

A SHORT SUMMARY OF THE REPRISE TRIAL

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PRESENTER DISCLOSURE

I have no conflicts of interest to declare.



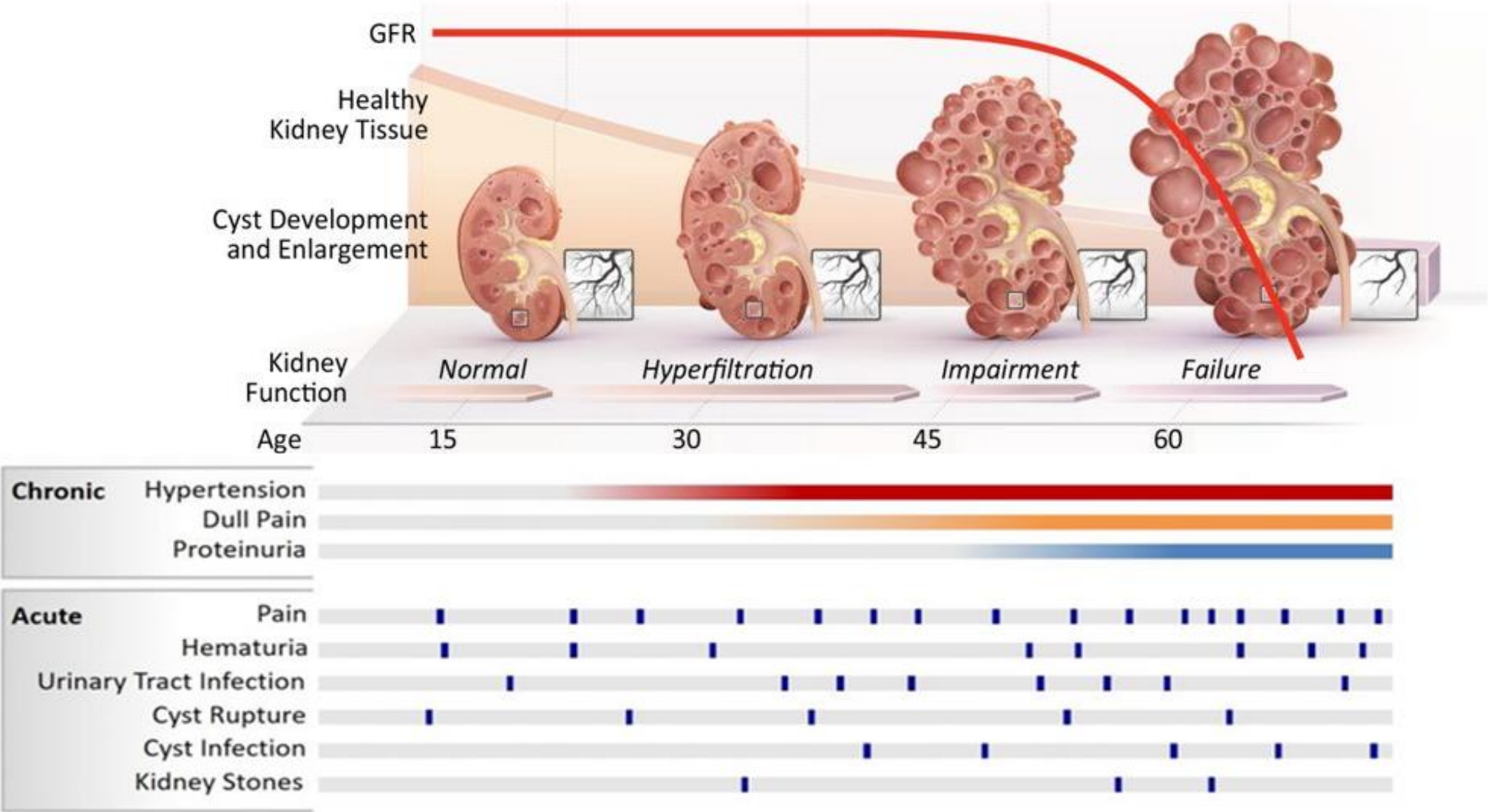
BACKGROUND



AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

- Most common inherited renal disorder
 - Prevalence of 1:500 to 1:1000
- Mutation of genes encoding polycystin 1 and polycystin 2 in tubular epithelial cells lead to cyst development
- Vasopressin and second messenger adenosine-3',5'-cyclic monophosphate (cAMP) are promoters of kidney-cyst cell proliferation and luminal fluid secretion
- An estimated 45%-70% of patients progress to end-stage renal disease (ESRD) by 65 years of age

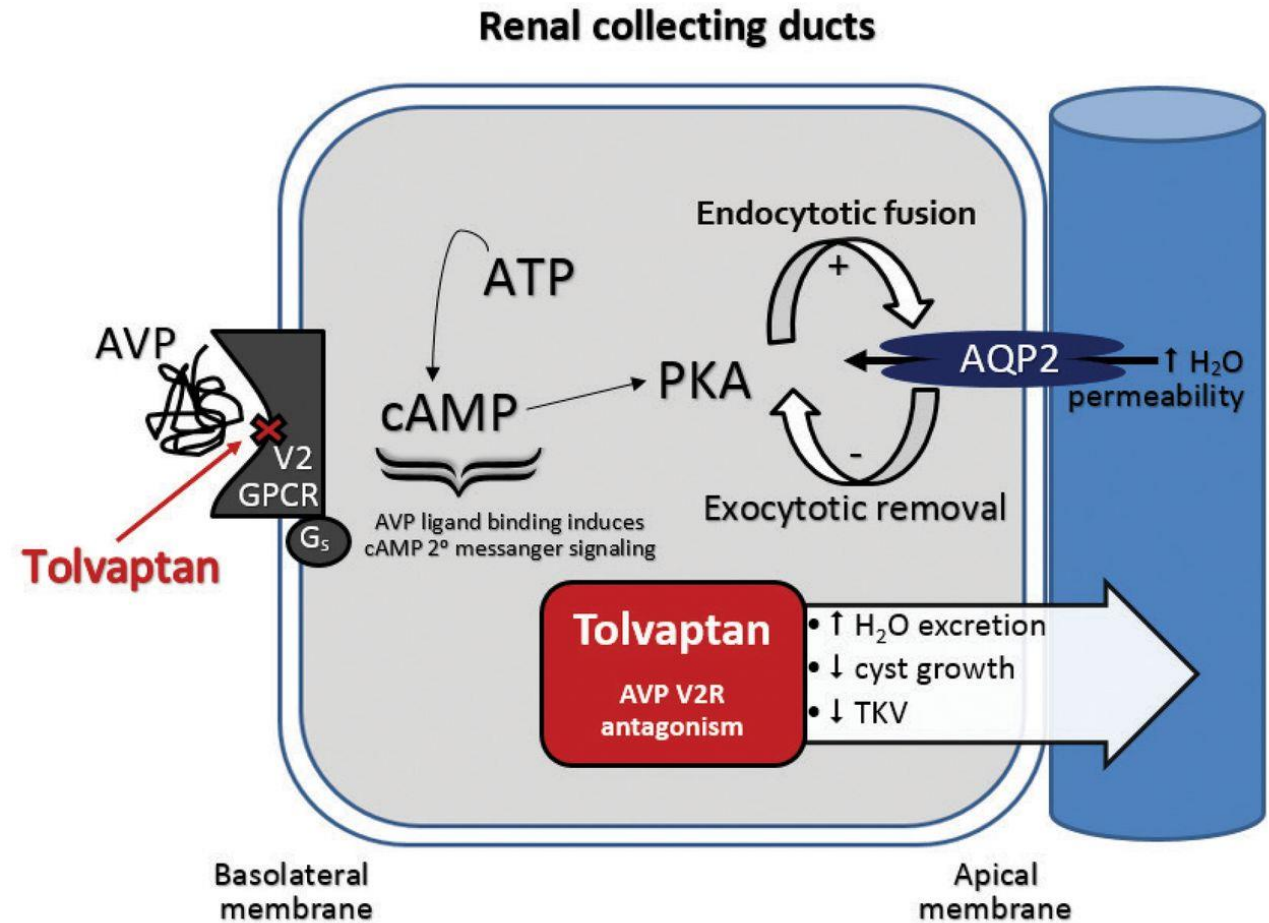
PROGRESSION OF ADPKD



Graphics adapted from <http://palladiobio.com/polycystic-kidney-disease/>; <http://axs3d.com/portfolio-item/kidney-disease-progression-in-adpkd/>

TOLVAPTAN IN ADPKD

- JINARC™
- Selective vasopressin V2-receptor antagonist



PREVIOUS TRIALS

Trial	ADPKD Population	Duration	Efficacy				Safety	
			TKV	Worsening kidney function*	Kidney pain	Rate of kidney function decline	Aquaretic AE	Hepatic AE
TEMPO 3:4 (N = 1445)	<ul style="list-style-type: none"> 18-50 years of age TKV ≥750 mL eCrCl ≥60 mL/min 	3 years	Tolvaptan vs. Placebo					
			↓	↓	↓	↓	↑	↑
TEMPO 4:4 (N = 871)	<ul style="list-style-type: none"> TEMPO 3:4 subjects within 6 months of trial completion eGFR ≥30 mL/min/1.73 m² within 45 days of baseline visit 	2 years	Early vs. Delayed Tolvaptan Treatment					
			↔ in % change, ↑ in slope of growth	Not reported	Similar rate	Non-inferior	↓	Similar rate

eCrCl = estimated creatinine clearance; TKV = total kidney volume

*Worsening kidney function = 25% reduction in the reciprocal of the serum creatinine level from the value at the end of the dose-adjustment period, reproduced after at least 2 weeks

EFFICACY AND SAFETY IN PREVIOUS TRIALS

- In TEMPO 3:4, tolvaptan was associated with a reduction in decline in eGFR by 3.3 mL/min/1.73 m² over 3 years
 - This effect was maintained in TEMPO 4:4
- Tolvaptan was associated with hepatic adverse events
 - With monitoring every 4 months, transaminase >3x ULN occurred in 4.4% of tolvaptan-treated patients, vs 1% in placebo-treated patients
 - Hepatocellular toxicity meeting Hy's law criteria occurred in 3 out of 1271 tolvaptan-treated patients

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Nephrology > General Nephrology

FDA Panel Vetoes New Tolvaptan Indication

by [David Pittman](#), Washington Correspondent, MedPage Today

August 05, 2013

0 Comments



REPRISE TRIAL



ORIGINAL ARTICLE

Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease

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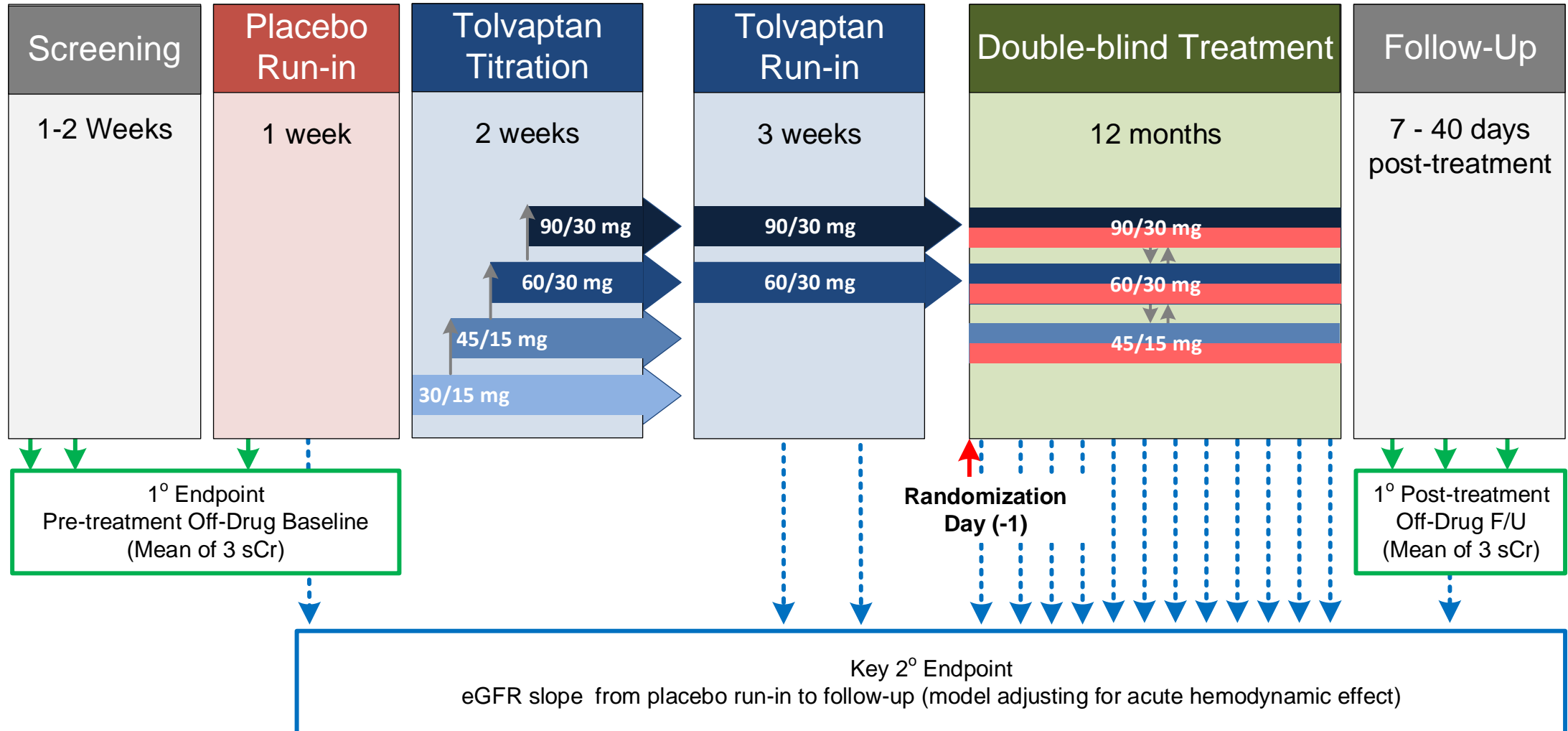


Design	Phase 3, randomized withdrawal, placebo-controlled, double-blind trial across 213 sites globally
Population (N=1370)	Tolvaptan-naïve ADPKD patients with CKD stage 2 to early stage 4 <ul style="list-style-type: none">• 18-55 years of age with eGFR 25-65 mL/min/1.73 m², or• 56-65 years of age with eGFR 25-44 mL/min/1.73 m² and historical evidence of decline in eGFR of >2.0 mL/min/1.73 m²/year
	<u>Key exclusion criteria:</u> <ul style="list-style-type: none">• Chronic diuretic use• Liver function abnormalities• Advanced diabetes (eg. A1c > 7.5%)• Additional significant renal disease• Pregnant or breastfeeding

Intervention	Tolvaptan at maximally tolerated dose x 1 year
Control	Placebo x 1 year
Outcomes	<u>Primary:</u> <ul style="list-style-type: none"> • Change in eGFR from baseline to after completion of trial
	<u>Secondary:</u> <ul style="list-style-type: none"> • Slope of the change in eGFR from baseline to completion of trial (key secondary end point) • Adverse events (AEs) • Hepatic safety <ul style="list-style-type: none"> - Events in 1 of 5 liver-related Standardized MedDRA queries (SMQs)* - Elevations in hepatic aminotransferase levels > 3x upper limit of normal (ULN) - Elevations in total bilirubin level >2x ULN

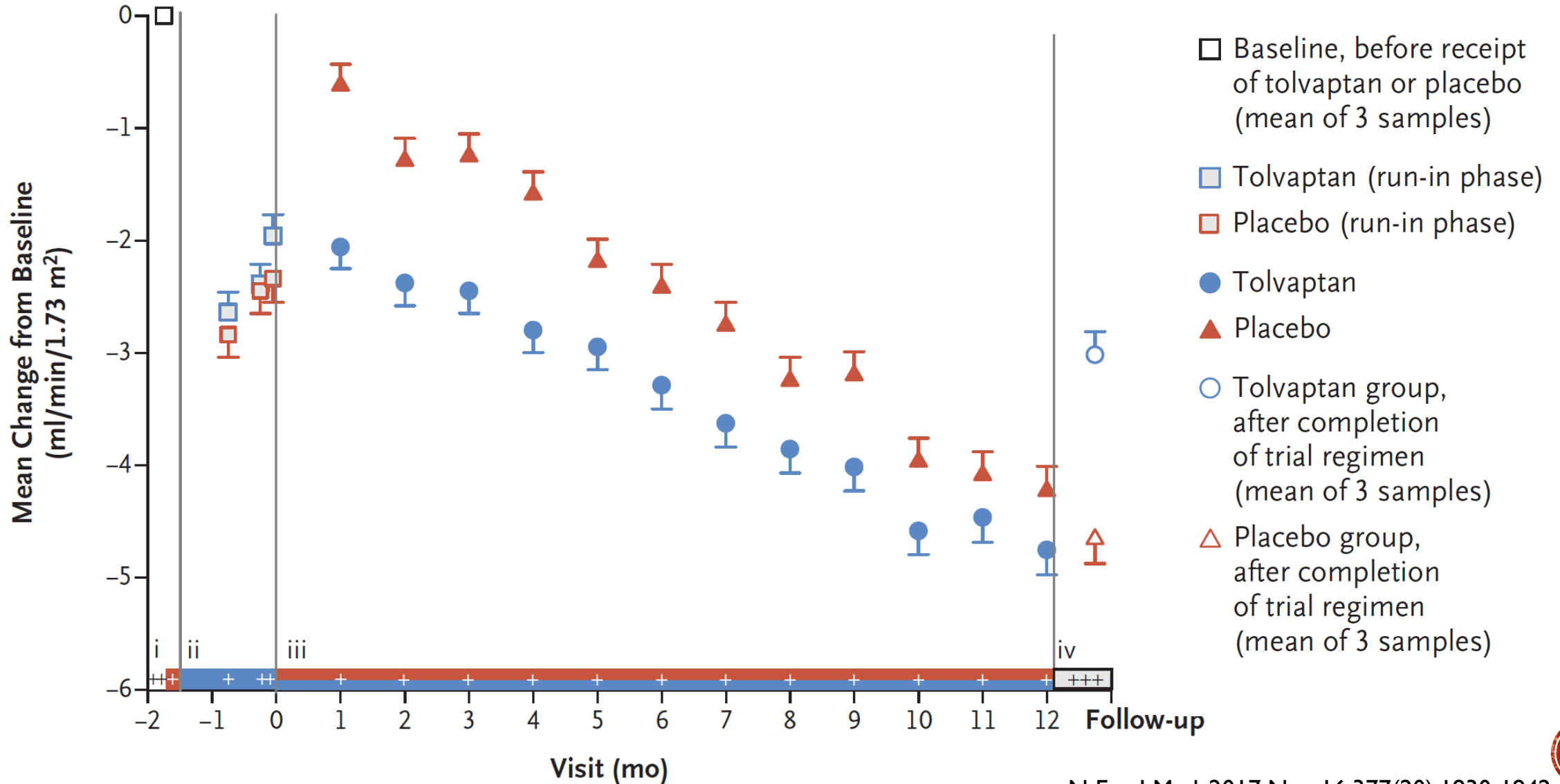
*These include adverse events related to cholestasis and jaundice of hepatic origin; hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; liver-related investigations, signs, and symptoms; and liver-related coagulation and bleeding disturbances

TRIAL DESIGN

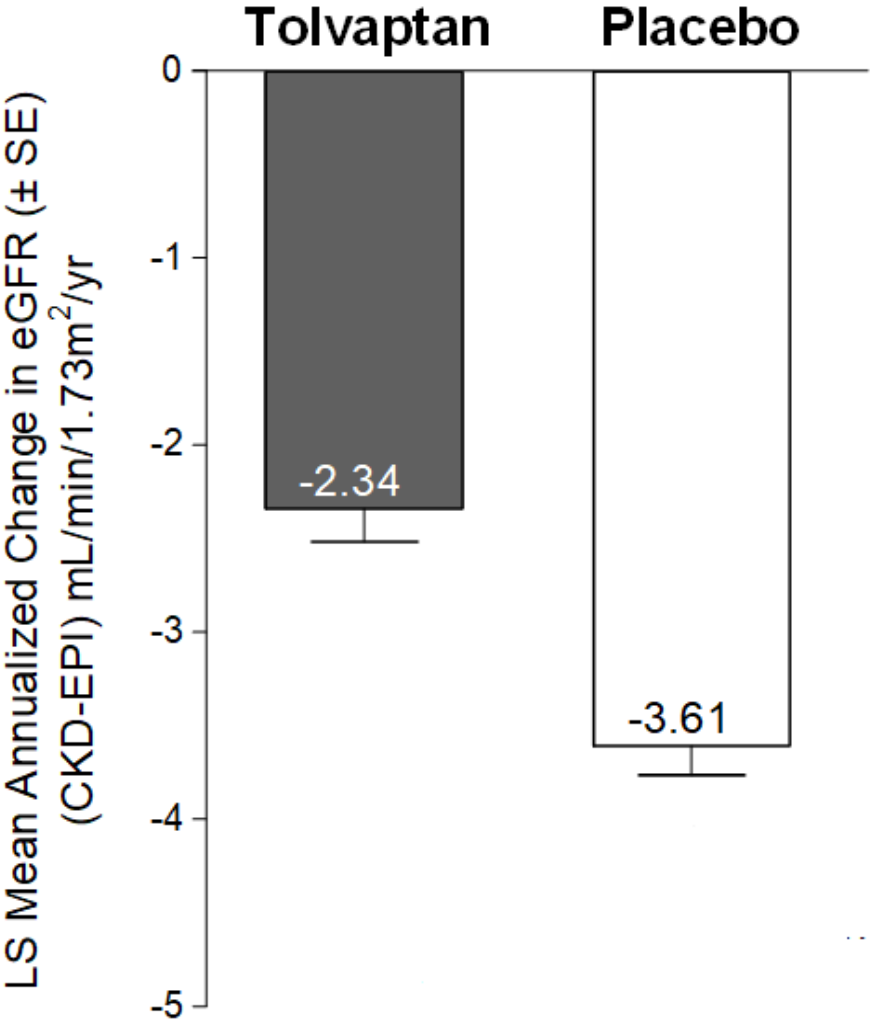


Baseline Characteristic	Tolvaptan (N = 683)	Placebo (N = 687)
Age, mean (years)	47.3	47.2
Male, %	50.8	48.5
Caucasian, %	91.7	92.0
Hypertension, %	92.8	93.2
On RAAS inhibitor therapy, %	87.1	84.6
Blood pressure, mean (mm Hg)	129/82	130/83
History of kidney pain, %	50.1	50.7
eGFR, mean (mL/min/1.73 m ²)	40.7	41.4
CKD Stage, %		
CKD 2	4.7	5.7
CKD 3a	30.6	29.4
CKD 3b	44.4	45.9
CKD 4	20.4	18.6
Daily dose at end of single-blind tolvaptan, %		
60 mg + 30 mg	17.3	18.0
90 mg + 30 mg	82.7	82.0

CHANGE IN eGFR FROM BASELINE

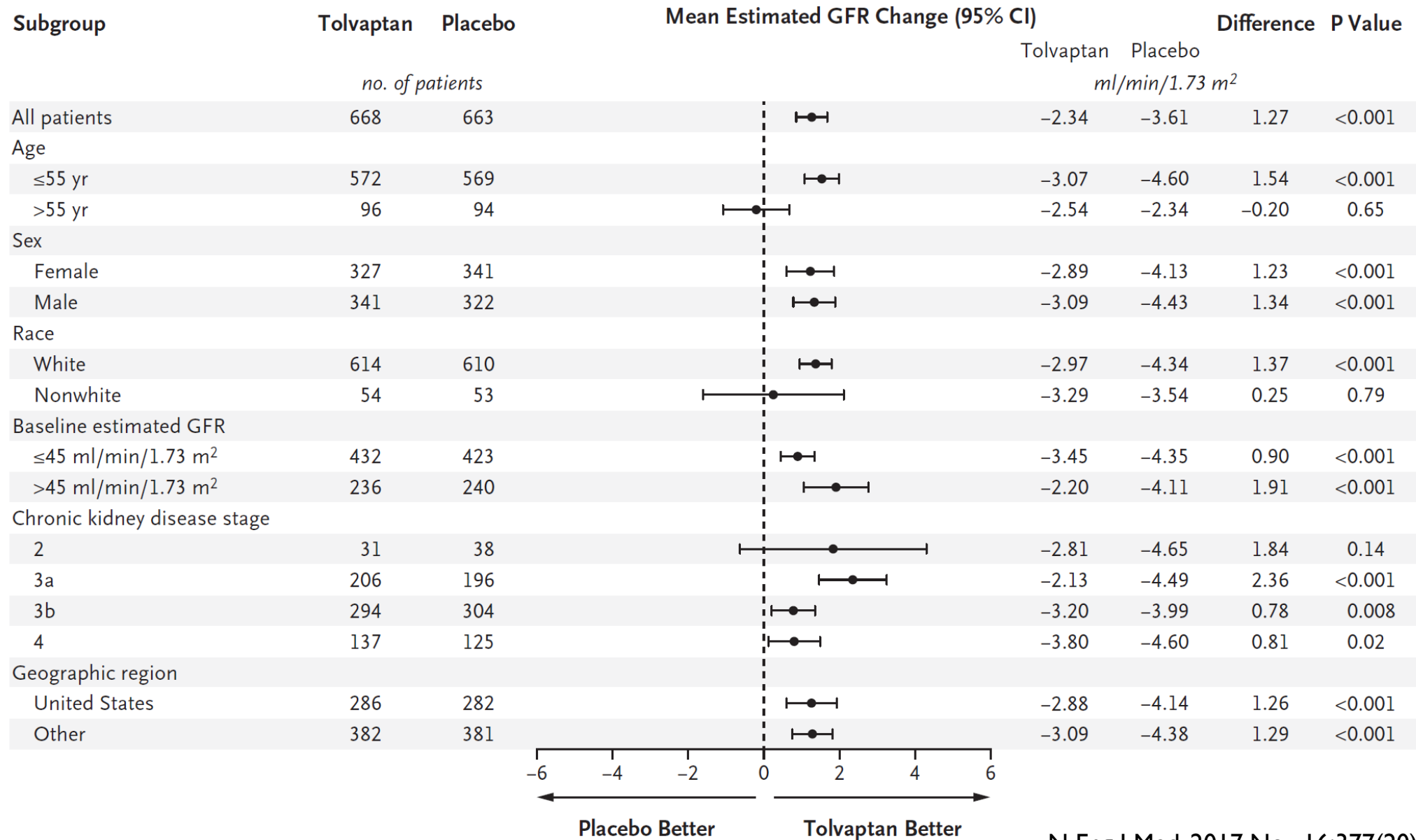


PRIMARY ENDPOINT: CHANGE IN eGFR

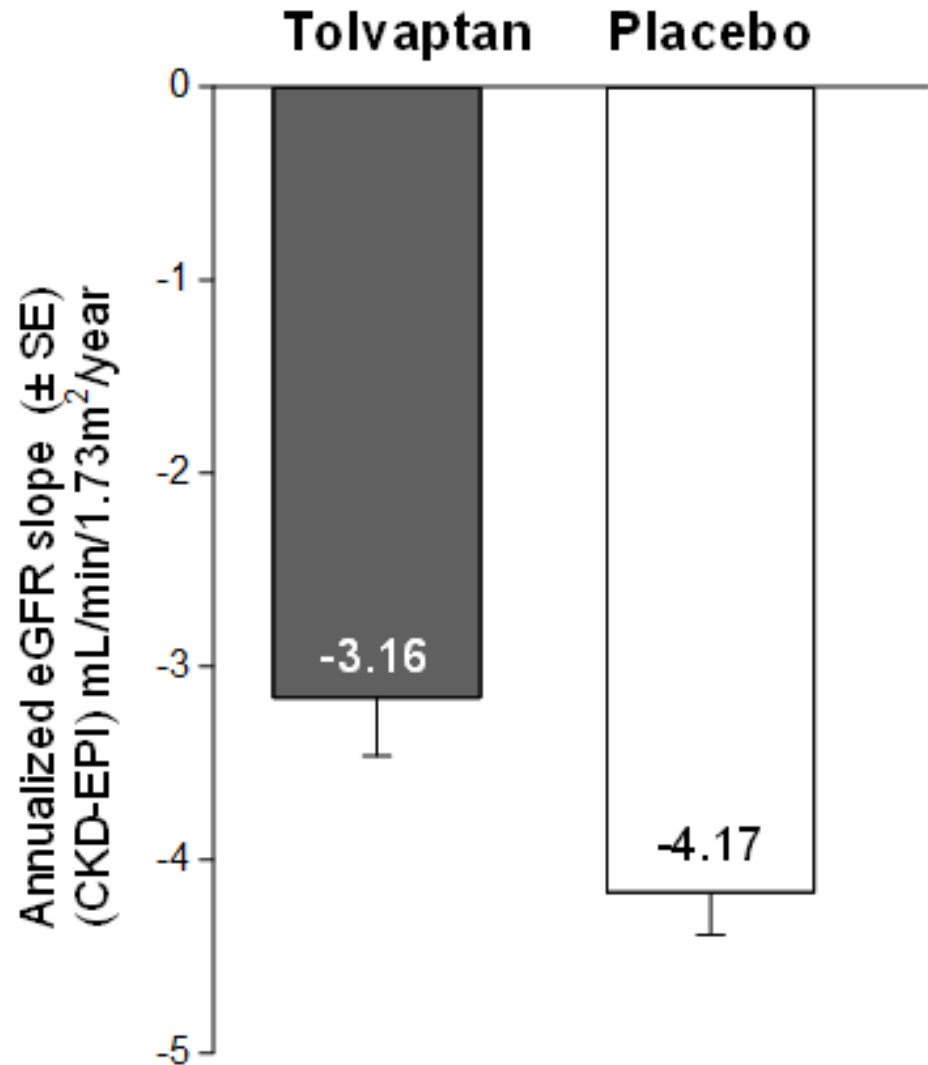


Difference: 1.27 mL/min/1.73 m² at 1 year (35%)
p < 0.0001

SUBGROUP ANALYSES OF PRIMARY ENDPOINT



KEY SECONDARY ENDPOINT: RATE OF eGFR DECLINE



Difference: 1.01 mL/min/1.73 m²/year (24%)
p < 0.0001

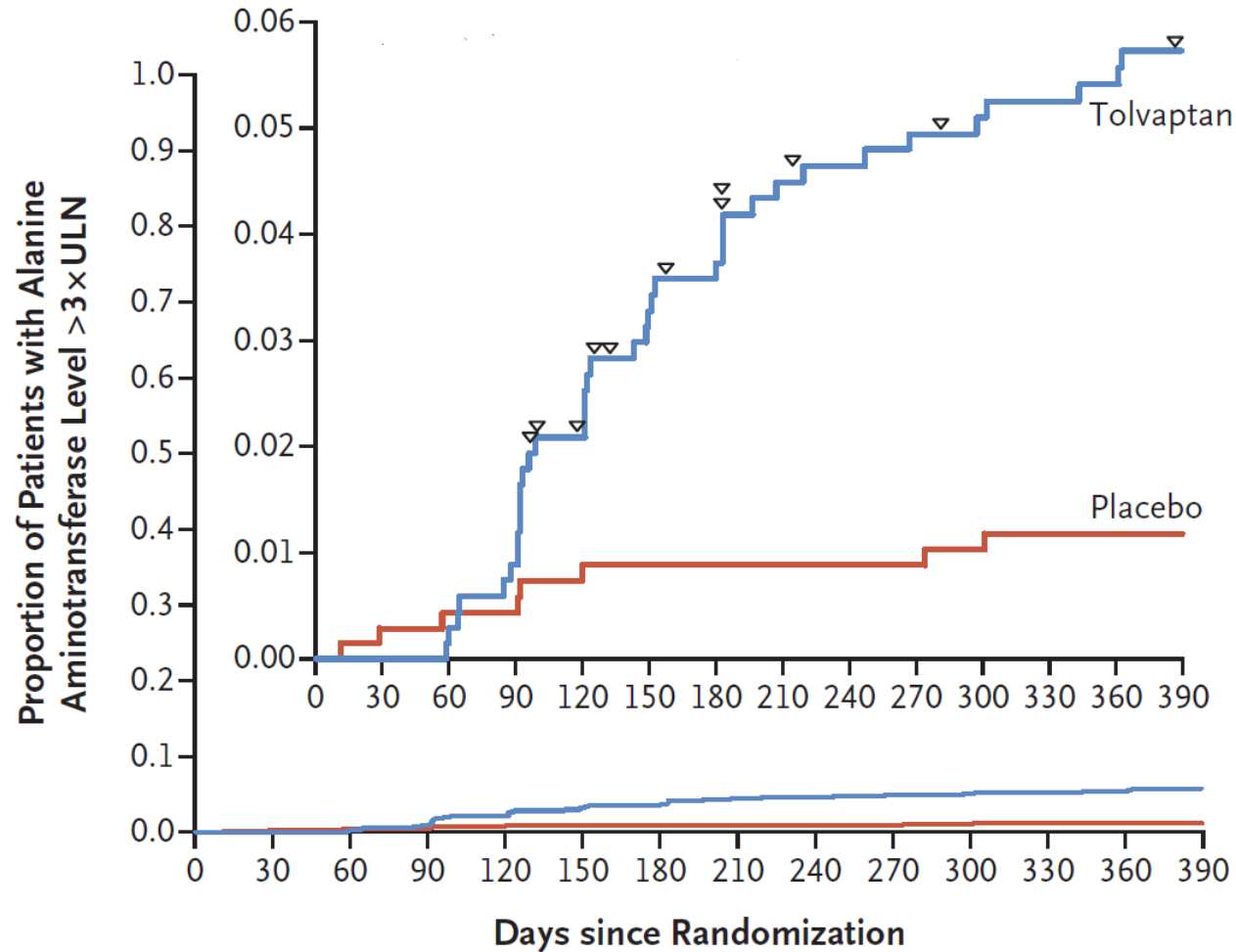
ADVERSE EVENTS

Event, %	5-week single-blind tolvaptan period (N = 1491)	1-year double-blind period	
		Tolvaptan (N = 685)	Placebo (N = 685)
Any AE	70.5	85.3	82.3
Serious AE	2.9	12.5	8.8
Discontinuation of trial regimen due to AE	6.8	9.5	2.2
Due to aquaretic AE	4.6	2.1	0.1
Due to event in 1 of 5 liver-related SMQs	0.3	1.6	0.1
Death	0.1	0	0.1
Most common AEs			
Polyuria	31.7	5.3	1.6
Nocturia	20.5	4.7	1.8
Thirst	28.7	4.0	1.9
Polydipsia	9.7	1.8	0.4
Dry mouth	8.9	1.9	0.9
Diarrhea	1.9	6.9	3.4
Fatigue	4.3	6.8	3.5
Peripheral edema	0.9	4.4	6.6
Kidney pain	2.6	16.6	19.0
Urinary tract infection	0.5	5.7	8.0

HEPATIC SAFETY

Event, %	5-week single blind tolvaptan period (N = 1491)	1- year double-blind period	
		Tolvaptan (N = 685)	Placebo (N = 685)
Events in 1 of 5 liver-related SMQs			
Any AE	1.5	10.9	5.3
Serious AE	0.5	4.6	0.6
Clinically significant elevations in hepatic laboratory values			
Elevation in alanine aminotransferase (ALT) > 3x ULN	0.2	5.6	1.2
Elevation in bilirubin > 2x ULN	0.0	0.0	0.0
Meeting Hy's law criteria	0.0	0.0	0.0

ELEVATION IN ALT > 3X ULN



Hazard ratio 4.91 (95% CI 2.29-10.53)

Elevated liver enzymes returned to normal with interruption or discontinuation of therapy in all cases

No. at Risk

Tolvaptan	680	677	671	666	657	649	639	632	629	625	620	616	595	36
Placebo	684	680	678	675	673	672	671	668	665	661	660	656	645	40

CRITIQUE - STRENGTHS

- Large, multicenter study that met sample size needed based on power calculation
- Clinically relevant outcomes
- Attempted to maintain blinding by asking participants to drink 2-3 L fluid/day and 1-2 cups of water before bedtime, regardless of perceived thirst
- Similar baseline characteristics in tolvaptan and placebo groups
- High trial completion rate; 96% completed 12-month trial in both arms

CRITIQUE - LIMITATIONS

- Did not examine factors other than baseline eGFR that could have affected rate of disease progression and tolvaptan response
 - Eg. Genotype, age-adjusted total kidney volume
- Benefit of tolvaptan compared to placebo may have been underestimated
 - Patients > 55 years included in the trial appeared to be enriched for slowly progressive disease
 - Patients in placebo group were asked to maintain good hydration
- Short trial duration
 - Unable to assess long-term efficacy, including hard end points (eg. 50% decline in eGFR, end-stage renal disease)
 - Unable to assess long-term safety
- Sponsored by Otsuka Pharmaceuticals
 - Involved in trial design and conduct, data analysis, manuscript

CONCLUSIONS

- Tolvaptan slowed progressive loss of renal function in ADPKD patients with more advanced stages than those of the patients included in the TEMPO 3:4 trial
- Monthly monitoring of liver enzyme levels likely reduced the frequency of drug-induced liver injury
- Long-term effectiveness of tolvaptan treatment remains to be determined



SUMMARY OF THE EVIDENCE AND APPLICATION TO PRACTICE



SUMMARY OF THE PIVOTAL TRIALS

Trial	Tolvaptan vs. Placebo						
	Efficacy				Change in eGFR from baseline	Safety	
	Total kidney volume	Worsening kidney function*	Kidney pain	Rate of kidney function decline		Aquaretic AE	Hepatic AE
TEMPO 3:4	↓	↓	↓	↓	Not reported	↑	↑
REPRISE	Not reported	Not reported	↓ (not a prespecified outcome)	↓	↓	↑	↑

*Worsening kidney function = 25% reduction in the reciprocal of the serum creatinine level from the value at the end of the dose-adjustment period, reproduced after at least 2 weeks

OVERALL EFFICACY AND SAFETY OF TOLVAPTAN

Efficacy, assuming tolvaptan effect is maintained	TEMPO 3:4	REPRISE
	<ul style="list-style-type: none"> • Mean eGFR 81 mL/min/1.73 m² • Every 4 years of treatment would delay the incidence of ESRD by ~1 additional year 	<ul style="list-style-type: none"> • Mean eGFR 41 mL/min/1.73 m² • Continuous treatment would extend the time to reach ESRD from 6.2 to 9.0 years
Safety	TEMPO 3:4, TEMPO 4:4, and REPRISE	
	<ul style="list-style-type: none"> • The most common adverse events were aquaresis-related • With more frequent hepatic monitoring, the potential risk of permanent or life-threatening hepatocellular injury decreased from 1:3000 in 2013 to 1:6200 in May 2017 	

TO WHOM SHOULD WE RECOMMEND TOLVAPTAN?

✓ Patients who are at risk of rapid progression of ADPKD

- Strongest evidence for those who meet enrollment criteria of TEMPO 3:4 or REPRISÉ

✓ Patients who are willing to accept the potential adverse effects of tolvaptan

- Will be compliant to the necessary laboratory tests
 - Liver function tests monthly x first 18 months, then every 3 months x 12 months, then every 3-6 months
- Have a lifestyle that can accommodate polyuria and polydipsia
 - Limiting sodium and protein intake can minimize aquaretic adverse effects
 - Appropriate timing of tolvaptan doses can improve tolerability

BREAKING NEWS

HEALTHCARE APRIL 24, 2018 / 7:48 PM / UPDATED 2 HOURS AGO

BRIEF-Otsuka's tolvaptan approved by U.S. FDA as first treatment to slow kidney function decline in adults at risk of rapidly progressing ADPKD



QUESTIONS?

