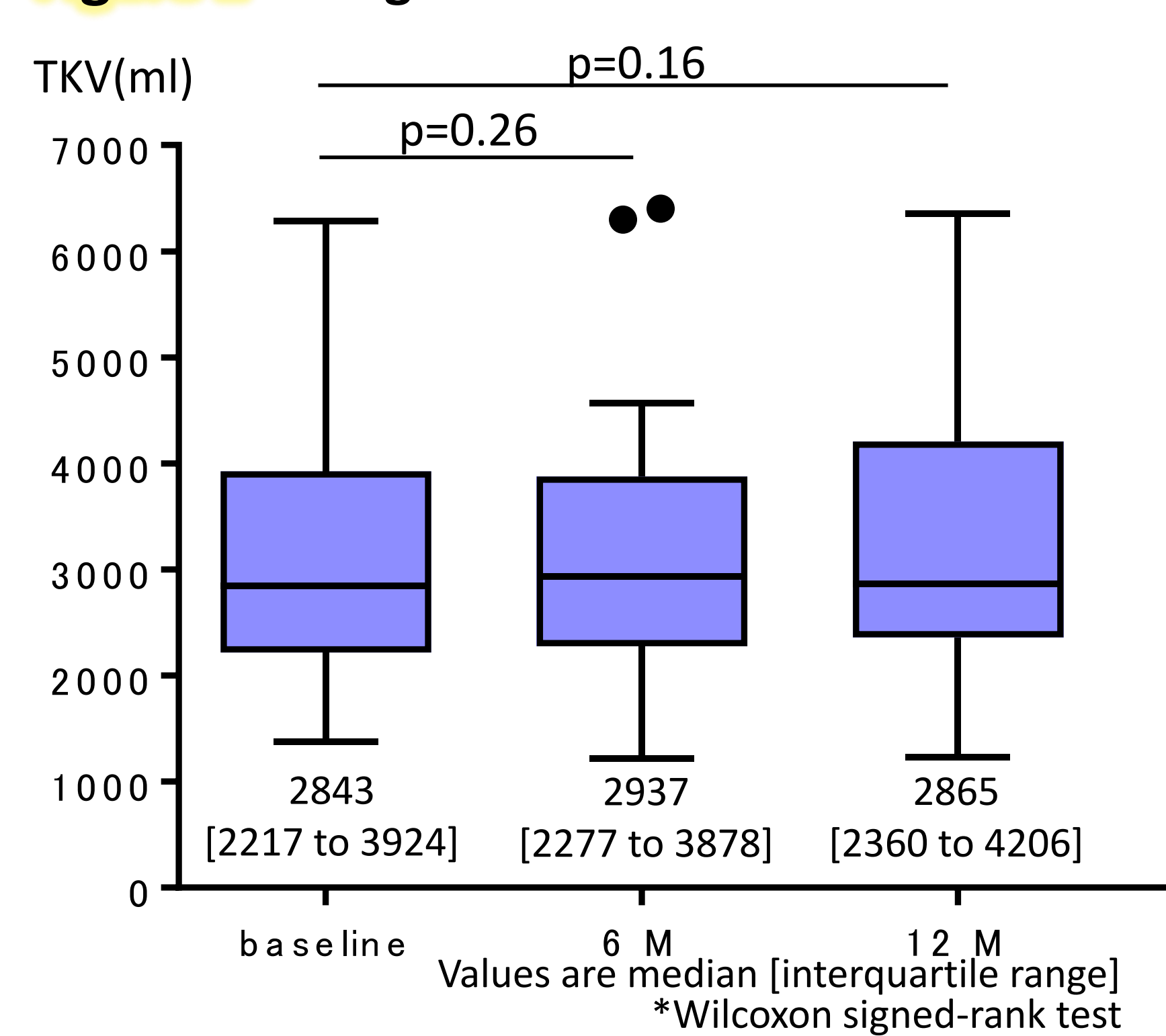


Figure 2 Waterfall plots of annual rate of percentage change in TKV(Δ TKV) at baseline and 12 months

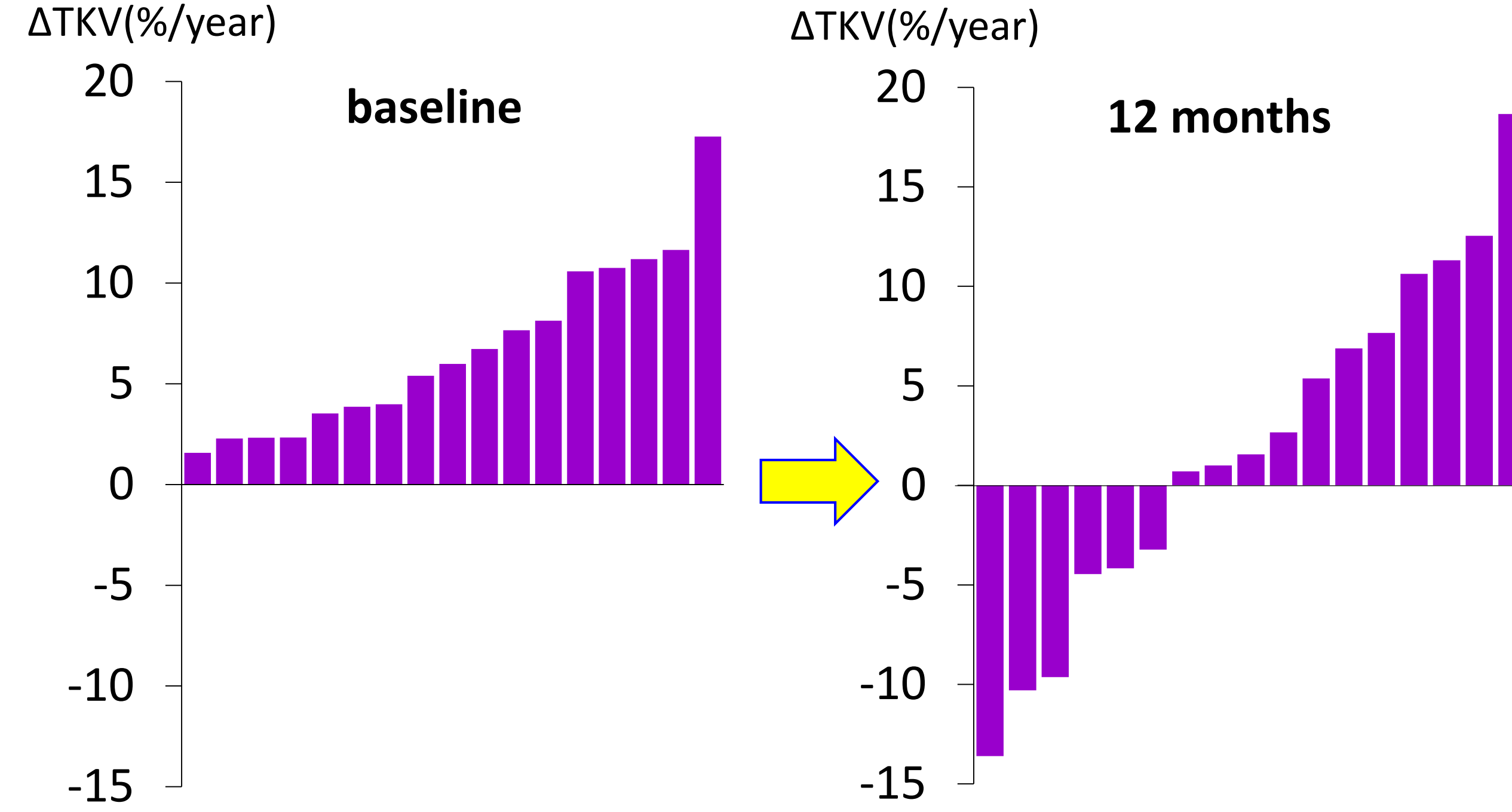


Figure 3 Annual rate of percentage change in TKV (Δ TKV)

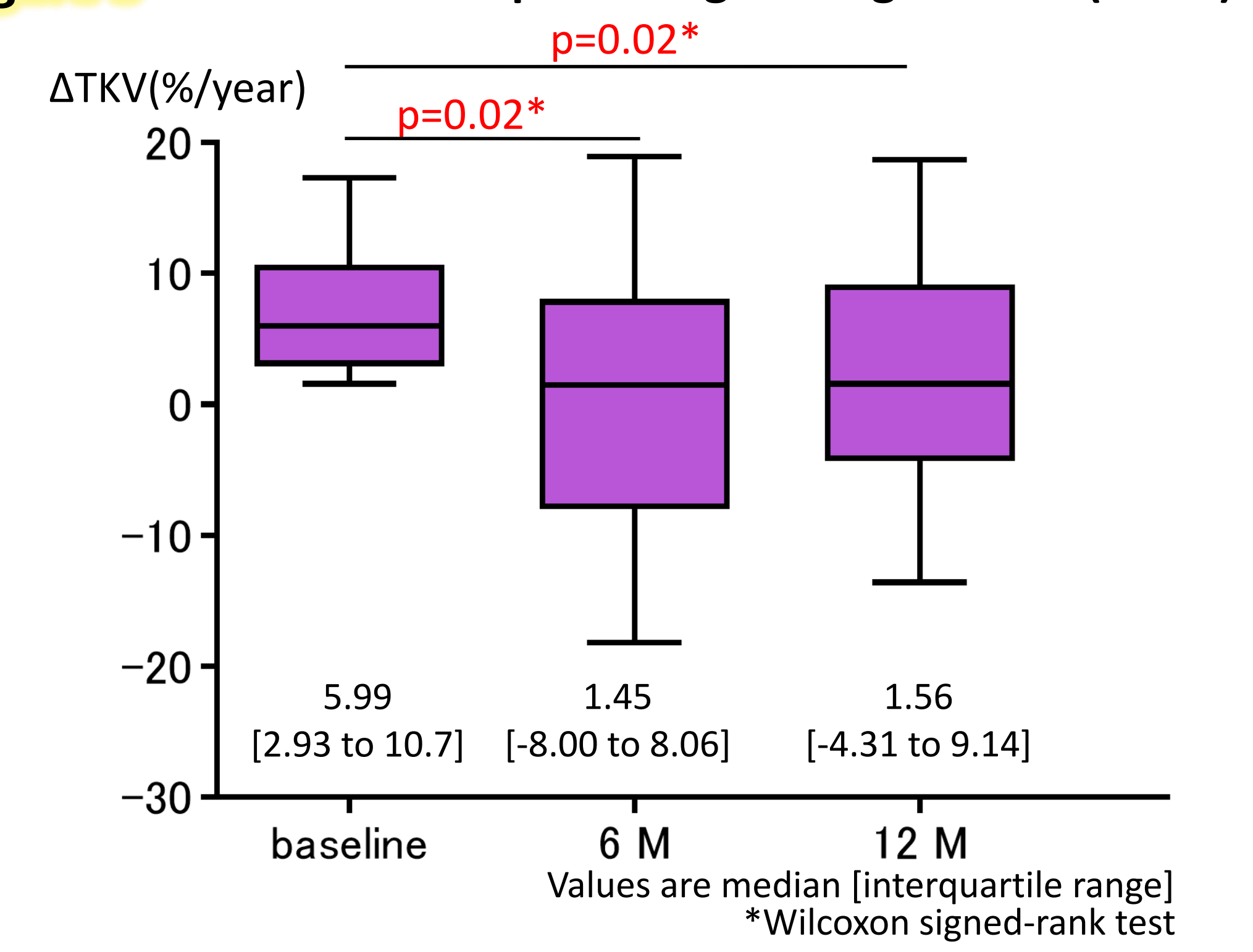


Figure 4 Change in eGFR from baseline and 1 month after initiating treatment with tolvaptan

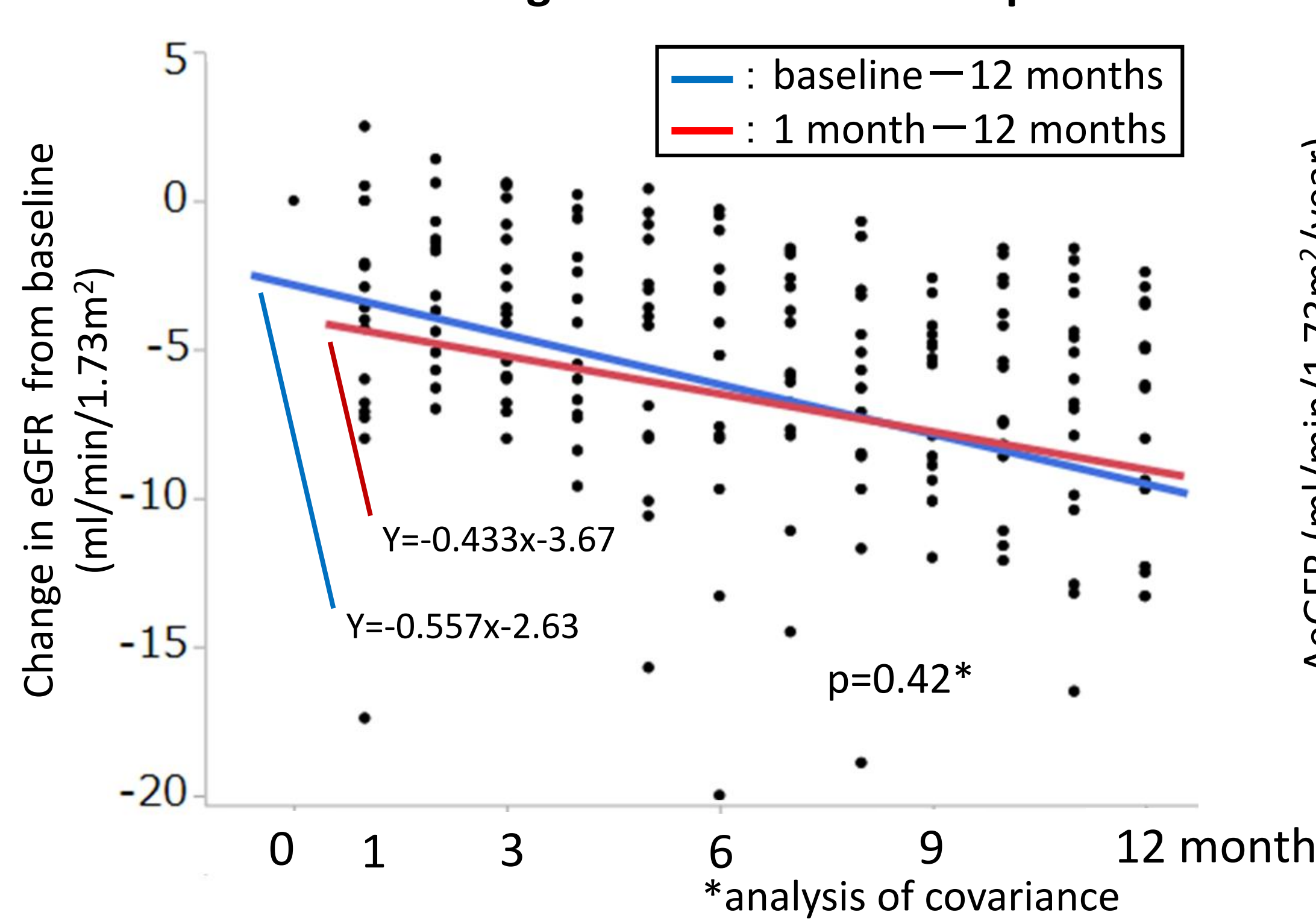


Figure 5 Annual rate of change in eGFR(Δ eGFR) from baseline to 12 months

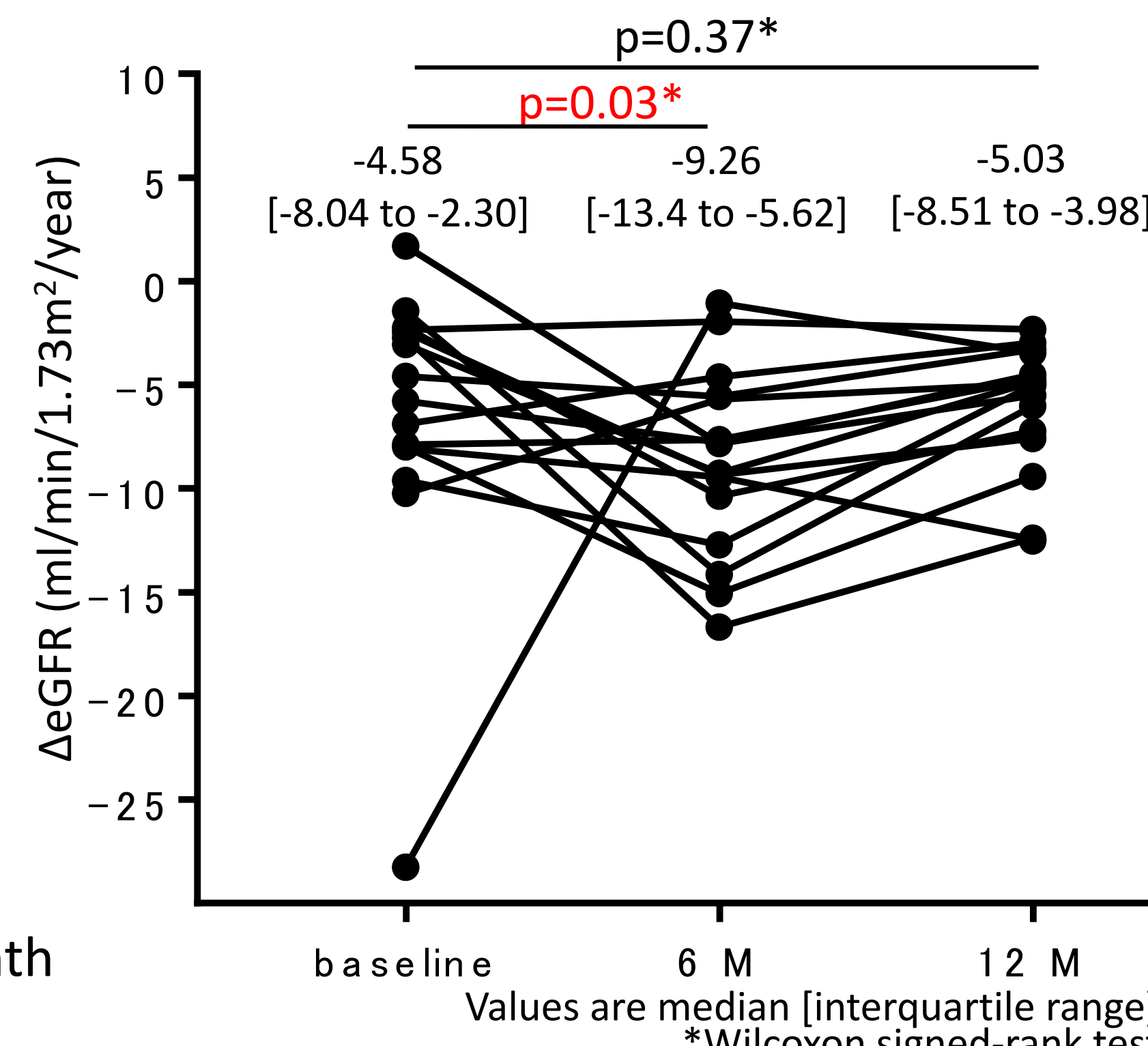
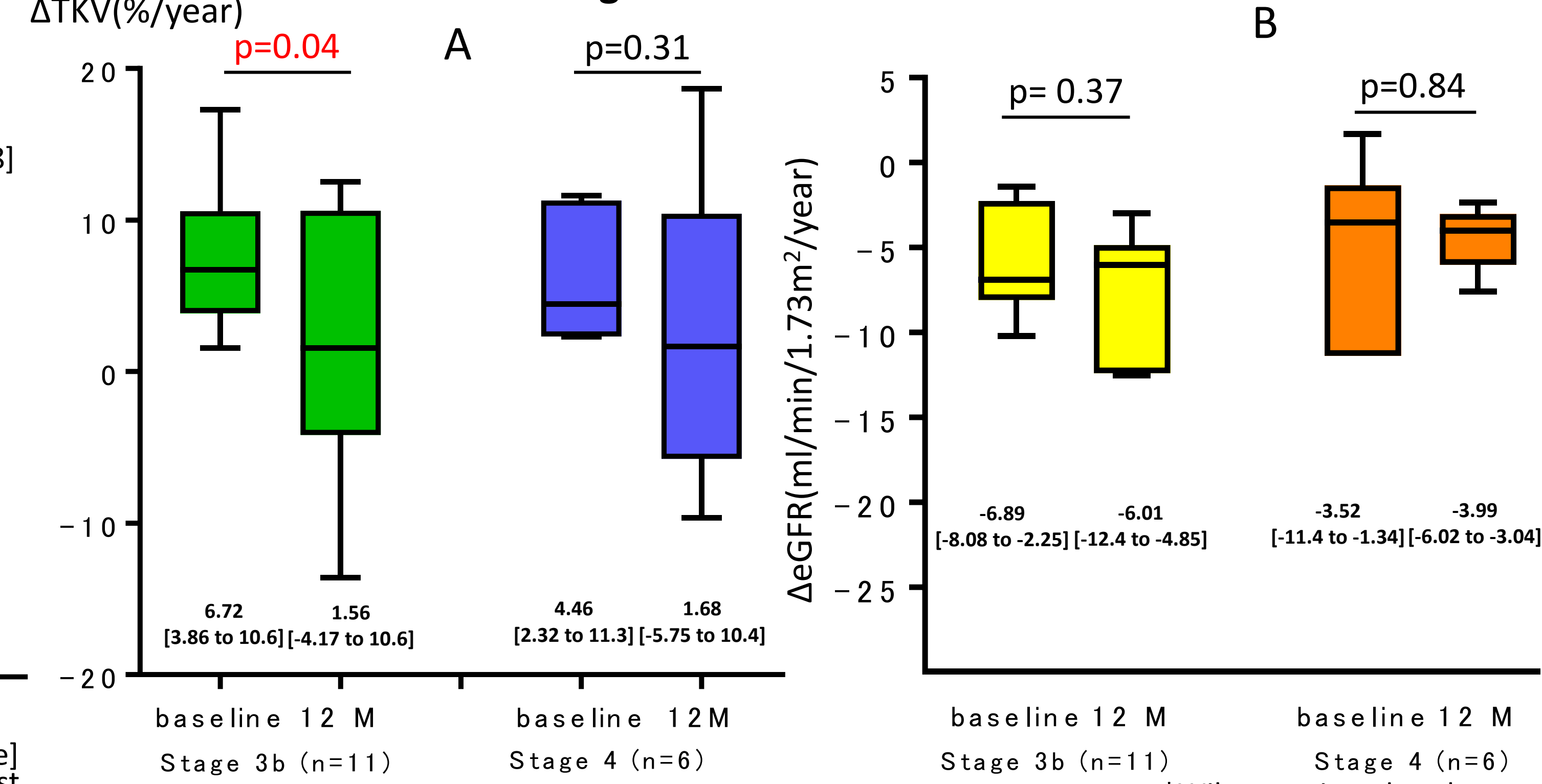


Figure 6 Change in Δ TKV (A) and Δ eGFR (B) from baseline to 12 months based on CKD stage



Results

- TKV did not change, and Δ TKV was decreased throughout the 12 months.
- At 6 months, Δ eGFR was lower than at baseline. But Δ eGFR had no significant difference between baseline and after 12 months.

Discussion

Late-stage ADPKD has thick-walled cysts surrounded by interstitial fibrosis¹⁾ and tolvaptan seems to be less effective in slowing cyst growth in late-stage ADPKD patients²⁾. However, our study revealed that tolvaptan slowed TKV-growth (Figure 1-3). Tolvaptan increase plasma copeptin level and free-water clearance regardless of kidney function²⁾, indicating its pharmacological activity and capacity to suppress the growth of TKV on late-stage ADPKD.

Acute decline in GFR occurred just after starting tolvaptan (Figure 4). Vasopressin (AVP) increases glomerular filtration by tubuloglomerular feedback⁴⁾. Tolvaptan blocks AVP binding to Vasopressin 2 receptor and makes a reversible decrease in GFR²⁾. After the temporary decline, the progress of kidney dysfunction became slow (Figure 4) and Δ eGFR had no statistically significant difference between the baseline and the 12 month follow-up (Figure 5), which reveals tolvaptan can prevent GFR decreasing in the long term.

1) Norman J. *Biochim Biophys Acta* 1812(10):1327-1336, 2011
2) Zarabal MV, et al. *Kidney Int* 80(3): 295-301, 2011
3) Boertien WE, et al. *Am J Kidney Dis* 65(6): 833-841, 2015
4) Bankir, et al. *Kidney Int* 49(6):1598-1607, 1996

Conclusion

12 months treatment with tolvaptan in ADPKD patients with CKD-stage3b and 4 slowed TKV growth and did not worsen kidney function.