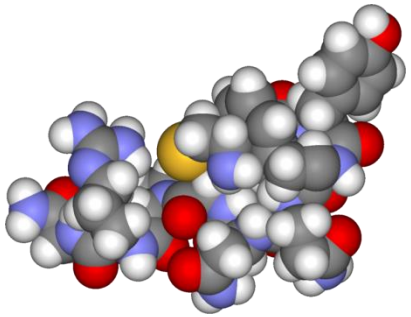
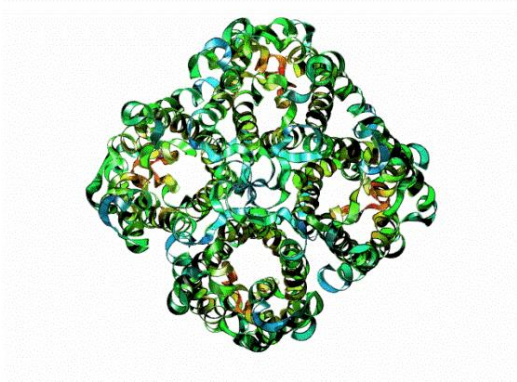
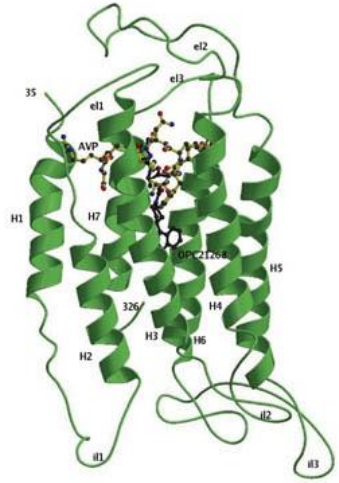
Clinical Experience with Tolvaptan







Prof. Dr. med. O. Devuyst

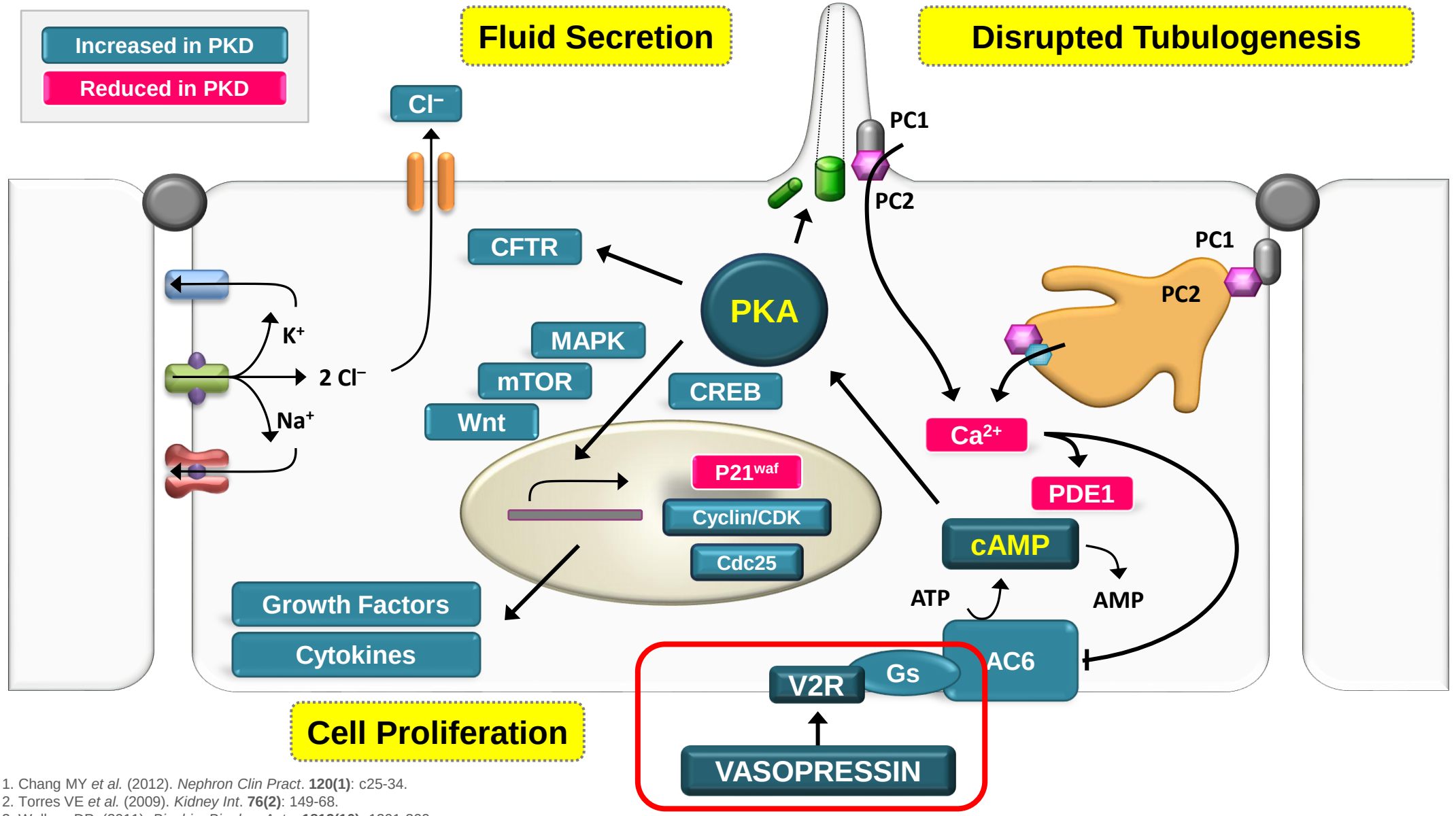
UCL Université catholique de Louvain

University of Zurich[UZH]

Outline

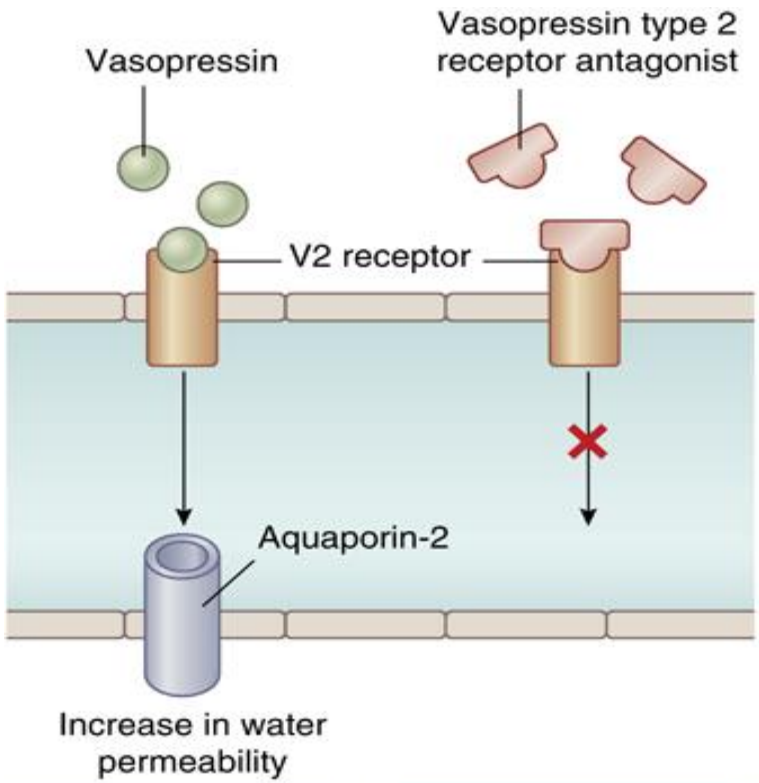
1. *ADPKD generalities and tolvaptan in ADPKD*
2. *Who to treat with tolvaptan? How to start?*
3. *Clinical experience with tolvaptan in ADPKD*

Intracellular Signaling in ADPKD



1. Chang MY *et al.* (2012). *Nephron Clin Pract*. **120(1)**: c25-34.
2. Torres VE *et al.* (2009). *Kidney Int*. **76(2)**: 149-68.
3. Wallace DP. (2011). *Biochim Biophys Acta*. **1812(10)**: 1291-300.

Tolvaptan: Mechanism of action



- Concentrated urine
- Decreased free water clearance
- Lowering of serum sodium

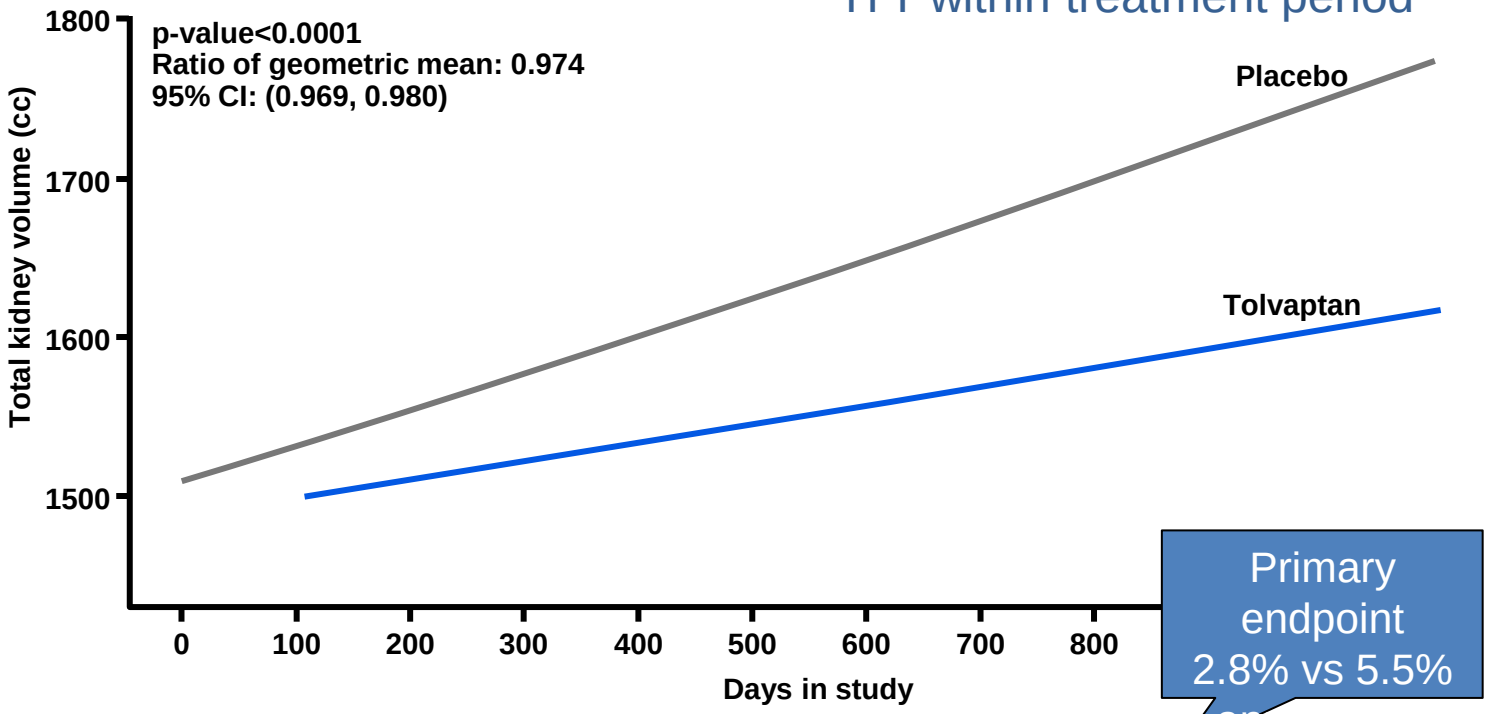
- Dilute urine
- Increased free water clearance
- Raising of serum sodium

Rosner MH. Kidney Int 82; 1154-6, 2012

TEMPO 3:4: Tolvaptan reduces rate of kidney volume growth by 49 % - 2.8 vs. 5.5%/yr

Primary endpoint

ITT within treatment period

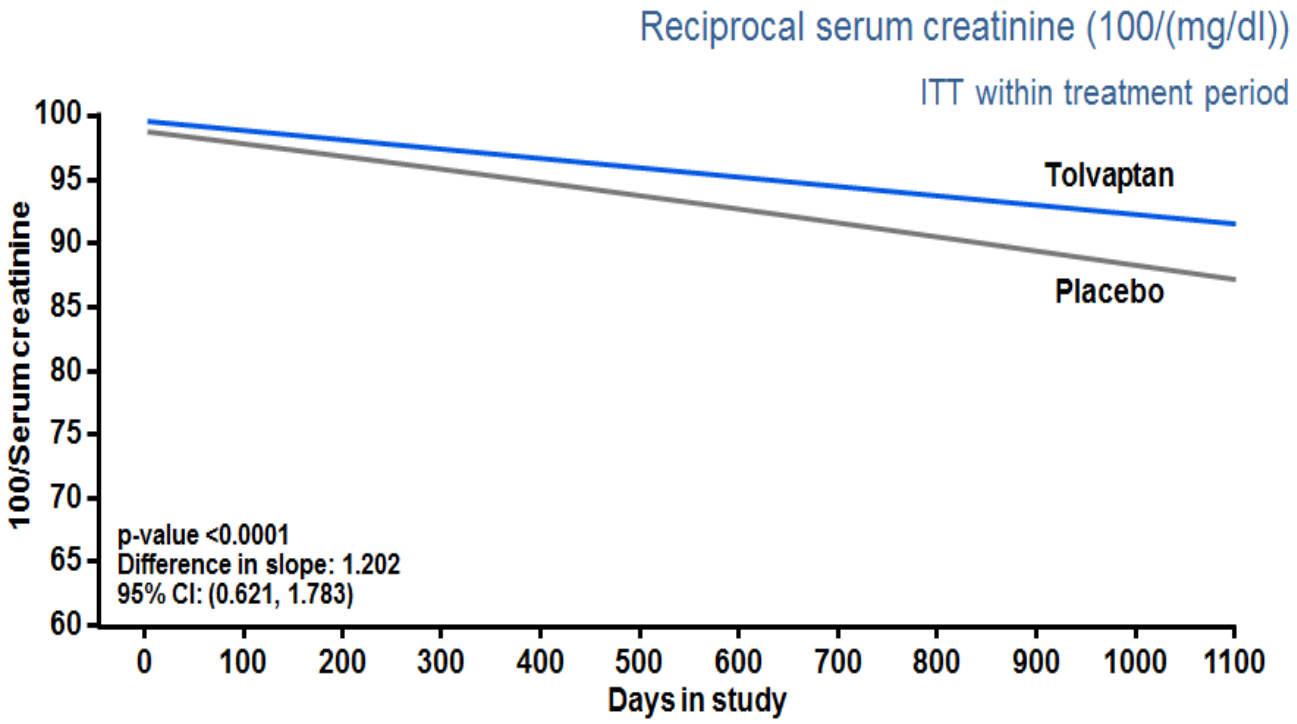


		Rate of % growth/year				
Treatment group	**N**	**Mean**	**Med**	**SD**	**Slope**	**p-value§**
Tolvaptan	**819**	**2.777**	**2.265**	**5.659**	**0.028**	**<0.0001**
Placebo	**458**	**5.608**	**5.585**	**5.330**	**0.055**	

Torres V.E., et al. (2012). N Engl J Med. 367(25):2407-18.

Tolvaptan reduces renal function decline: -2.6 vs. -3.8 (mg/ml)$^{-1}$/yr

Other secondary endpoint

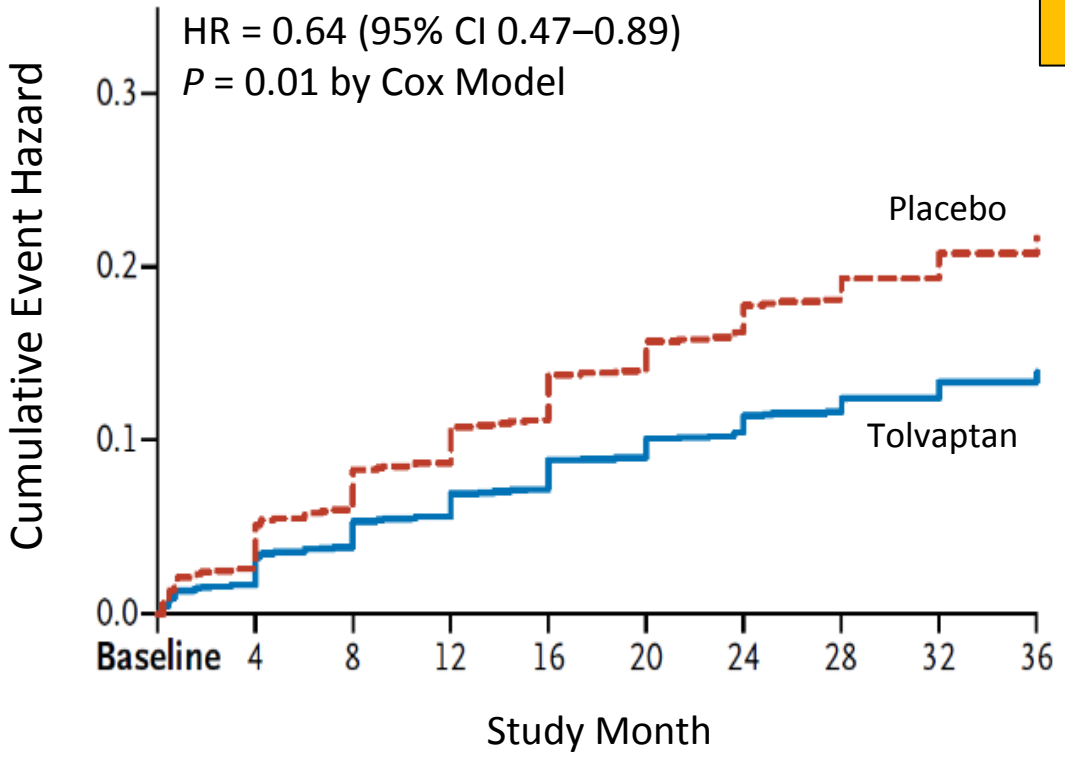


		Annual eGFR rate of change				
Treatment group	N	Mean	Med	SD	Slope	p-value
Tolvaptan	842	-2.555	-2.353	9.767	-2.610	<0.0001
Placebo	464	-3.682	-3.326	6.361	-3.812	

Torres V.E., et al. (2012). N Engl J Med. 367(25):2407-18.

Tolvaptan Reduced The Risk of Clinically Significant Renal Pain in ADPKD

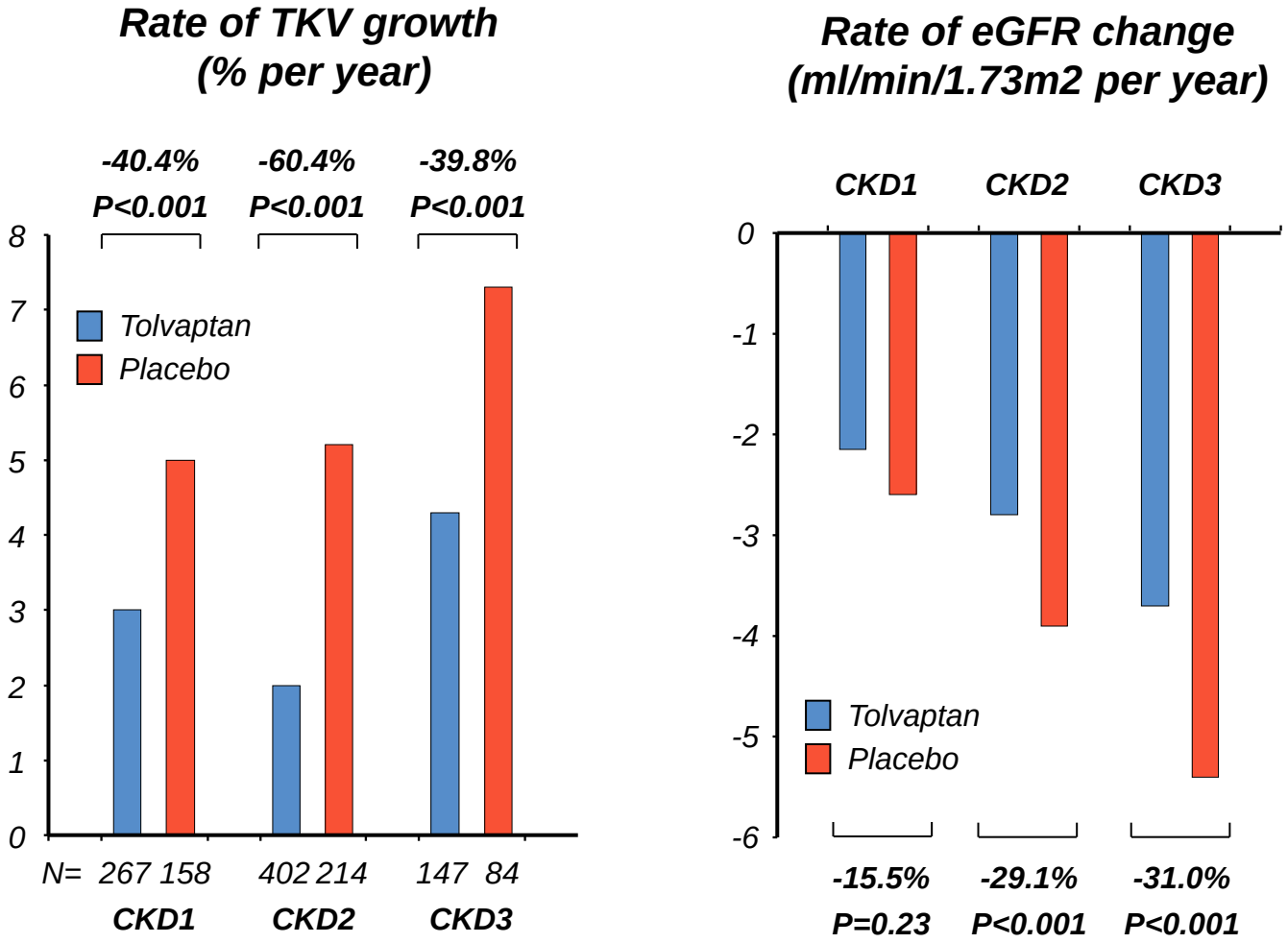
Other secondary endpoint



No. at Risk										
Tolvaptan	961	870	835	811	792	776	763	752	744	642
Placebo	483	472	463	454	446	438	428	422	418	359

Torres V.E., et al. (2012). N Engl J Med. 367(25):2407-18.

Tempo 3:4: Tolvaptan is effective trough all studied CKD stages



Post hoc analys TEMPO[3]
Torres et al. Clin J Am Soc Nephrol 2016

Adverse events and laboratory abnormalities

	Tolvaptan (N=961) %	Placebo (N=483) %
Any Adverse Event	97.9	97.1
Any Serious Adverse Event	18.4	19.7
AEs >10% and significantly more common in tolvaptan group		
Thirst	55.3	20.5
Polyuria	38.3	17.2
Nocturia	29.1	13.0
Pollakiuria	23.2	5.4
AEs >10% and significantly more common in placebo group		
Renal pain	27.0	35.0
Haematuria	7.8	14.1
Urinary tract infection	8.3	12.6
Elevated laboratory values at any visit		
Serum sodium >150 mEq/L	4.0	1.4
Serum uric acid >7.5 mg/dL	6.2	1.7

Torres V.E., et al. (2012). N Engl J Med. 367(25):2407-18.

Hepatic Adverse Events

	Tolvaptan			Placebo		
Abnormality	Subjects	Subjects Meeting Criteria	%	Subjects	Subjects Meeting Criteria	%
ALT >3x ULN	958	42	4.4	484	5	1.0
ALT >3x ULN with bilirubin >2x, but ALP <2x ULN (Hy's laboratory criteria)	957	2	0.2	484	0	0
Death or liver failure		0	0		0	0

ALP, alkaline phosphatase; ALT, alanine aminotransaminase; ULN, upper limit of normal

Torres V.E., et al. (2012). N Engl J Med. 367(25):2407-18.

Risk Management Plan to mitigate risk of liver injury

- Monthly liver enzyme tests for the first 18 month of treatment
- Then every three months
- Educational material for the nephrologist
- Educational material for the patients to self monitor for any symptoms from liver dysfunction
- Adequate pregnancy protection

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

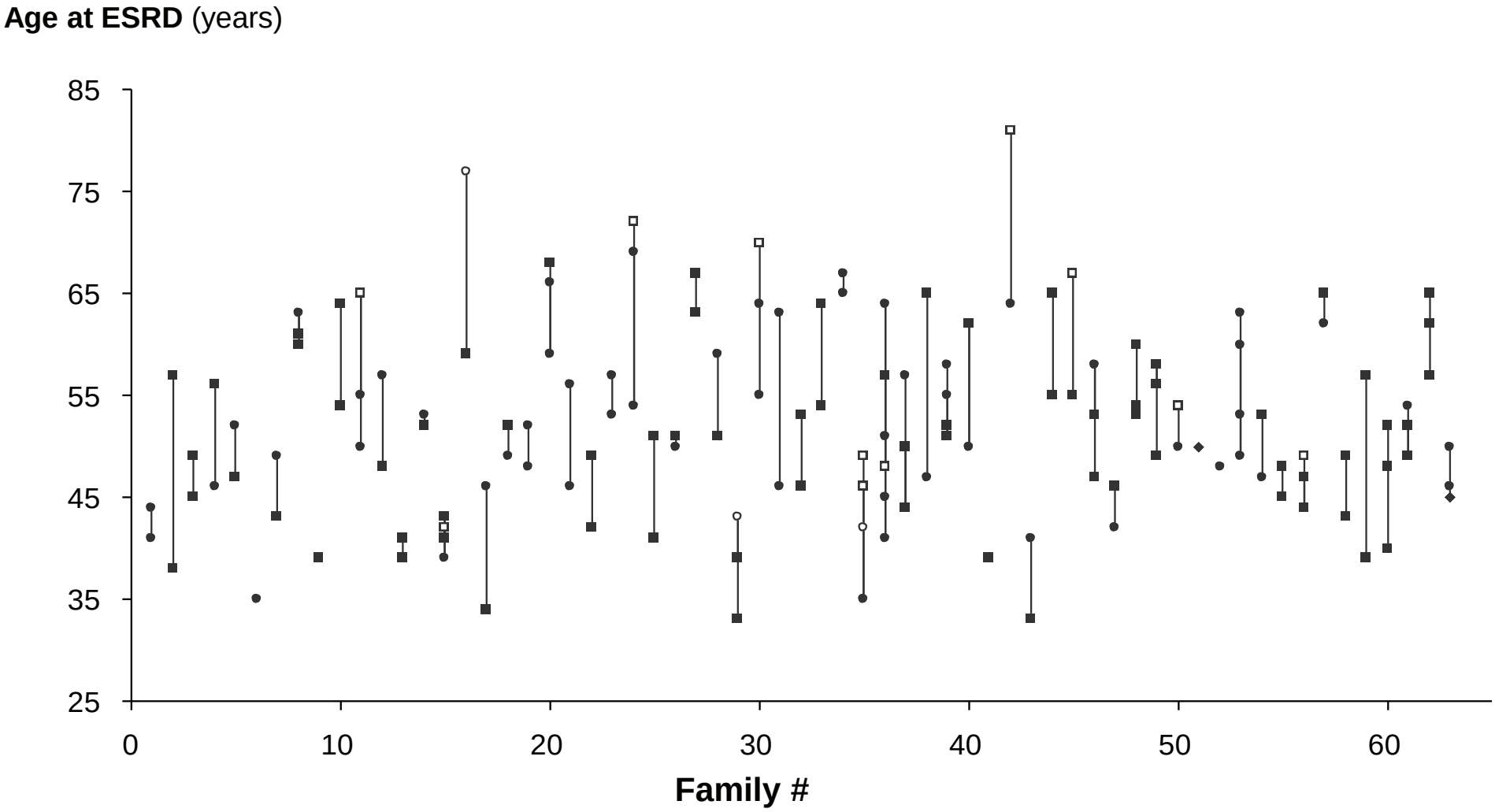
27/05/2015

Jinarc approved in rare kidney disease

Medicine to slow down cyst formation

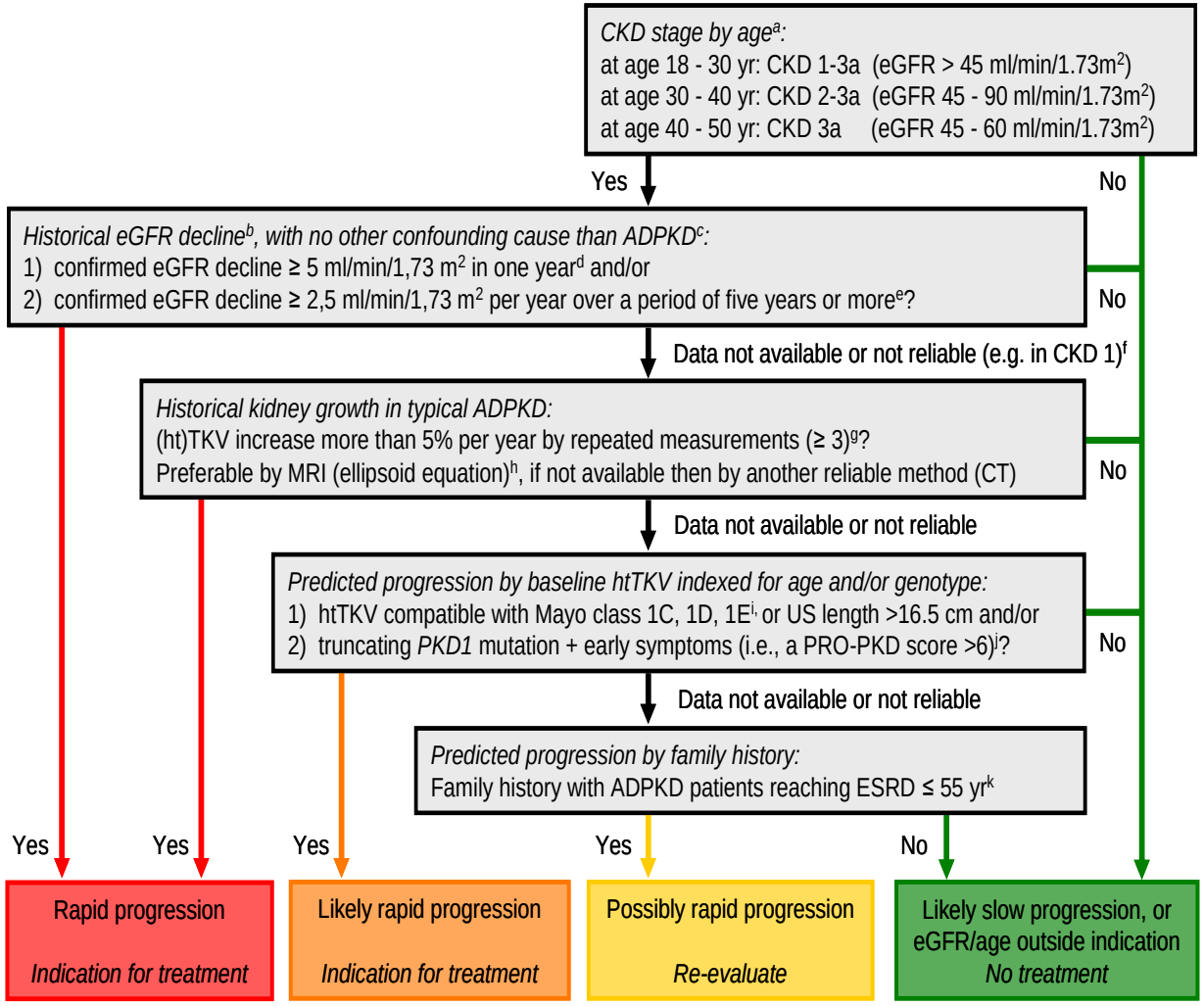
Jinarc is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease.

Inter- and Intra-familial Variability in ADPKD : A Multicentric Sib-pair Study



Persu et al. Kidney Int 66, 2004

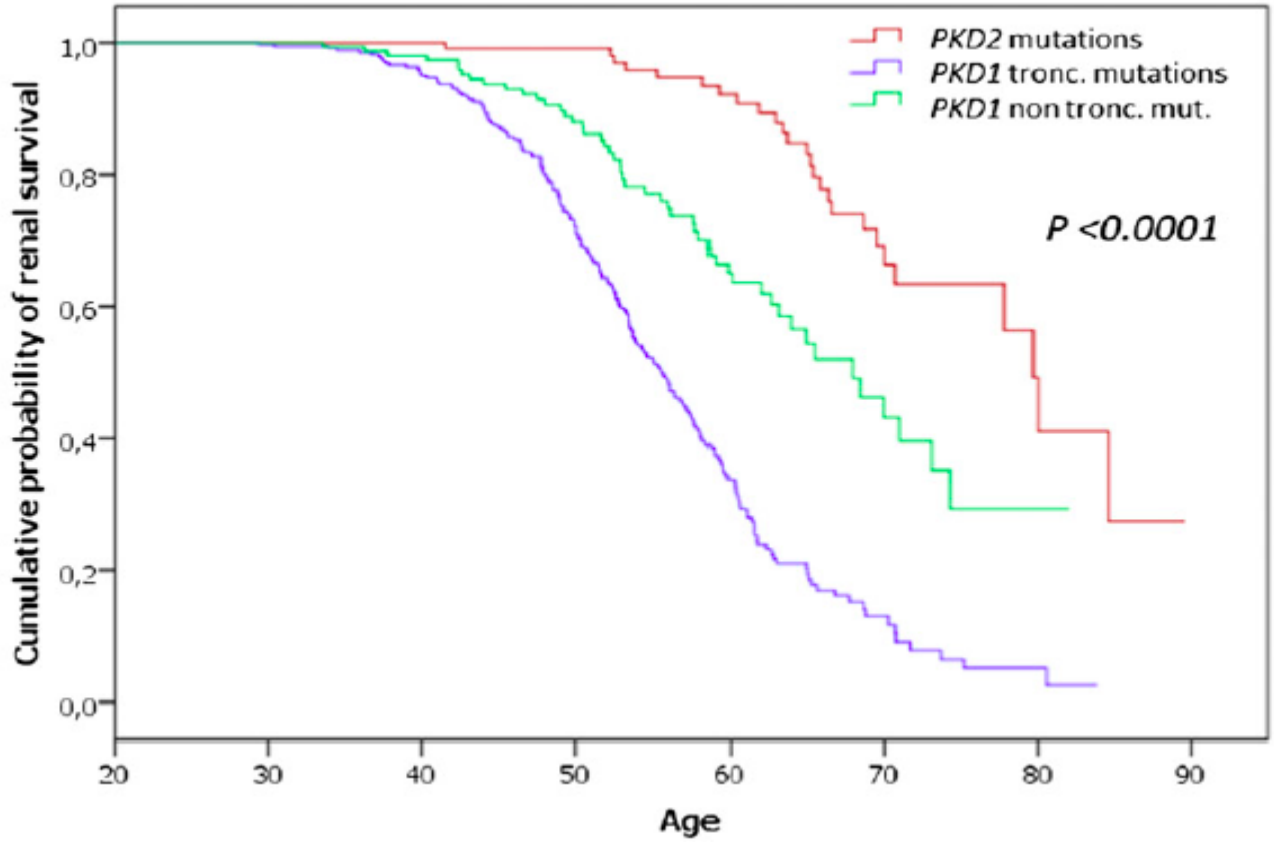
Selection of Patients for Tolvaptan Treatment?



Gansevoort, R.T. et al., Nephrol Dial Transplant. 2016 Mar;31(3):337-48

Cornec-Le Gall et al. JASN 24, 2013

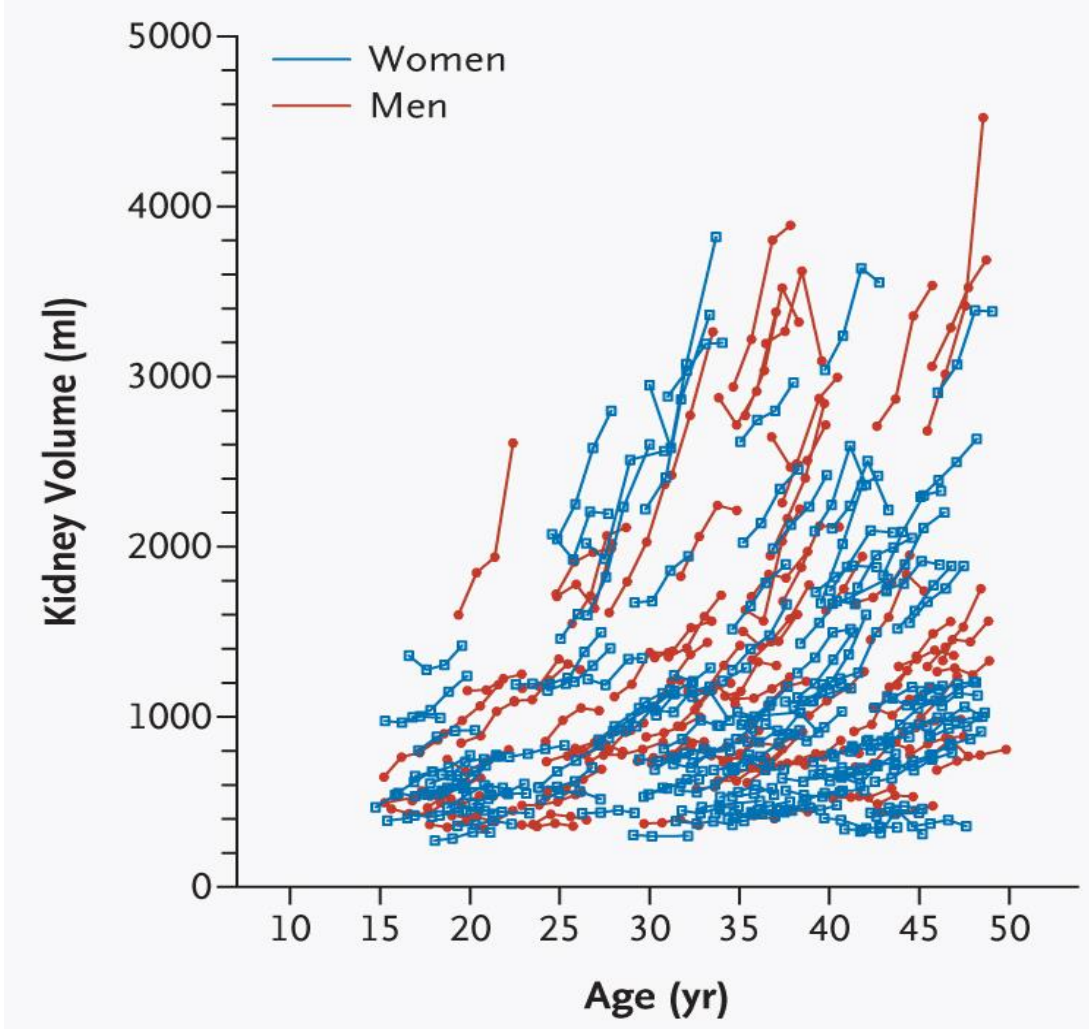
Type of *PKD1* Mutation Influences Renal Outcome in ADPKD



Genkyst: 741 patients from 519 pedigrees

Exponential Progression of TKV in ADPKD: CRISP

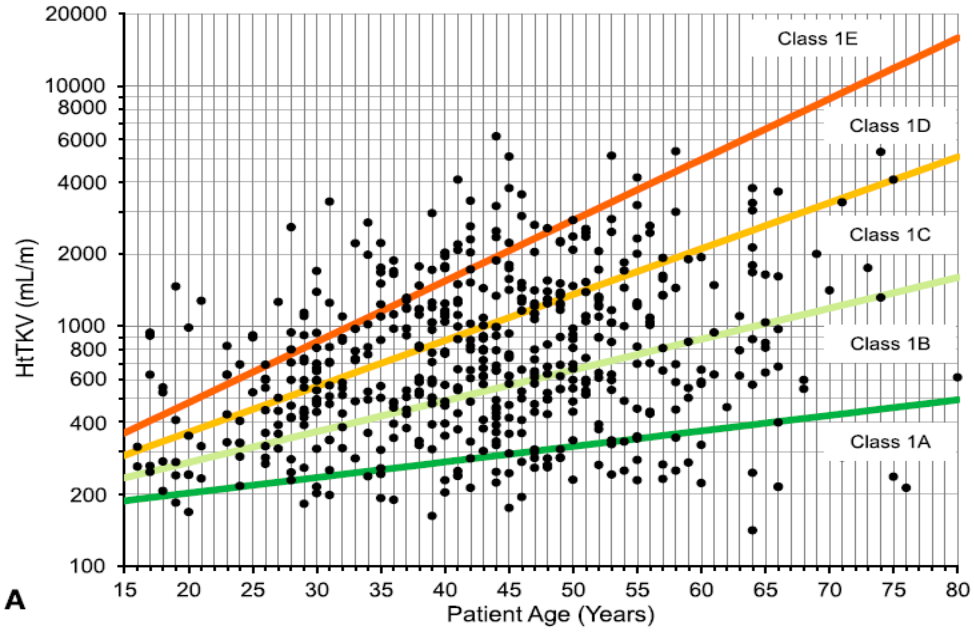
TKV measured by MRI

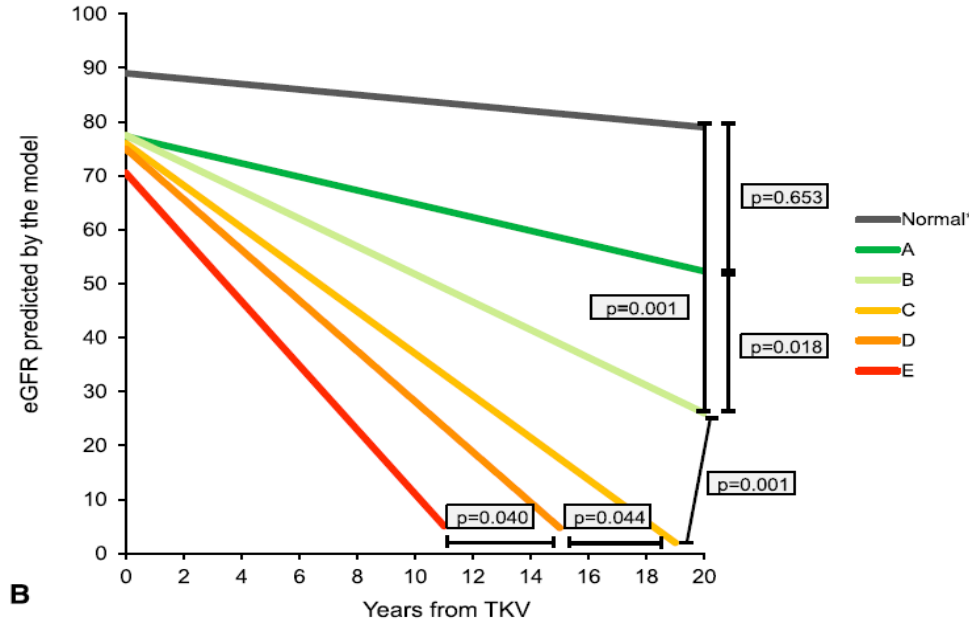


Grantham JJ et al., N Engl J Med 2006; 354 : 2122-30

Imaging Classification of Autosomal Dominant Polycystic Kidney Disease: A Simple Model for Selecting Patients for Clinical Trials

Irazabal MV, et al. J Am Soc Nephrol 26:160-172, 2015





eGFR decline in 538 ADPKD patients from Mayo, with TKV imaging

Patient Eligibility: Reimbursement criteria in Belgium

Tolvaptan for the treatment of ADPKD has been introduced in Belgium in September 2016, and is subject to reimbursement criteria:

- Age **between 18 and 50 years old**
- **TKV ≥750 ml,** has an **$eGFR_{CKD-EPI}$ >30mL/min/1.73 m^2**
- Evidence of rapidly progressing disease with an annual growth of ≥3% in height adjusted TKV growth and therefore is in subclasses **1C, 1D or 1E** according to ref. Irazabal et al JASN, 2015
- Does not have hypernatremia or volume depletion, hepatic disease or a history of hepatotoxic reactions to medication

- Reimbursement must be approved by an internal medicine physician specialized in nephrology and experienced in the treatment of ADPKD, and attached to an Academic Hospital
- Physician agrees to stop treatment when the patient has an $eGFR_{CKD-EPI}$ <30mL/min/1.73 m^2

https://www.inami.fgov.be/webprd/appl/pssp/SSP/CNS2/Pages/SearchingFunction.asp?qs_CrtSeaA=J--JINARC&qs_CrtSeaG=825 (accessed, 20-oct-2017)
Irazabal, M. V et al J Am Soc Nephrol, 2015

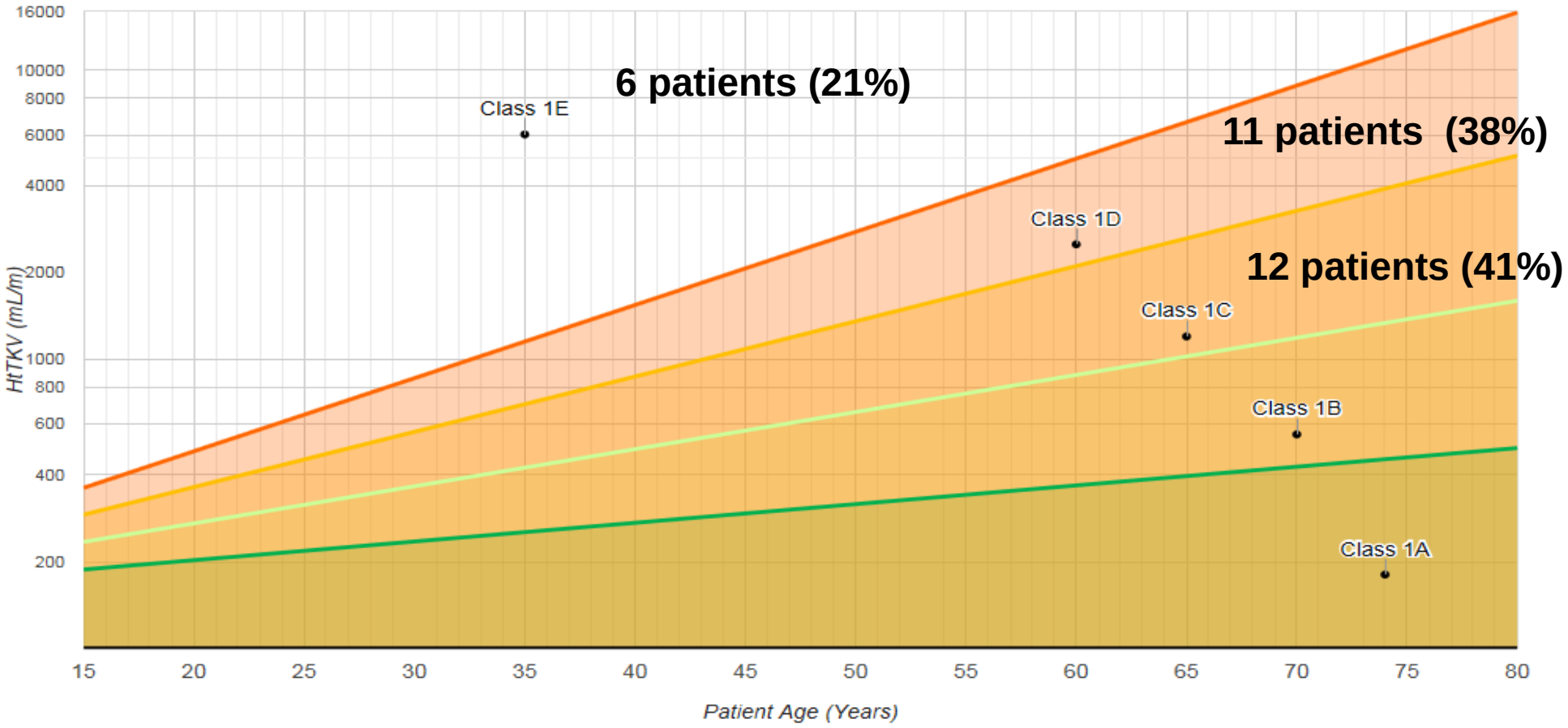
Expérience avec le Jinarc à Saint-Luc

- 41 patients
- Jinarc débuté entre 10/2016 - 05/2018

N=41	
Age	41 ± 9
Age à l'initiation du Jinarc (N=32)*	38 ± 8
Femmes	18 (44%)
Patients des études TEMPO	9 (22%)
Patients du réseau CUSL	13 (32%)

*Patients TEMPO exclus

Classification selon le volume rénal total, corrigé pour la taille, à un âge donné (Mayo Clinic)



Patients TEMPO non inclus

Irazabal MV et al J Am Soc Nephrol 2015; 26: 160

Do patients reach the target tolvaptan dose?

Saint-Luc experience: 45 patients

Cliniques universitaires SAINT-LUC UCL BRUXELLES

About ¼ on the highest dose 90/30 mg

About ¼ on the middle dose 60/30 mg

About ½ on the initial dose 45/15 mg

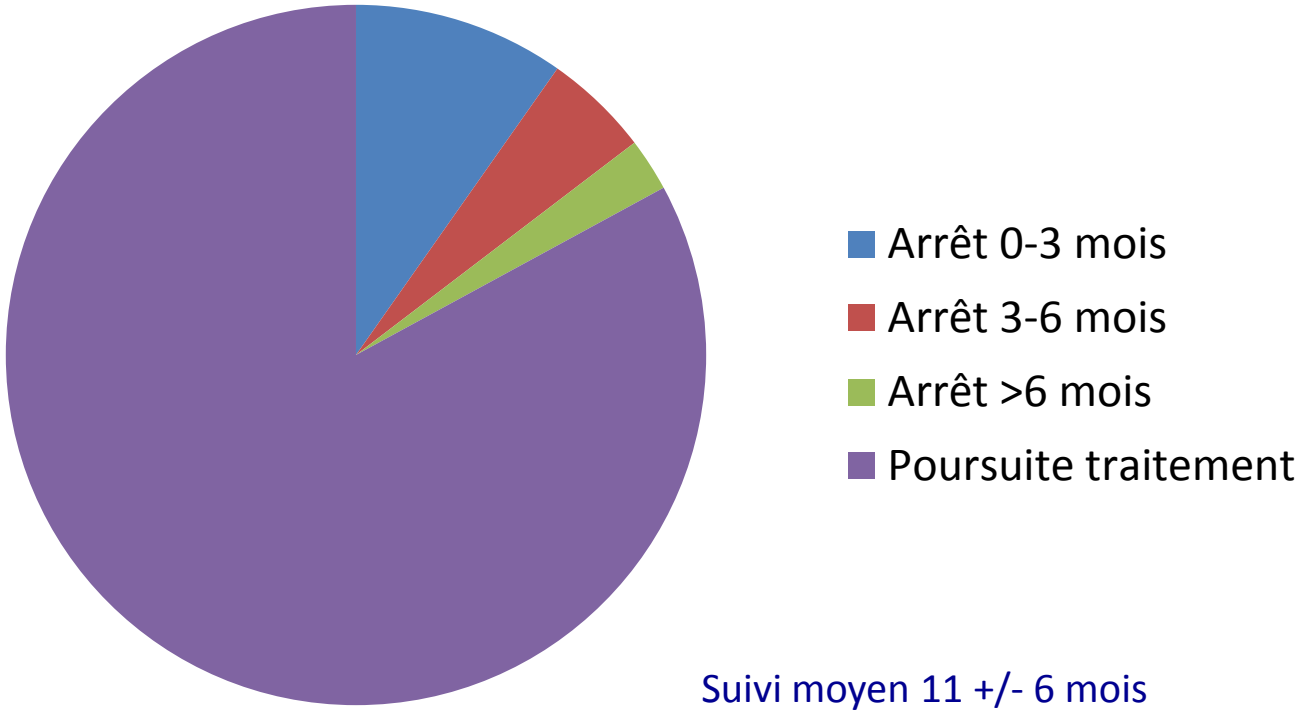
Cave: Delta dose – polyuria does not match; try to go high dose in two months

Personal communication w Dr N Demoulin, May 2018

Données biologiques de suivi

	Avant Jinarc	Après Jinarc
Débit de filtration glomérulaire estimé	63 ± 24 ml/min	57 ± 20 ml/min
Sodium	141 ± 2 mmol/l	142 ± 2 mmol/l
Acide urique	5.8 ± 1.6 mg/dl	6.7 ± 1.6 mg/dl
Osmolalité urinaire	392 ± 188 mOsm/kg	226 ± 111 mOsm/kg

Tolérance au traitement



Suivi moyen 11 +/- 6 mois

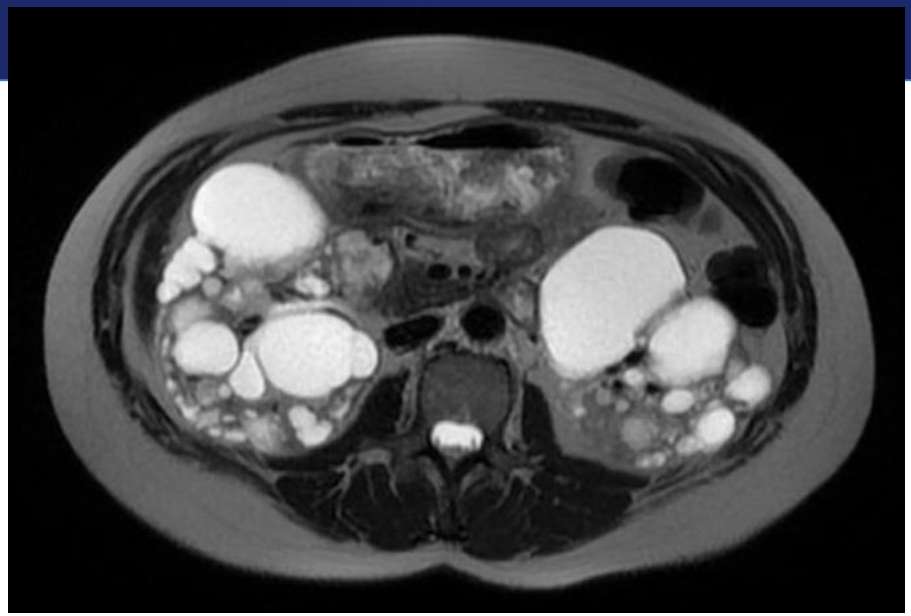
7 arrêts

5 cas de polyurie – polydypsie, arrêt entre 0-6 mois

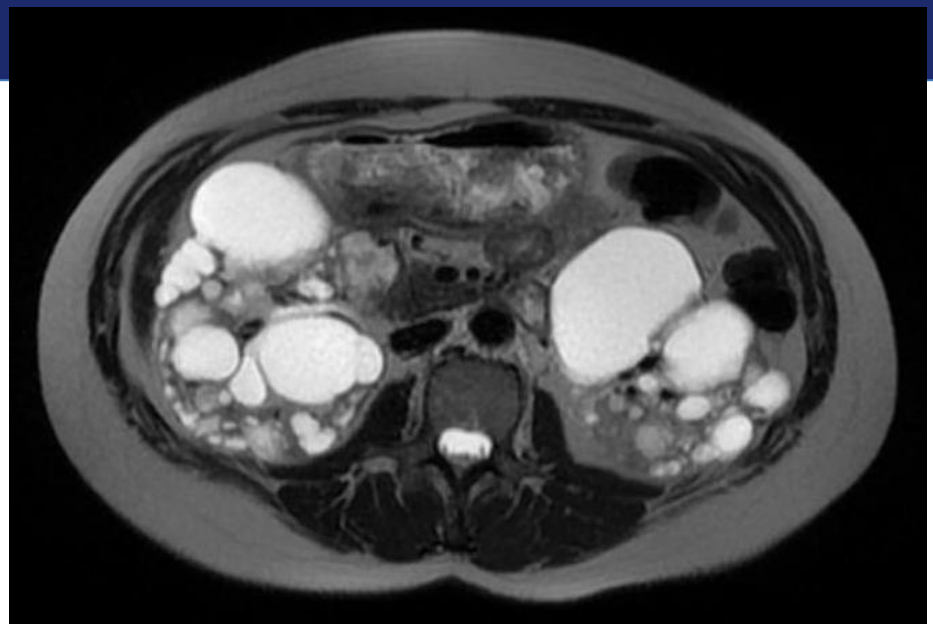
1 cas de CKD4, arrêt à 6 mois

1 patiente enceinte, après arrêt du traitement à 12m

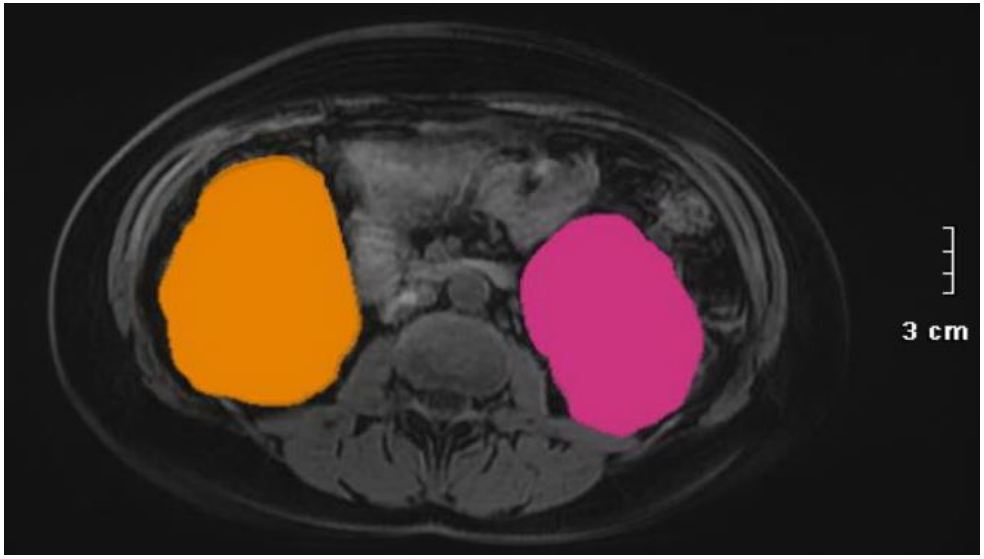
Evolution du volume rénal

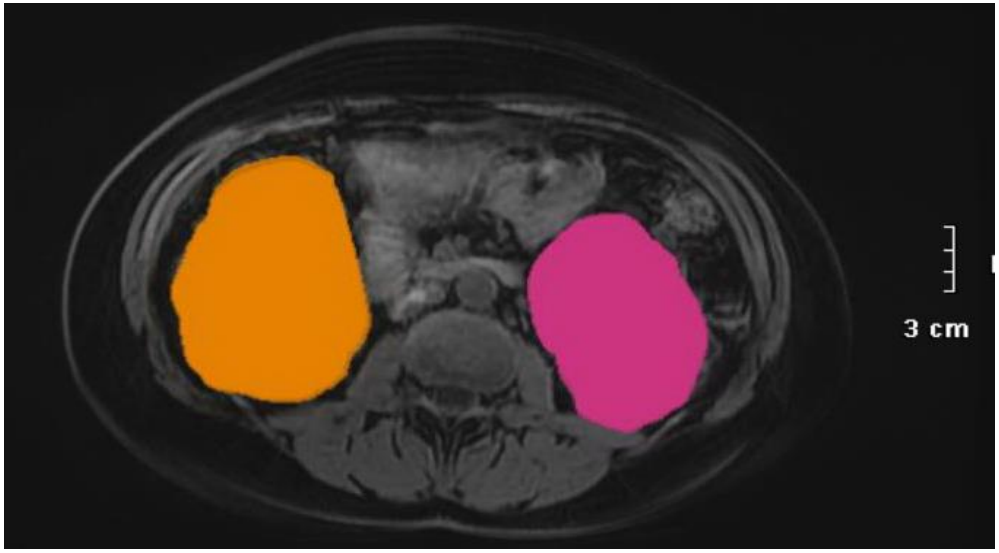


2007: TKV = 1749 ml



2015: TKV = 1170 ml





Our clinical approach at UCL-St. Luc

- Identification of eligible patients – MRI - Mayo
- Discuss the natural progression of ADPKD
- Explanation of drug mechanism of action and side-effects
- Explanation of potential benefits and risks

  Discuss aquaretic symptoms & importance of maintaining hydration
- Importance of monitoring of hepatic enzymes once monthly
- Recommendations and follow-up: *weight, heart rate, blood pressure*

Please note this take time – 1 hour first discussion

Patient recommendations: A few exemples

- Regular water intake is absolutely essential: always carry along a bottle of water, do not wait too long until getting thirsty, stop Tolvaptan in cases of dehydration, diarrhae, vomitting, lacking access to water ...
- Do not compensate the water deficit with calory-rich drinks (milk, soft drinks)
- Take the first pill at ~ 6 am in the morning and the second pill 8 hours later
- Start therapy on a weekend rather than a working day
- Take advantage of helpful tools (apps, patient groups...)
- Stop tolvaptan and seek medical advice in case of symptoms pointing towards liver damage (e.g. fatigue, brown urine, jaundice, complaints of the upper abdomen)
- Avoid salt excess (osmotic load)
- Avoid grapefruit juice
- Stop 4 weeks before trying to get pregnant
- Do not take during pregnancy or breastfeeding
- LFT checkup monthly for the first 18 months, then every 3 months
- Check serum creatinine, uric acid and electrolytes
- Check Uosm (adherence, effect)
- Stop therapy when reaching ESRD

Adherence and tolerability

- Our experience - the majority takes the high dose
- Stop when lack of access to water, inability to drink sufficient amount of fluid and in situations with increased water loss
- When patients stop they stop early (4 out of 45 stopped due to AAE) – Risk factors: young age, high Uosm
- MOA, flexibility, long-term treatment/inhibition

TEMPO 3:4 : Tolerability

ARTICLE IN PRESS

KI REPORTS
KIReports.org

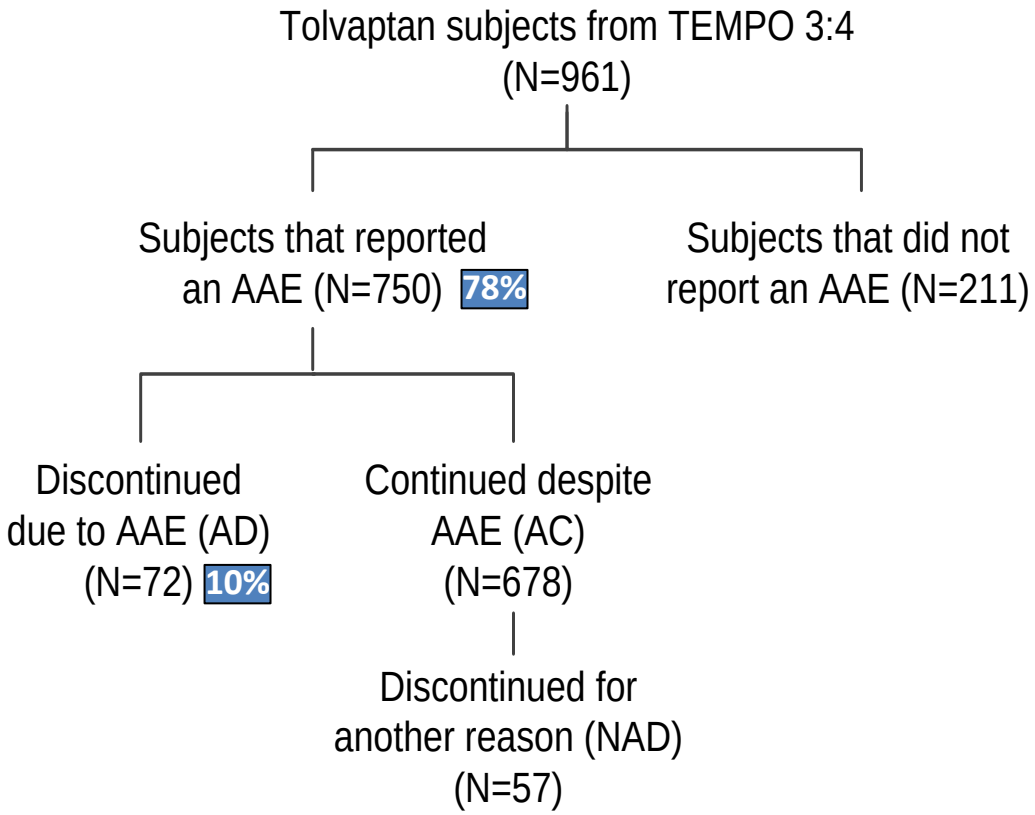
CLINICAL RESEARCH

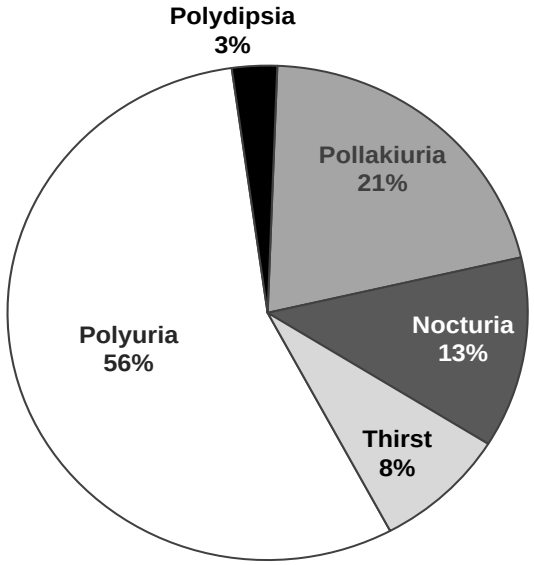
Tolerability of Aquaretic-Related Symptoms Following Tolvaptan for Autosomal Dominant Polycystic Kidney Disease: Results From TEMPO 3:4

Devuyst et al., 2017, *Kidney International Reports,* DOI: http://dx.doi.org/10.1016/j.ekir.2017.07.004

Tolerability – Nature of the aquaretic adverse events

Aquaretic AEs (AAE) associated with tolvaptan: *Polyuria, thirst, nocturia, pollakiuria, polydipsia*



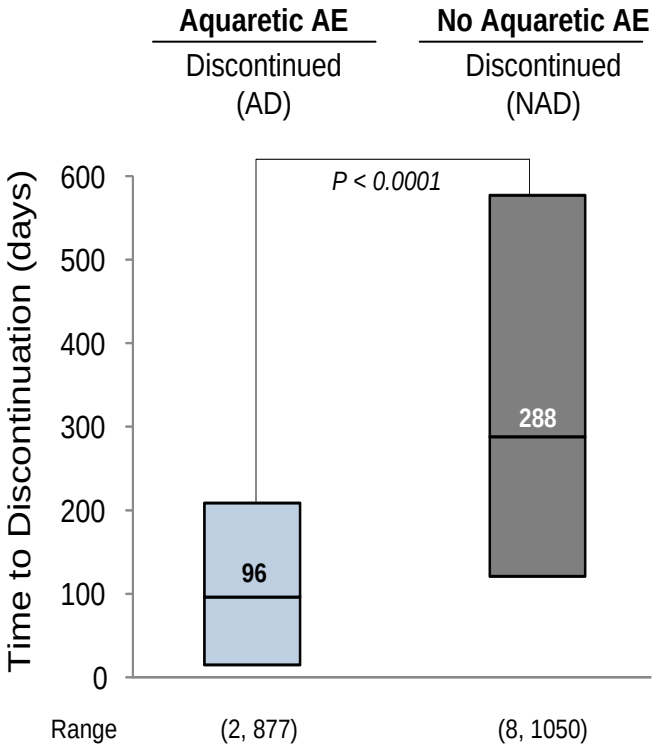


Median time to first report of AAE: 2 days

Devuyst et al., 2017, *Kidney International Reports*,
DOI: http://dx.doi.org/10.1016/j.ekir.2017.07.004

30

AD subjects dropped out earlier than subjects who discontinued for non-aquaretic related adverse events

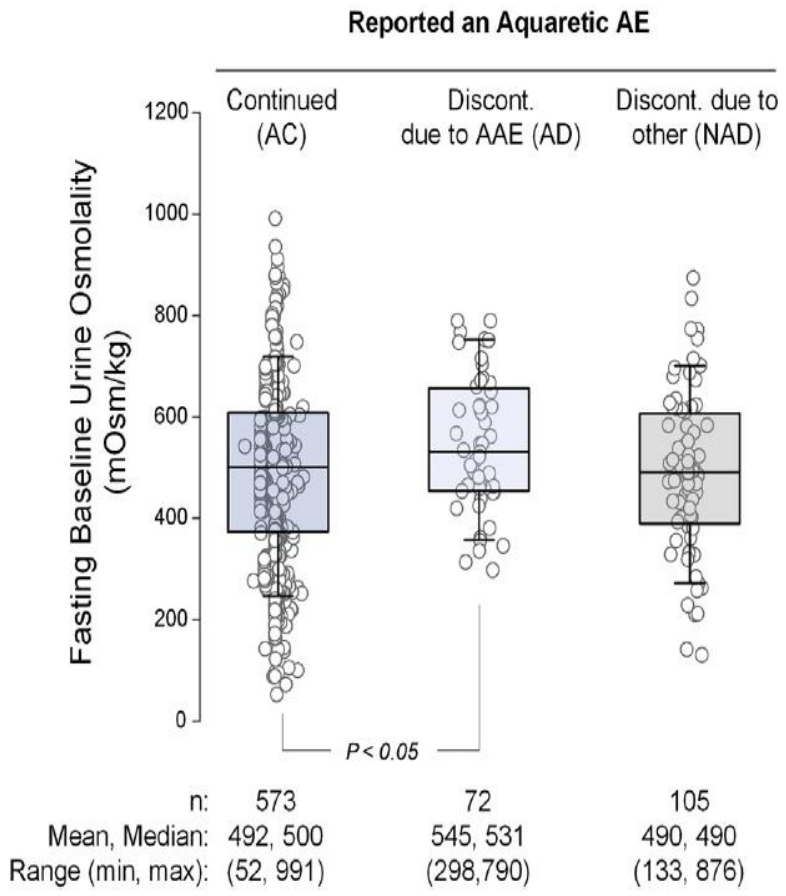


Median time to discontinuation for AD subjects was 96 days, significantly faster than subjects who discontinued for non-aquaretic related adverse events, 288 days

Devuyst et al., 2017, *Kidney International Reports,*
DOI: http://dx.doi.org/10.1016/j.ekir.2017.07.004

Profile of the subjects dropping out due to aquaretic side effects

Aquaretic-Discontinued subjects: were significantly younger, had higher baseline renal function, and higher fasting baseline uOsm than Aquaretic-Continued subjects



ADPKD patients in earlier stages of disease and better renal function may experience more difficulty with the aquaretic side effects of tolvaptan.

Devuyst et al., 2017, *Kidney International Reports,*
DOI: http://dx.doi.org/10.1016/j.ekir.2017.07.004

TEMPO 3:4 : Tolerability – Summary

- In TEMPO 3:4, 78% of tolvaptan-treated subjects reported at least one AAE. Of these, 10% discontinued due to the adverse event(s) and 90% remained in the trial. AAEs remain relatively well tolerated.
- The majority of those that discontinued (56%) reported polyuria as the precipitating cause.
- At the end of the 3-year trial, 75% of subjects who were still receiving tolvaptan indicated they could tolerate their current dose of medication for the rest of their lives, compared with 85% of placebo patients.
- Those who discontinued due to aquaretic AEs were younger, had higher baseline renal function and fasting urine osmolality: at-risk population for the aquaretic side-effects of tolvaptan.

Devuyst et al., 2017, *Kidney International Reports,*

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Experience with tolvaptan in ADPKD

Number of patients across the globe: soon 9’000 patients

Japan ~ 4’800

Canada ~ 1’000

Europe ~ 3’000

Approved by the FDA in April under the name JYNARQUE

PKD FOUNDATION
Polycystic Kidney Disease

FDA U.S. FOOD & DRUG ADMINISTRATION

High Water Intake in ADPKD: Practical

- Sustained increase in water intake: 3L/day
- Target: Uosmo < 300 mOsm/kg (gravimeter)
- Water: no sugar, no caffeine, tap vs. bottled ?
- Compliance : years
- Side-effects: urinary tract retention, social, nycturia
- Trials ongoing : Australia/NZ – Drink (UK)

Water therapy: Which type of water ?

Devuyst et al J Am Soc Nephrol. 2017 May;28(5):1592-1602.

35

Reserve slides

Our Collaborative Approach

Identification of eligible patients by the referring nephrologist

- Discuss treatment, experience with the drug, any questions remaining
- Treatment started directly after visit at St-Luc, phone call after one week
- Titration and Monthly monitoring of hepatic enzymes: done locally
- Follow-up by their local nephrologist

Letter sent to nephrologist and GP about the treatment

Nephrol Dial Transplant (2017) 1–13
doi: 10.1093/ndt/gfx043

ndt
Nephrology Dialysis Transplantation

Original Article

Multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with tolvaptan in autosomal dominant polycystic kidney disease: the TEMPO 4:4 Trial

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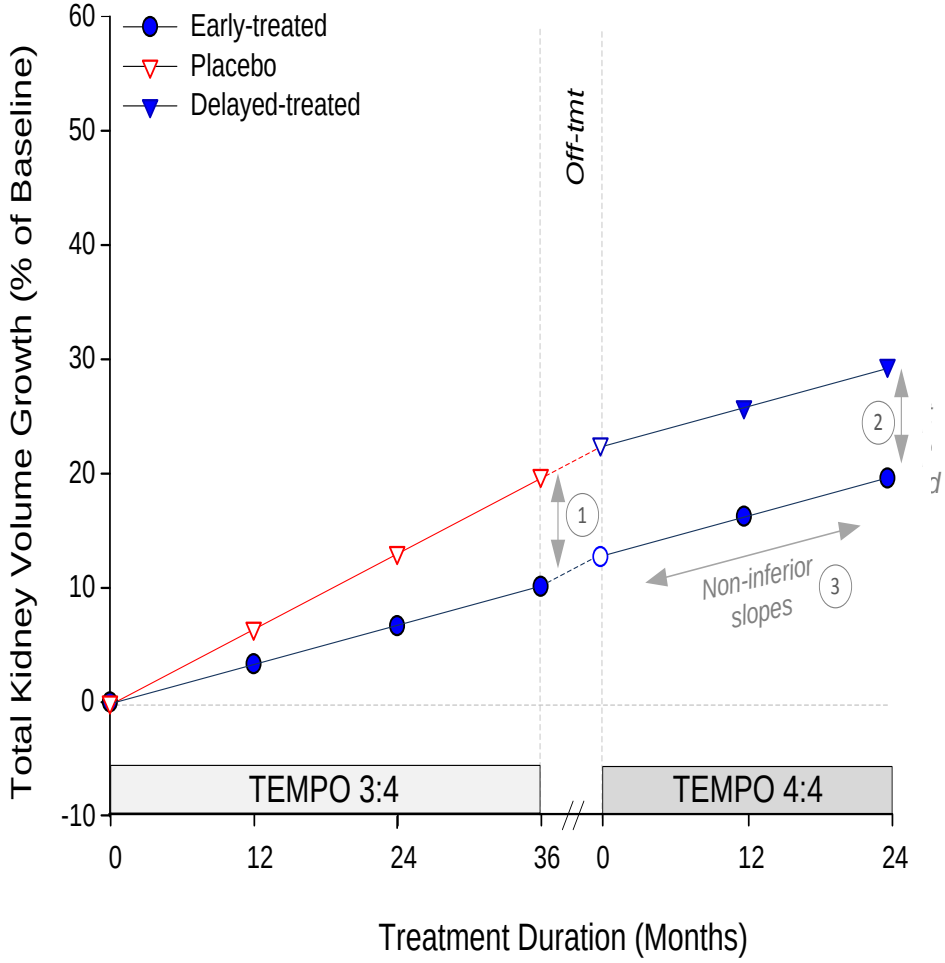
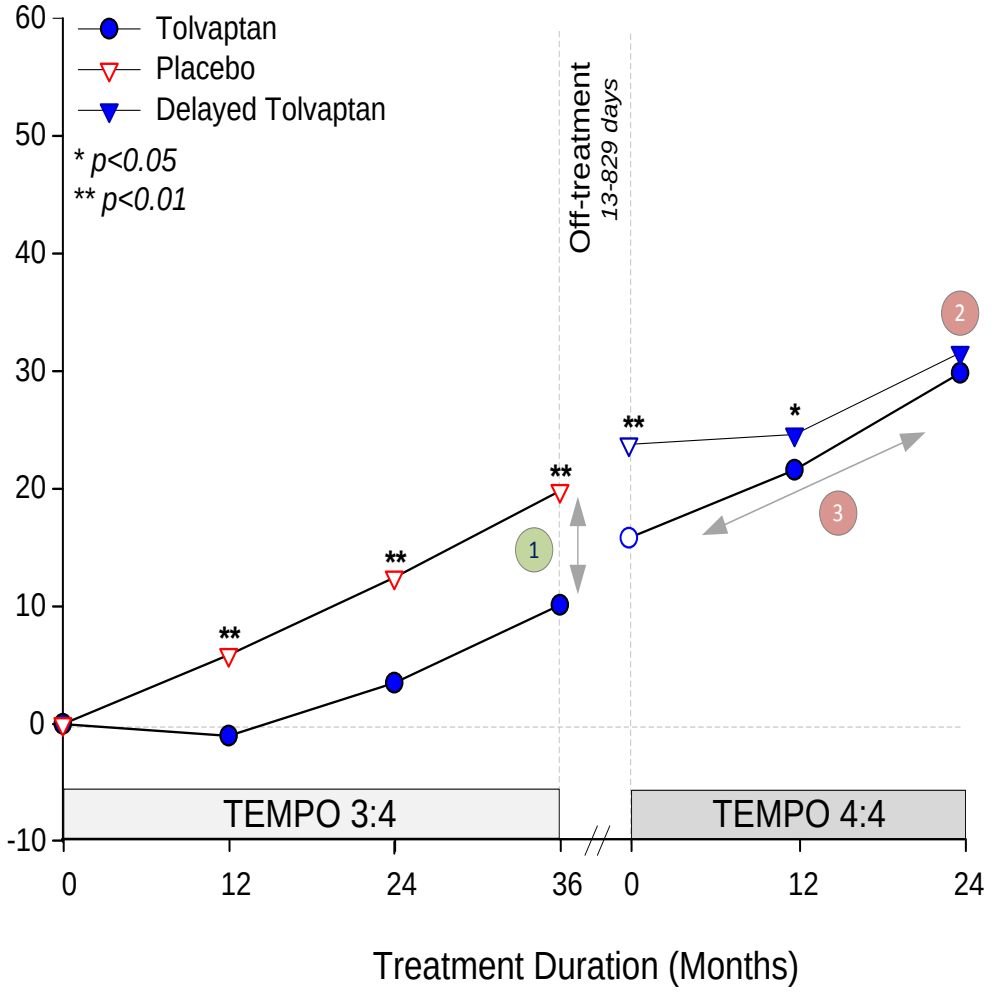
TKV results, no significant difference after two years

Hypothetical graph of TKV



Observed



Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Perrone RD, Dandurand A et al. 2017. Nephrol Dial Transplant. DOI:https://doi.org/10.1093/ndt/gfx043

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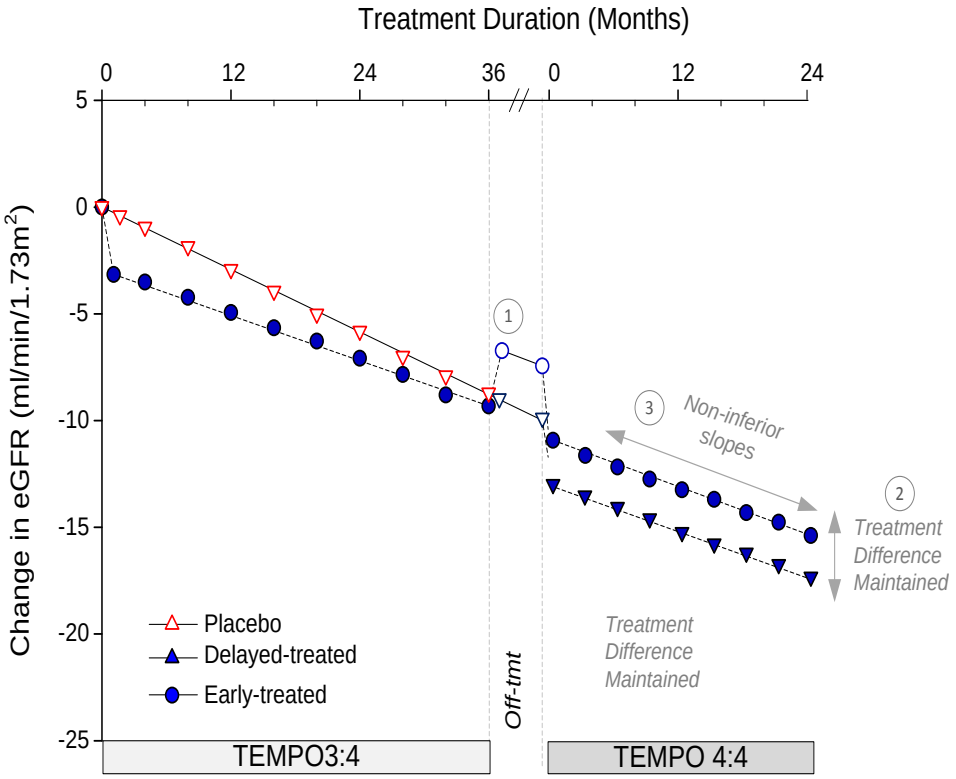
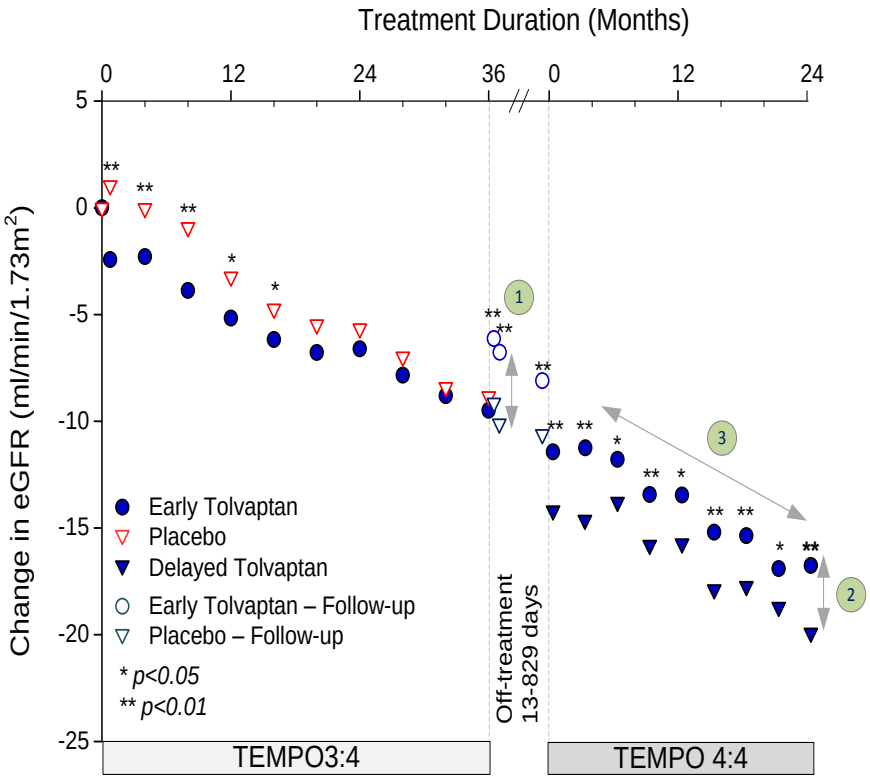
eGFR – difference after two years





eGFR, mL/min/1.73m²						
	n	Slope (/year)	Tmt Diff	95% CI	p-value	NI margin
Early-Treated	548	-3.26	-0.11	-0.75, 0.52	0.73	0.65
Delayed-Treated	304	-3.14				

*Results are nominal, not confirmatory

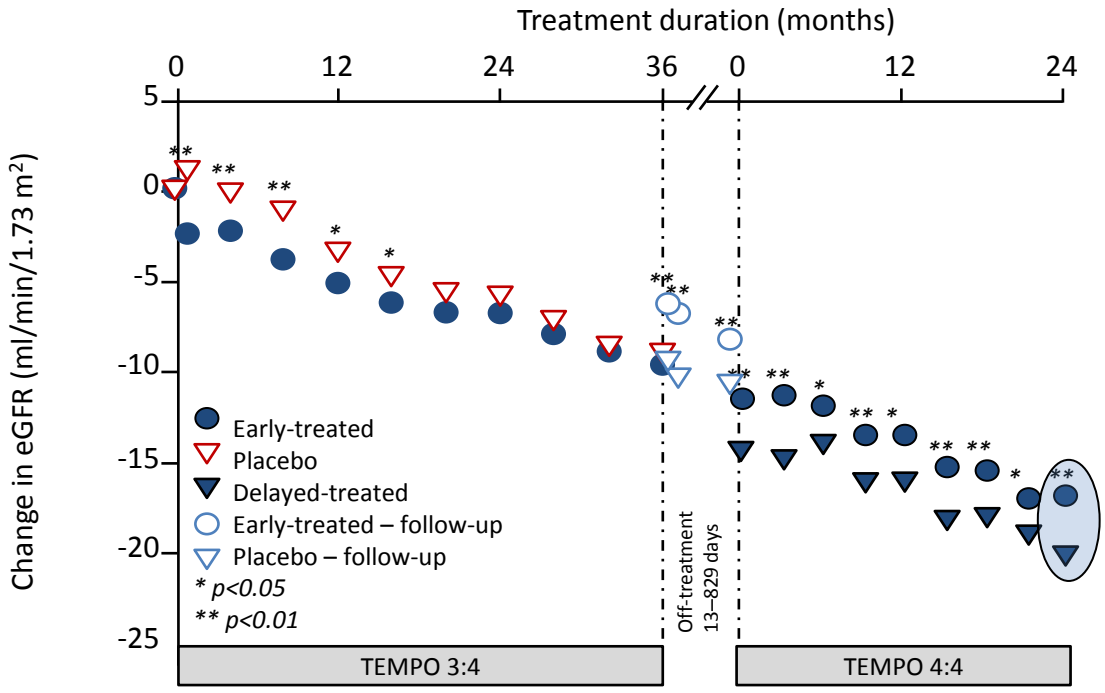
Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Perrone RD, Dandurand A et al. 2017. Nephrol Dial Transplant. DOI:https://doi.org/10.1093/ndt/gfx043

Tempo 4:4 Efficacy: conclusions

- TEMPO 4:4 did not reach its primary endpoint
  - Change in TKV from TEMPO 3:4 baseline to TEMPO 4:4 month 24 in early- *vs* delayed-treated subjects did not reach statistical significance (29.9% *vs* 31.6%; p=0.38)
  - The lack of a sustained treatment difference between the two groups may be accounted for, in part, by limitations of the trial design
  - Adjusting for covariates improved the between-group TKV treatment difference at month 24
- The effect of early treatment on eGFR was maintained during TEMPO 4:4, suggestive of a disease-modifying effect of tolvaptan on renal function
- The post-hoc analyses show that the subjects with image class 1C-E, with CKD2-3 maintained the treatment effect of tolvaptan not only on eGFR but also on TKV for an additional 2 years in TEMPO 4:4.

eGFR, estimated glomerular filtration rate; TKV, total kidney volume
Torres VE *et al*. Nephrol Dial Transplant 2017; in press.

Secondary endpoint: change in eGFR from TEMPO 3:4 baseline to month 24 of TEMPO 4:4



Open circles and triangles represent off-treatment time points

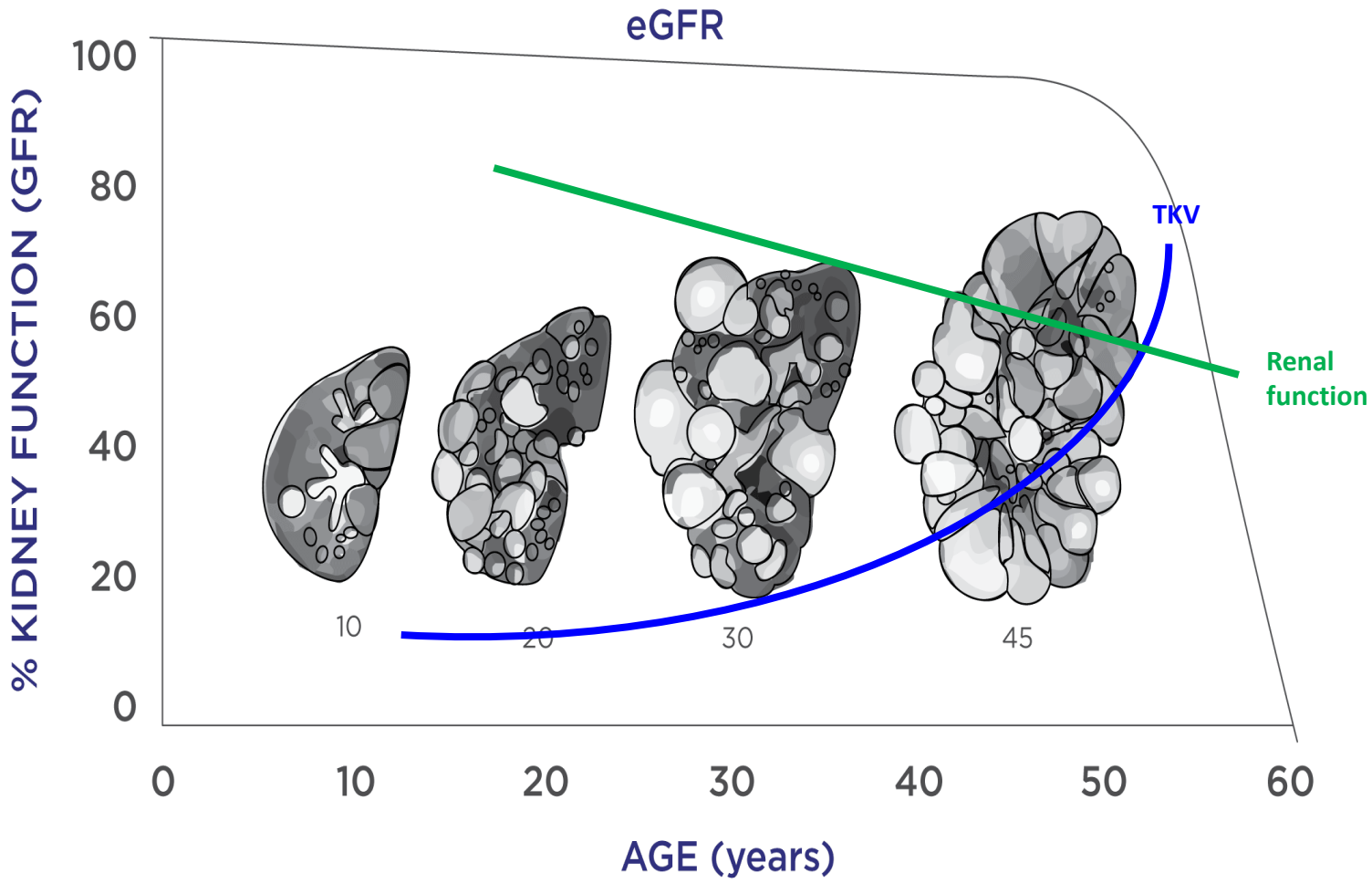
- Prior 3-year treatment effect of tolvaptan *vs* placebo on eGFR maintained when both groups were given tolvaptan in TEMPO 4:4 ((3.15 ml/min/1.73 m2; p<0.001)
- Results are suggestive of a disease-modifying effect of tolvaptan on renal function

The primary endpoint of TEMPO 4:4 did not reach statistical significance. Since the primary endpoint was not reached, pre-specified analyses of the secondary endpoints must be considered exploratory, not confirmatory.

eGFR, estimated glomerular filtration rate

Torres VE *et al*. Nephrol Dial Transplant 2017; in press.

Disease progression in ADPKD: eGFR vs TKV



Torres Mayo < aupCP1047707-9, adapted by Prof. Olivier Devuyst

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Original Article

Multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with tolvaptan in autosomal dominant polycystic kidney disease: the TEMPO 4:4 Trial

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ABSTRACT

Background. In TEMPO 3:4, the vasopressin V2 receptor antagonist tolvaptan slowed total kidney volume (TKV) growth and estimated glomerular filtration rate (eGFR) decline relative to placebo.

Methods. TEMPO 4:4 was designed to provide an additional 2 years of data on the long-term safety and efficacy of tolvaptan in subjects completing TEMPO 3:4. The objective was to assess the disease-modifying effects of tolvaptan on TKV and eGFR endpoints including change from baseline over the combined duration of TEMPO 3:4 and TEMPO 4:4, and non-inferiority of slopes during TEMPO 4:4.

Results. Of the 1445 subjects randomized to TEMPO 3:4, 871 (60.3%) enrolled in TEMPO 4:4. Percent changes in TKV from TEMPO 3:4 baseline to TEMPO 4:4 Month 24 were 29.9% and 31.6% (prior tolvaptan versus prior placebo, $P = 0.38$). Adjusting for baseline covariates improved the TKV treatment difference at Month 24 in TEMPO 4:4 from −1.70% to − 4.15% between the groups ($P = 0.04$). Slopes of TKV growth during TEMPO 4:4 were higher in early- versus delayed-treatment groups (6.16% versus 4.96% per year, $P = 0.05$). Analysis of secondary eGFR endpoints demonstrated a persistent effect on eGFR (3.15 mL/min/1.73 m^2, $P < 0.001$), and non-inferiority in eGFR slopes. The safety profile on exposure to tolvaptan in TEMPO 4:4 was similar to that in TEMPO 3:4.

Conclusions. The results of TEMPO 4:4 support a sustained disease-modifying effect of tolvaptan on eGFR. The lack of a sustained treatment difference on TKV may be accounted for by limitations of the trial design, including loss of randomization and baseline imbalances ensuing TEMPO 3:4. The safety profile was similar to that observed in TEMPO 3:4.

Keywords: autosomal dominant polycystic kidney disease, chronic kidney disease, polycystin kidney disease, vasopressin, vasopressin v2 receptor antagonist

TEMPO 4:4: objectives

- Designed to provide 2 additional years of efficacy and safety data for tolvaptan[1]
- To investigate the disease modifying effect of tolvaptan on:[1]
  - Total kidney volume (TKV)
  - Estimated glomerular filtration rate (eGFR)
- To provide continued access to tolvaptan to subjects who completed TEMPO 3:4[2]

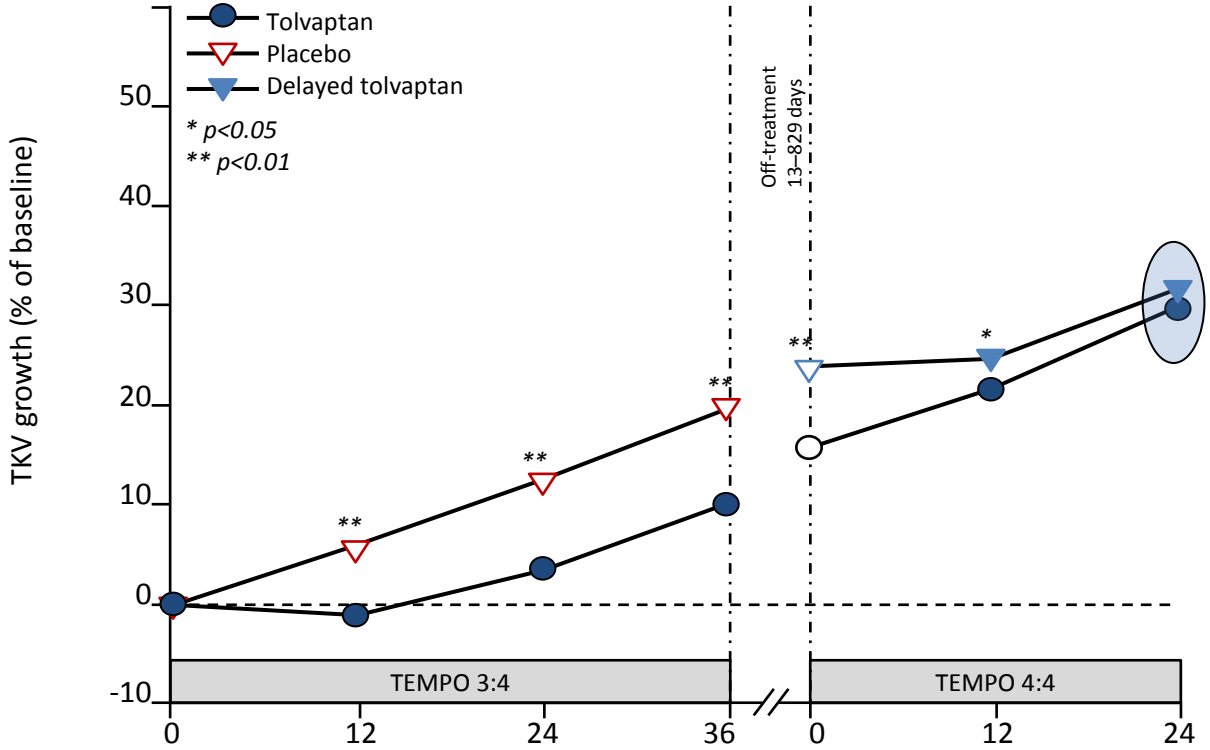
Differences in design:

- **TEMPO 3:4**
  - Multicentre, randomised, double-blind, placebo-controlled 36-month trial of tolvaptan or placebo in adults (N=1,445) with evidence of rapidly progressing, early ADPKD[1]
  - Showed that tolvaptan compared to placebo slowed the increase in total kidney volume and decline in renal function over 3 years
- **TEMPO 4:4**
  - Non-randomised, 24-month, open-label extension in 871 subjects, all of whom received tolvaptan and who had previously completed TEMPO 3:4

1. Torres VE *et al*. *Nephrol Dial Transplant* 2017;in press; 2. Otsuka Pharmaceutical Development & Commercialization, I. 2016.

Primary endpoint: change in TKV from TEMPO 3:4 baseline to TEMPO 4:4 month 24 in early- *vs* delayed-treated subjects

Percentage change in TKV from TEMPO 3:4 baseline to month 24 visit of TEMPO 4:4



Early-treated N	555	554	555	552	499	535	505
Delayed-treated N	331	312	313	312	289	287	267

Change in TKV from TEMPO 3:4 baseline to month 24 of TEMPO 4:4 in early- *vs* delayed-treated groups: 29.9% *vs* 31.6%, respectively; p=0.38

Open circles and triangles represent off-treatment time points

TKV, total kidney volume

Torres VE *et al*. Nephrol Dial Transplant 2017.

TEMPO 4:4: results

Factors affecting TKV assessment

- Staggered and delayed roll-over from TEMPO 3:4 to TEMPO 4:4 (13–829 days)
- Large effect on TKV growth during the first year of exposure to tolvaptan and smaller effects in subsequent years
- Blunted or absent acute treatment effect on TKV upon reintroduction of tolvaptan in early-treated subjects
- Imbalance of relevant covariates in TEMPO 4:4 due to uneven withdrawal and re-enrollment
- Different age and disease stage in early- and delayed-treated subjects upon first tolvaptan exposure, along with TKV growth acceleration with disease progression

TKV, total kidney volume
Torres VE *et al*. Nephrol Dial Transplant 2017

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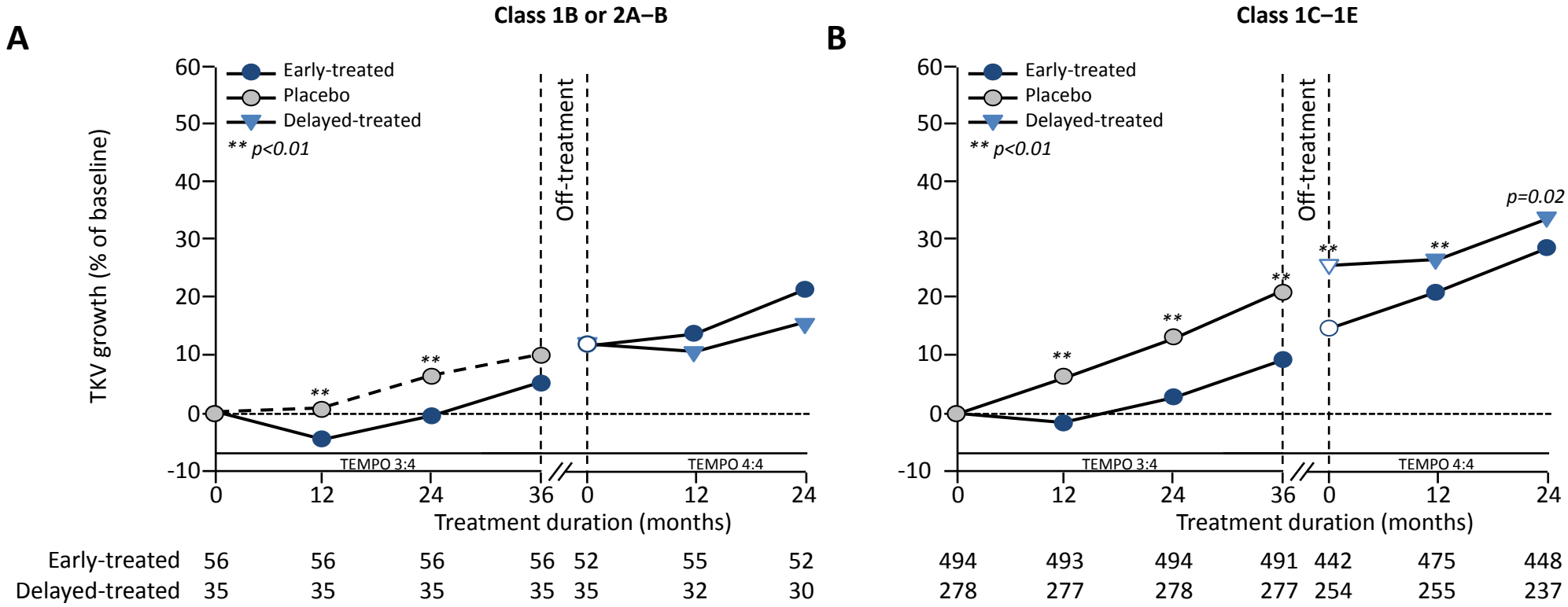
TEMPO 4:4: results

Change from baseline in TKV by imaging classification

- Percentage change in TKV from TEMPO 3:4 baseline to month 24 in TEMPO 4:4 for subjects in Class 2A/B and 1B (**A**) and Class 1C, D and E (**B**)



Open circles and triangles represent off-treatment time points.

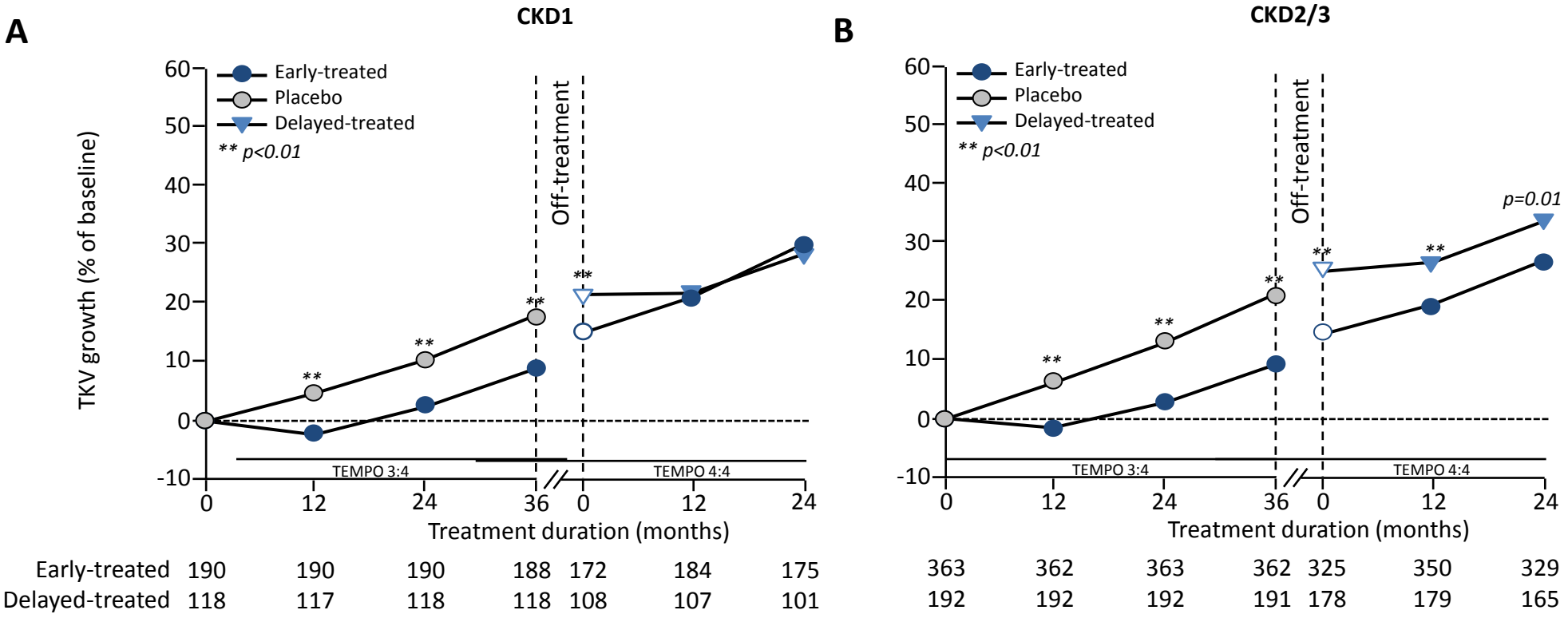
TKV, total kidney volume

Torres VE *et al*. *Nephrol Dial Transplant* 2017

TEMPO 4:4: results

Change from baseline in TKV by CKD stage

- Percentage change in TKV from TEMPO 3:4 baseline to month 24 in TEMPO 4:4 for subjects in CKD1 (**A**) and CKD2/3 (**B**)



Open circles and triangles represent off-treatment time points.

CKD, chronic kidney disease; TKV, total kidney volume

Torres VE *et al*. *Nephrol Dial Transplant* 2017

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Conclusions

- Although the pre-specified primary endpoint for TKV was not achieved, the data acquired are useful contributions to understanding tolvaptan's long-term effects in ADPKD and the selection of rapid progressors (post-hoc analysis)

- The safety profile of tolvaptan seen in TEMPO 3:4 was largely replicated in TEMPO 4:4 withdrawal rate of approximately 10%
  - aquaretic effects
  - hepatic lab abnormalities

- AE related withdrawal over the 3rd to 5th year of treatment with tolvaptan was only 5% which is in line with what is observed in clinical practice

- *A disease-modifying effect of tolvaptan* on eGFR was suggested

Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Perrone RD, Dandurand A et al. 2017. Neprol Dial Transplant. DOI:https://doi.org/10.1093/ndt/gfx043

TEMPO 3:4: Conclusions

- Tolvaptan slowed the increase in total kidney volume over a 3-year period in patients with ADPKD compared to placebo
- Tolvaptan slowed the decline in renal function over a 3-year period compared to placebo
- Tolvaptan decreased the time to multiple composite events, which was predominantly influenced by a reduction in events of worsening kidney function and kidney pain compared to placebo
- The most commonly reported tolvaptan related-AEs are consistent with the mechanism of action, ie aquaretic effect
- Idiosyncratic elevations in liver enzymes was more frequently reported in tolvaptan treated subjects, but the risk of more serious hepatocellular injury can be mitigated with stringent hepatic monitoring and timely discontinuation of treatment
- The potential risk of permanent or life-threatening hepatocellular injury has decreased from 1:3000 in 2013 to 1:6200 in 2018.

Torres VE *et al.* (2012). *NEJM* 367(25): 2407-18

Cornec-Le Gall et al. JASN 27, 2015

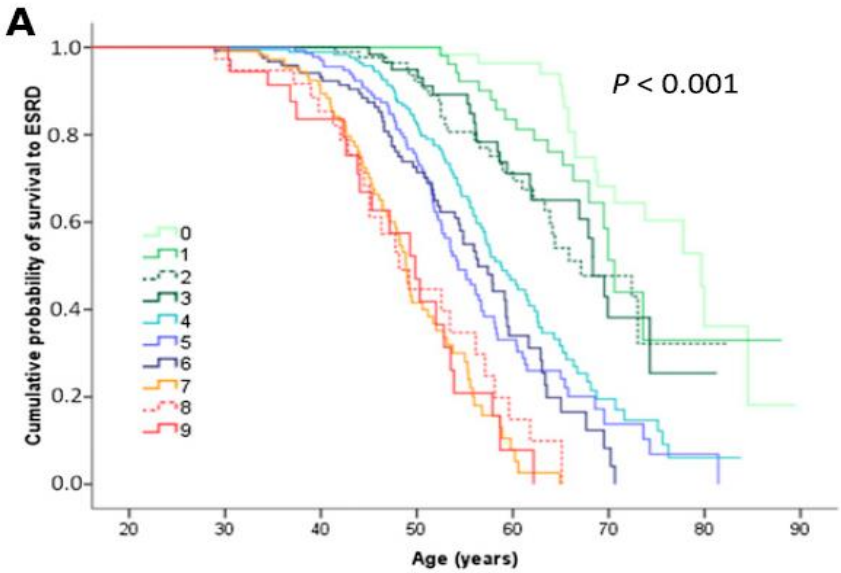
The PROPKD Score: A New Algorithm to Predict Renal Survival in Autosomal Dominant Polycystic Kidney Disease

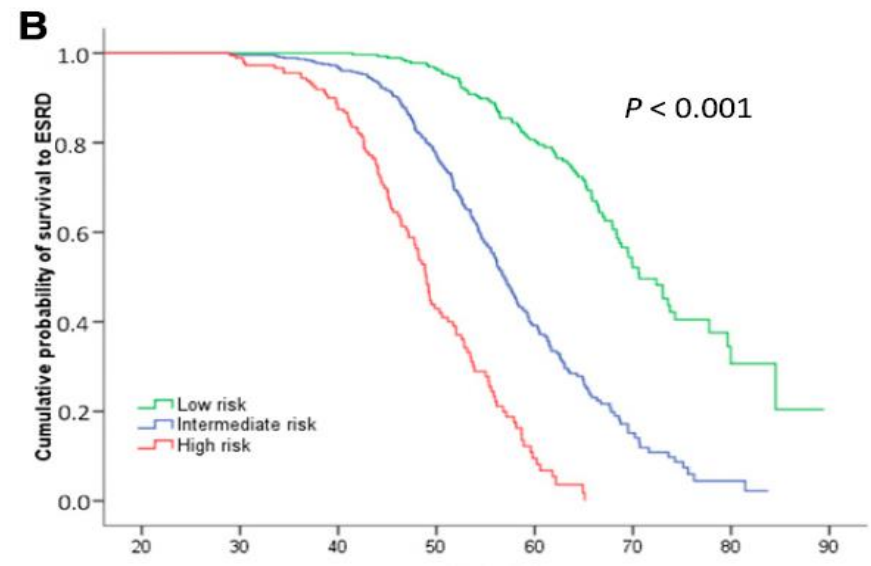
Variable	Patients (*n*)	HR (95% CI)	95% CI from Bootstrap Analysis	*P* Value	Points for PROPKD Score
Sex					
Female	541				0
Male	432	1.55 (1.29 to 1.88)	1.27 to 1.89	<0.001	1
Hypertension before age 35 yr					
No	679				0
Yes	294	2.11 (1.71 to 2.61)	1.71 to 2.62	<0.001	2
≥1 urologic event before age 35 yr					
No	734				0
Yes	239	1.73 (1.38 to 2.18)	1.35 to 2.24	<0.001	2
Mutation					
PKD2	186				0
PKD1 nontruncating	239	2.27 (1.57 to 3.28)	1.61 to 3.18	0.002	2
PKD1 truncating	548	4.75 (3.41 to 6.60)	3.63 to 6.60	<0.001	4

**Urologic event: hemorrage, flank pain, infection*

- Large GenKYST cohort from Brittany (N=1341)
- MV analysis: 4 risk factors → Score from 0 to 9
- Three risk categories

The PROPKD score enables stratification of risk of progression to ESRD in ADPKD patients





Renal survival based on PROPKD, with scores ranging from 0 to 9 points

Low risk (0–3 points), intermediate risk (4–6 points), and high risk (7–9 points)

→ Truncated *PKD1*, Pro-PKD score >6: rapid progressors

Cornec-Le Gall et al. JASN 27, 2015

Doses de traitement