Nephro Update Europe 2019

20 – 21 September, Prague

Hot Topic: ADPKD

Emilie Cornec-Le Gall, France

Outline

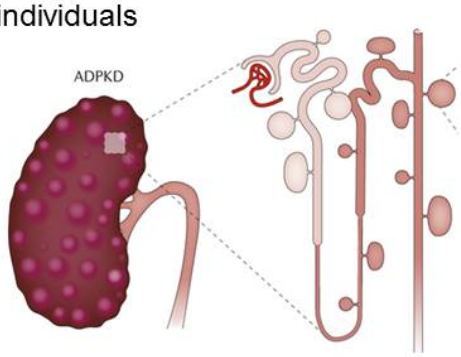
- Introduction
- Diagnosis of ADPKD
- Assessment of prognosis
- Therapies in ADPKD

State of the Art

Most common hereditary disorder causing ESRD
Lifetime risk of developping ADPKD ~1 in 1000 individuals
Prevalence of ADPKD ~1 in 2500 individuals
6-10% of ESRD patients
Renal cysts

- Begin *in utero*
- Develop in tubules
- Separate from tubules
- Grow slowly
- Full of secreted fluid
- Compress adjacent capillaries and tubules

High variability in term of disease severity
A systemic disorder: liver cysts, vascular complications



Bergman C et al., Nat Rev Dis Primers, 2018, 4(1): 50.

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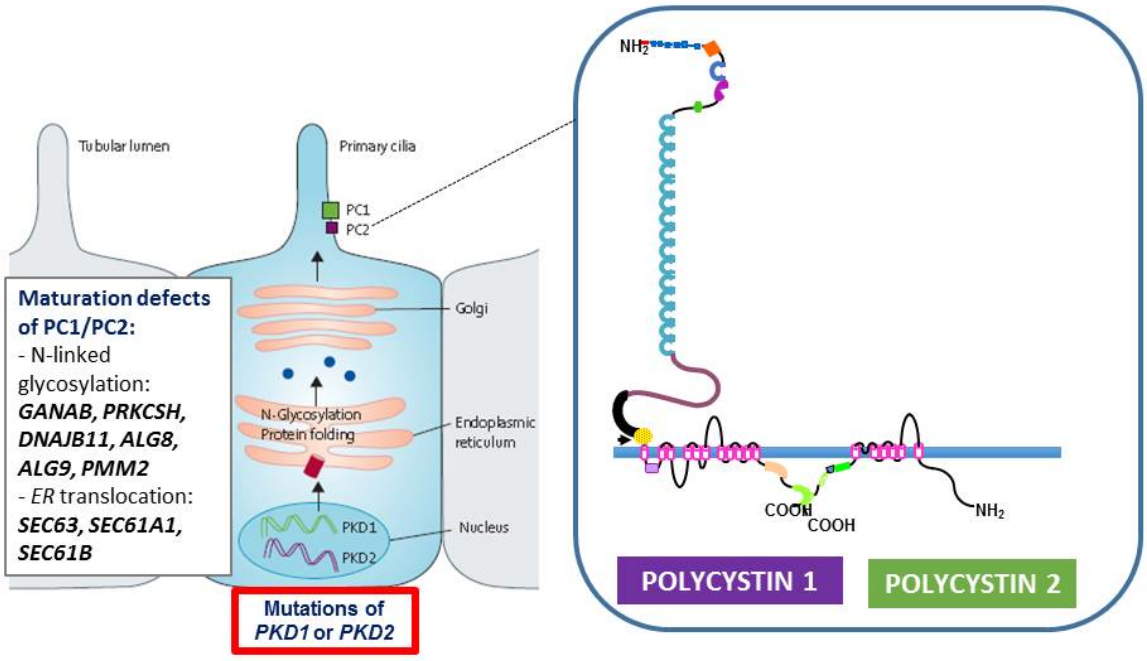
PKD genes and proteins



Cornec-Le Gall E, Alam A, Perrone RD, Lancet, 2019, 393: 920
Harris PC at al., Nature Reviews Nephrology, 2010, 6:197-206

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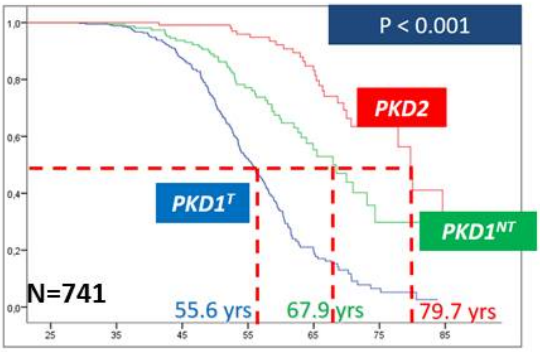
Introduction: ADPKD, a strong genetic heterogeneity

Genetic heterogeneity in ADPKD:

Two « main » genes
- *PKD1 (16p13.3)* 75% of the pedigrees
- *PKD2* (4q21) 15-18% of the pedigrees

>2000 mutations described
Strong influence on disease severity

Non *PKD1*/non *PKD2* 7%
- *GANAB (11q12.3)*
- *DNAJB11 (3q27.3)*
- Other genetic diseases (*HNF1B*…)
- Genetically unresolved cases



Hughes et al.,, Nat Genet 1995; 10: 151–60. – Mochizuki et al., Science 1996 Science 1996; 272: 1339–42 – Cornec-Le Gall et al., J Am Soc Nephrol 2013; 24: 1006–13

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Diagnosis of ADPKD

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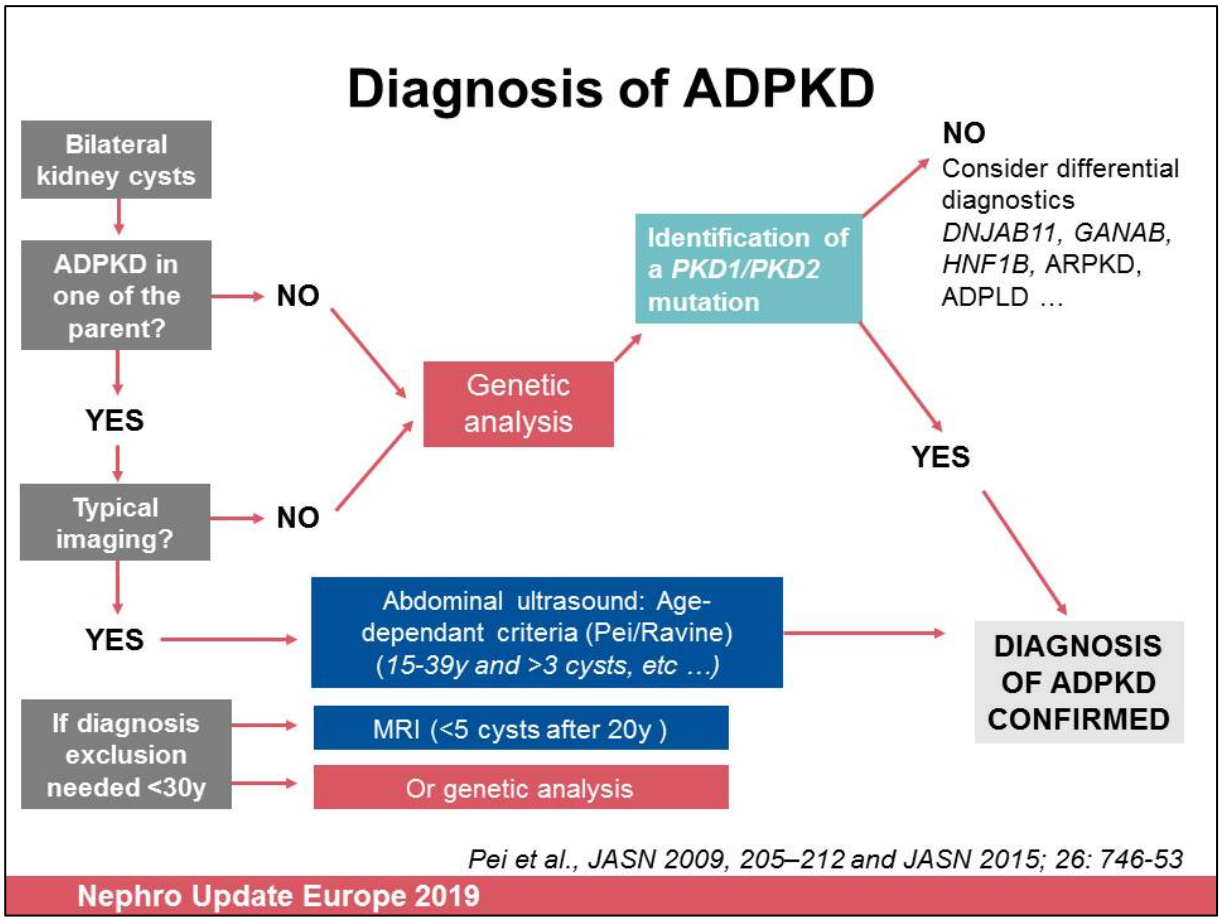
Diagnosis of ADPKD
Bilateral kidney cysts
ADPKD in one of the parent?
NO
YES
Typical imaging?
NO
YES
Genetic analysis
Identification of a PKD1/PKD2 mutation
NO
Consider differential diagnostics
DNJAB11, GANAB, HNF1B, ARPKD, ADPLD …
YES
Abdominal ultrasound: Age-dependant criteria (Pei/Ravine)
(15-39y and >3 cysts, etc …)
If diagnosis exclusion needed <30y
MRI (<5 cysts after 20y)
Or genetic analysis
DIAGNOSIS OF ADPKD CONFIRMED
Pei et al., JASN 2009, 205–212 and JASN 2015; 26: 746-53
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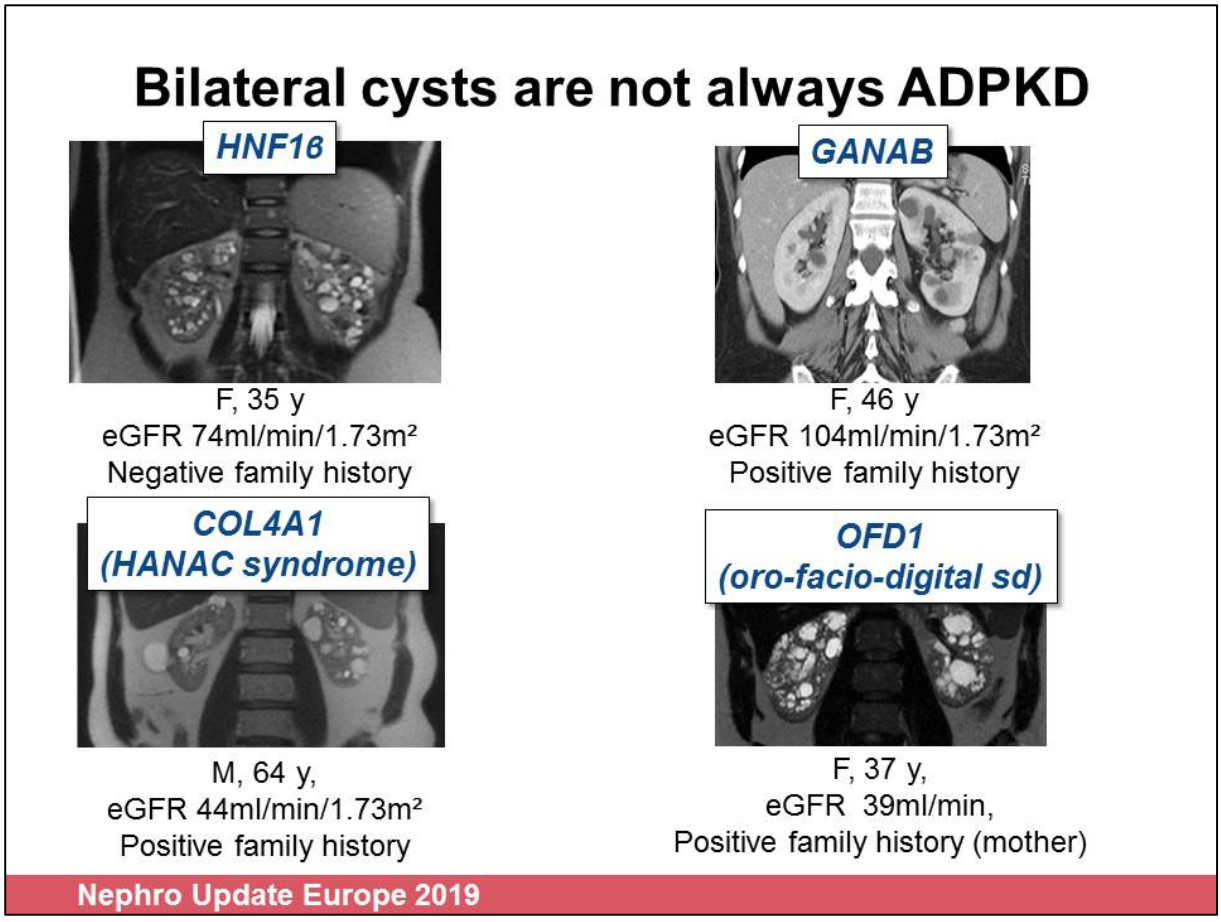
Bilateral cysts are not always ADPKD
HNF1β
F, 35 y
eGFR 74ml/min/1.73m²
Negative family history
GANAB
F, 46 y
eGFR 104ml/min/1.73m²
Positive family history
COL4A1 (HANAC syndrome)
M, 64 y,
eGFR 44ml/min/1.73m²
Positive family history
OFD1 (oro-facio-digital sd)
F, 37 y,
eGFR 39ml/min,
Positive family history (mother)
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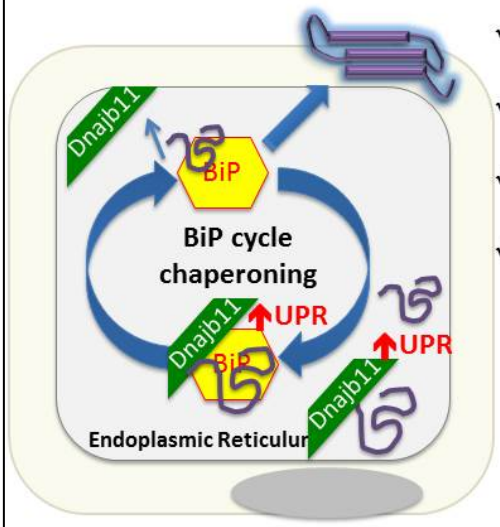
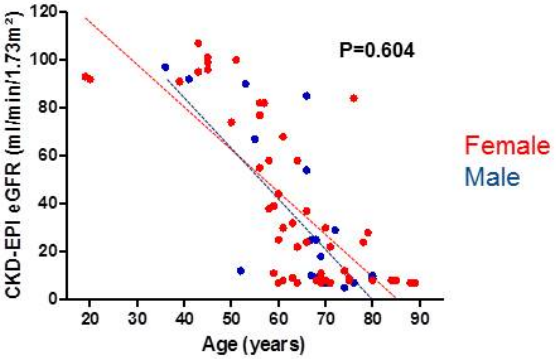
A new phenocopy: *DNAJB11*-associated nephropathy



Mutations to *DNAJB11* cause defective PC1 maturation

- ✓ Normal-sized polycystic kidneys, evolution to atrophy
- ✓ Marked interstitial fibrosis in non-cystic parenchyma
- ✓ Polycystic liver disease can be present
- ✓ ADPKD imaging diagnosis and prognosis criteria cannot be used

M - 68y – ESRD



Cornec-Le Gall et al ..Harris PC, 2018, AJHG (102):832–844

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Assessment of prognosis in ADPKD

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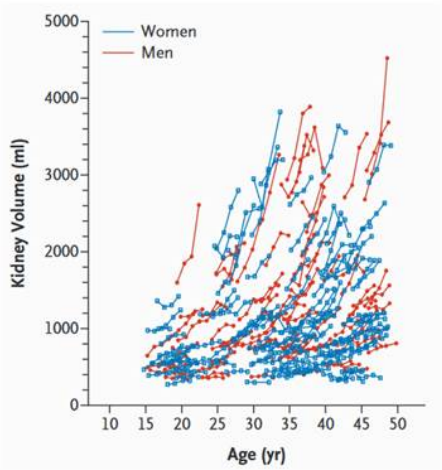
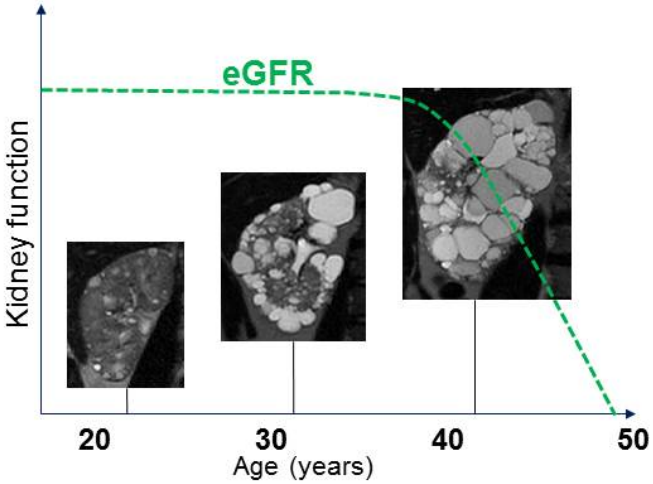
Prognostic value of Total Kidney Volume





Variability of TKV growth rate: ~5-7% /year [<0.5 - >20%]
Strong correlation between TKV growth rate and subsequent loss of eGFR

Grantham JJ et al, NEJM 2006, 354, 2122–2130

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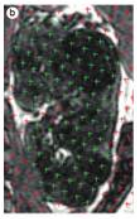
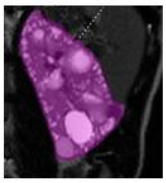
How to measure TKV?

In research setting :
Stereologic and planimetry methods

TKV= ∑ (area x slice thickness)

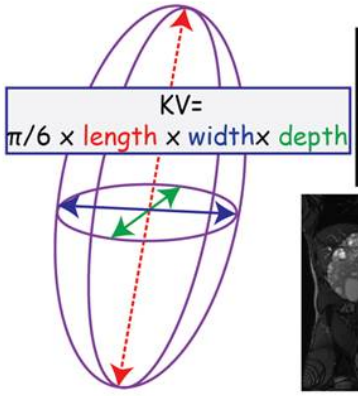


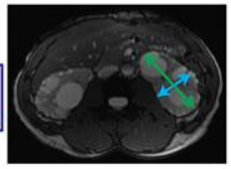


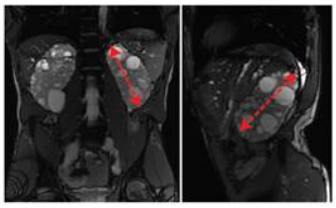
TKV=
N organ voxels
x voxel volume

Average time: 45 minutes

In clinical setting:
Ellipsoid method







Average time: 7 minutes

Bae KT, Nat Rev Nephrol. 2010 Feb;6(2):96-106 – Van Gastel M et al, J Am Soc Nephrol. 2019 Aug;30(8):1514-1522 - Irazabal et al., J Am Soc Nephrol 2015; 26: 160–172

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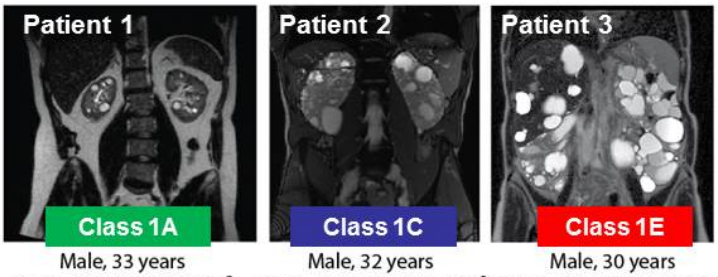
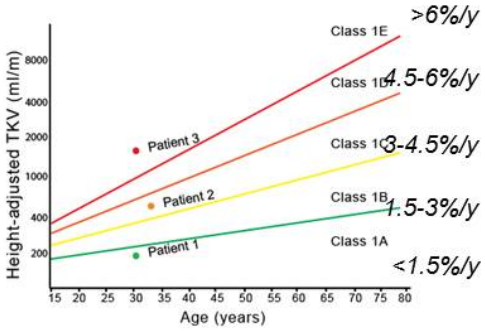
Using age-related HtTKV: The Mayo Imaging Classification

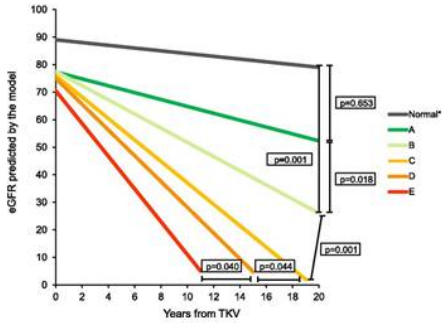


Male, 33 years
eGFR=97 ml/min/1.73m²
HtTKV 222 ml/m
Class 1A

Male, 32 years
eGFR=112 ml/min/1.73m²
HtTKV 452 ml/m
Class 1C

Male, 30 years
eGFR=114 ml/min/1.73m²
HtTKV 1396 ml/m
Class 1E





Irazabal et al., J Am Soc Nephrol 2015; 26: 160–172

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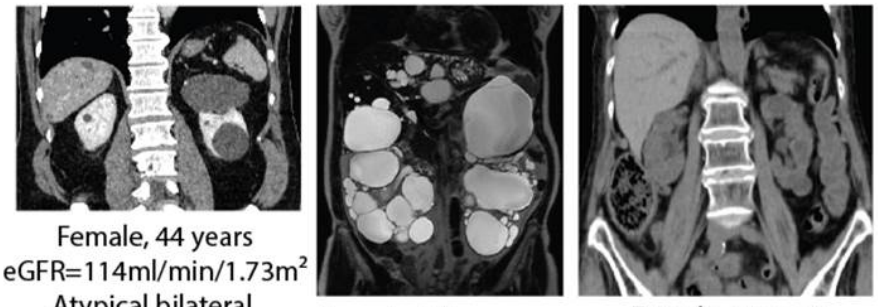
Atypical imaging in ADPKD (Class 2): Do not use TKV!



Female, 44 years
eGFR=114ml/min/1.73m²
Atypical bilateral presentation

Female, 65 years
eGFR=55 ml/min/1.73m²
Lopsided kidneys

Female, 68 years
eGFR=18 ml/min/1.73m²
Bilateral kidney atrophy

Class 2A — *GANAB*

Class 2A — *PKD2*

Class 2B — *DNAJB11*

Cornec-Le Gall E, Alam A, Perrone RD, Lancet, 2019, 393: 920

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Using genetic and clinical data: the PROPKD score
(Predicting Renal Outcome in ADPKD)

Genkyst

Inclusion of all consenting ADPKD patients in 24 public and private nephrology or hemodialysis center of the western part of France
2969 patients

Variable	Category	Pts
Gender	Female	**0**
	Male	**1**
Hypertension < 35 yrs	No	**0**
	Yes	**2**
At least one urological complication < 35 yrs	No	**0**
	Yes	**2**
Mutation	*PKD2*	**0**
	PKD1/Non-Truncating	**2**
	PKD1/Truncating	**4**
TOTAL		**0 to 9 points**

Cornec-Le Gall et al., J Am Soc Nephrol 2016; 27: 942–951

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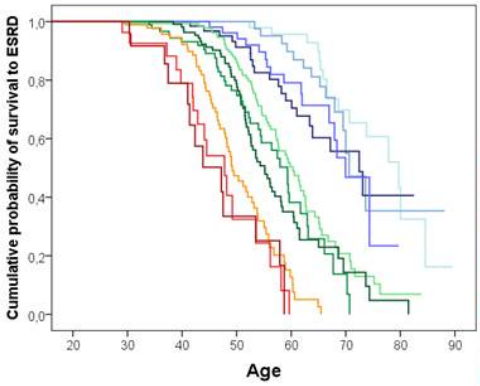
Using genetic and clinical data: the PROPKD score
(Predicting Renal Outcome in ADPKD)

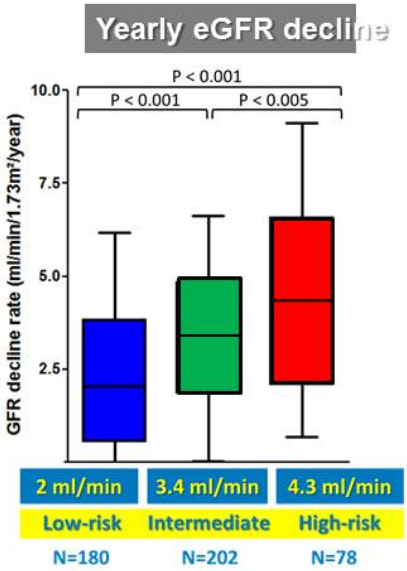


Low Risk
Median Age at ESRD 70.6 yrs [63.6-84.5]

Intermediate Risk
Median Age at ESRD 56.9 yrs [50.7-65.4]

High Risk
Median Age at ESRD 49 yrs [43.8-55.6]

Variable	N	HR	0.95 CI	P Value
Low-Risk	326			
Intermediate	455	**3.72**	*2.89-4.78*	<0.001
High Risk	192	**10.8**	*8.06-14.7*	<0.001



Cornec-Le Gall et al., J Am Soc Nephrol 2016; 27: 942–951

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Therapies in ADPKD

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General measures

Maintenance of optimal weight (Normal BMI)
Limit dietary salt intake to 5g per day
Limit protein intake to 0.8 g/kg/j
Water intake +++
Protect large kidneys from trauma

Early monitoring and treatment of hypertension

Chebib F, Torres VE, CJASN 2018; 13: 1765–76.

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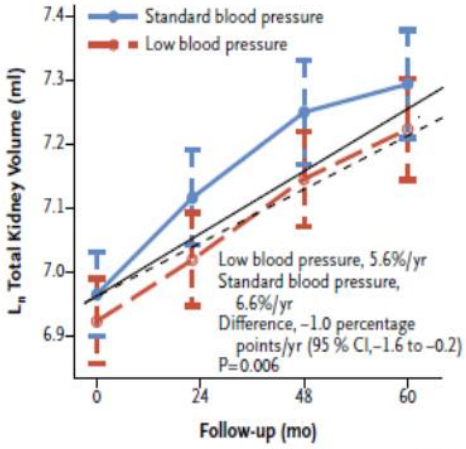
Management of hypertension

KDIGO guidelines

RAAS inhibitors in first intention (ARB or ACE inhibitors) +++

BP target: 140/90 mmHg, 130/80 mmHg if albuminuria >30mg/g

HALT Study A: Targeting lower BP



In individuals <50y with GFR>60 ml/min, and no cardiovascular disease:
Ambulatory BP target: 110/75 mmHg

KDIGO guidelines, Kidney int, Suppl. 3, 1–150 (2015)
Schrier et al., NEJM, 2014: 371: 2255–66

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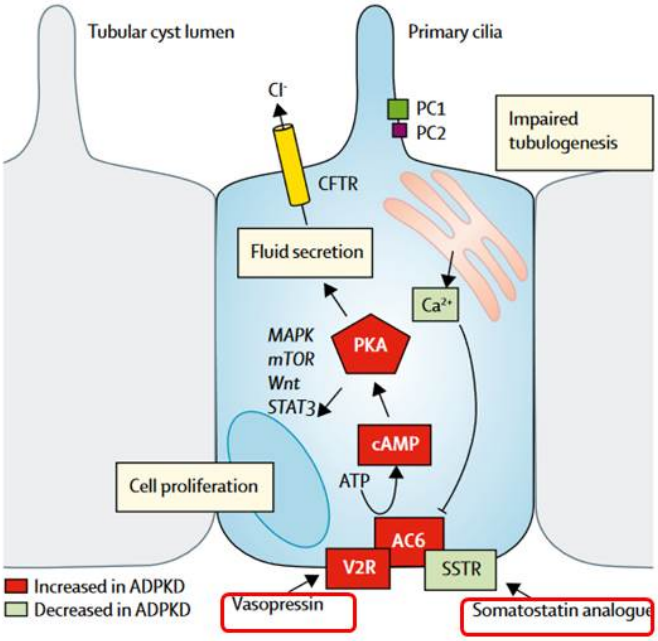
Mutations in *PKD1* or *PKD2* lead to a reduction in intracellular calcium and an increase in cAMP



Cornec-Le Gall E, Alam A, Perrone RD, Lancet, 2019, 393: 920

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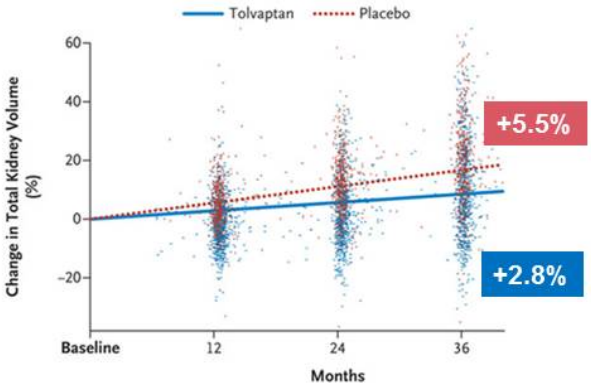
Tolvaptan in early-stage PKD: TEMPO 3:4

18-50 years
TKV > 750 ml
Creatinine clearance (CG) >60ml/min

→

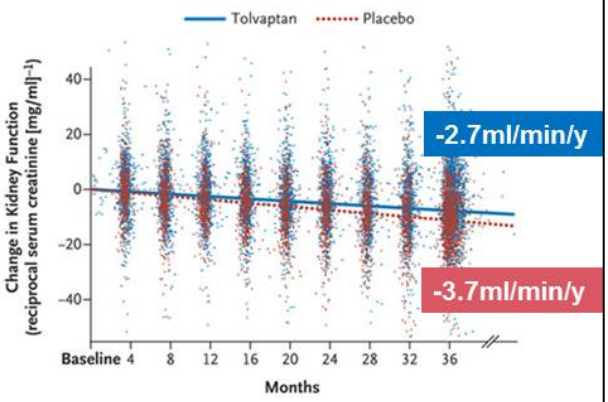
1445 subjects
randomization 2:1
36 months

Total kidney volume



49% reduction in TKV growth

Kidney function



26% reduction in GFR decrease

Torres VE et al.,N Eng J Med 2012;367:2407-18

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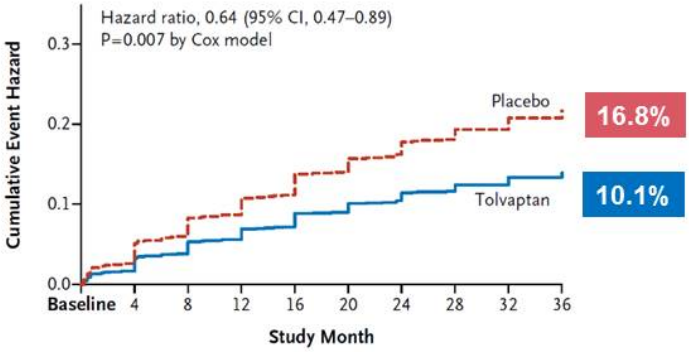
TEMPO 3:4 – Effect on kidney pain

Clinically significant pain (pharmacologic treatment or intervention)
Part of the composite secondary outcome



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

Risk reduction for clinically significant pain: 36% (HR 0.64; 95% CI, 0.48–0.86)

Casteleijn NK et al., Am J Kidney Dis. 2017, 69(2): 210–219.

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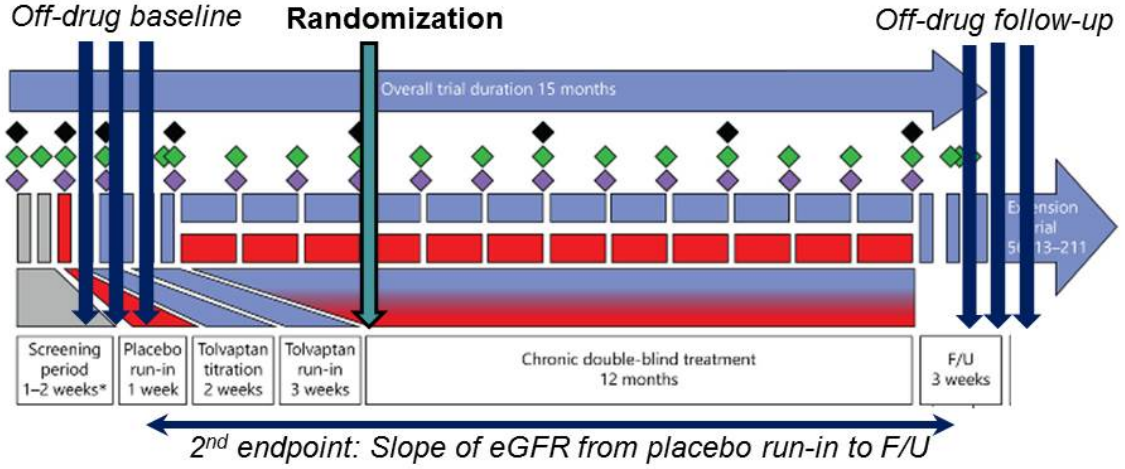
TOLVAPTAN in late-stage ADPKD : REPRISE

- 18-55 y and eGFR 25 to 65 ml/min/1.73m²
- 56-65 y and eGFR 25 to 44 ml/min/1.73m² with eGFR decline >2ml/min/y

→ 1370 subjects randomization 1:1 12 months

Randomized-withdrawal design



2nd endpoint: Slope of eGFR from placebo run-in to F/U

Torres VE et al., Am J Nephrol. 2017 ; 45(3): 257–266

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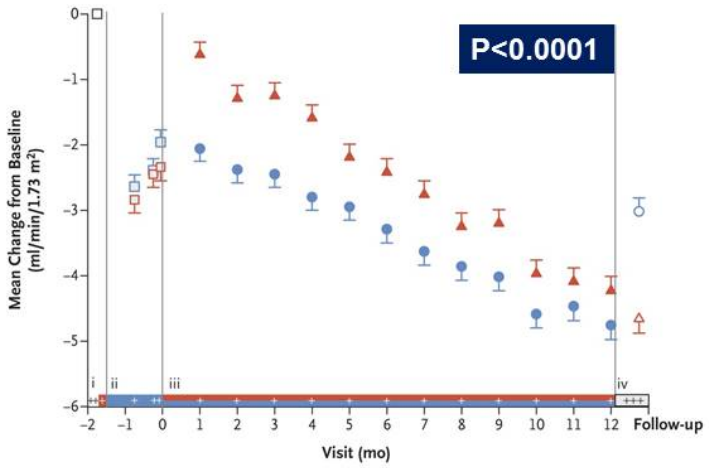
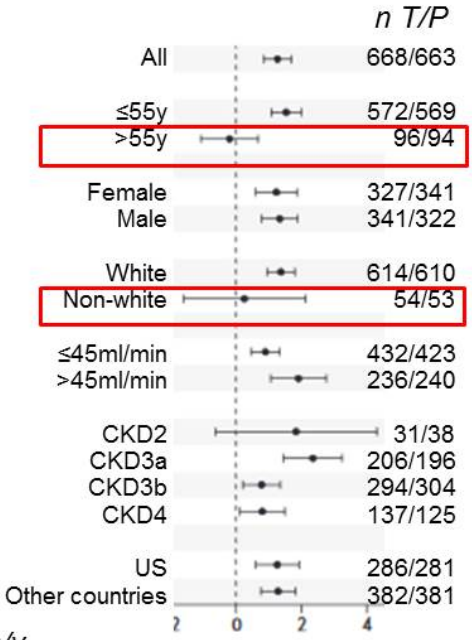
TOLVAPTAN in late-stage ADPKD : REPRISE

***Main primary**: 1 year-change in eGFR*

TOLVAPTAN -2.34 ml/min | **PLACEBO -3.61 ml/min**





***Main secondary**: eGFR slope difference of 1ml/min/y*
(-3.16 vs -4.17 ml/min/y)

Torres VE et al., N Engl J Med. 2017, 377(20):1930-1942

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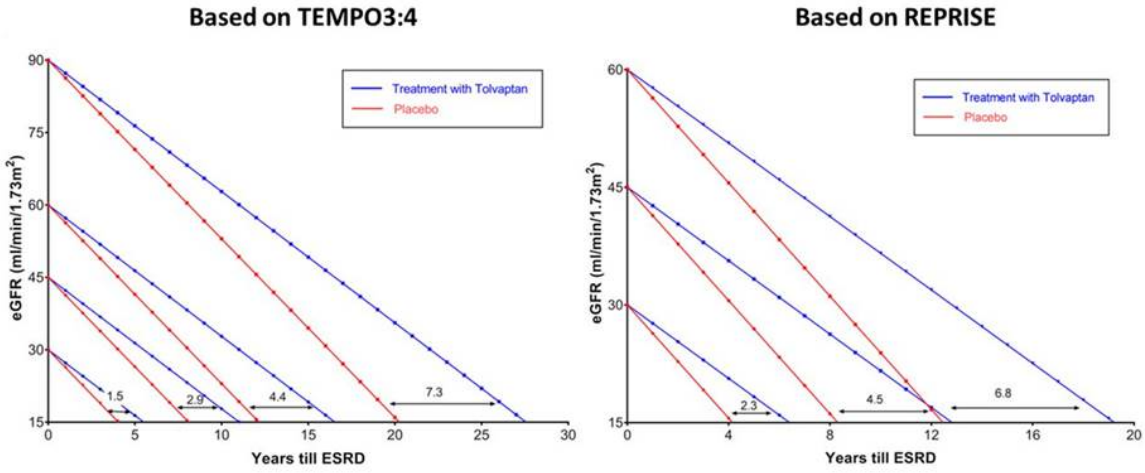
Extrapolation of Tolvaptan benefit on delaying ESRD



Chebib F et al, JASN October 2018, 29: 2458-70

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Tolvaptan – Main adverse events

	TEMPO 3:4	REPRISE Tolvaptan run-in - 1 y double-blind
Thirst	55.3% *(versus 20.5%)*	28.7% - 13% *(versus 1.9%)*
Polyuria	38.3% *(versus 20.5)*	31.7% - 5.3% *(versus 1.6%)*
Nocturia	29.1% *(versus 13%)*	20.5% - 4.7% *(versus 1.8%)*
Discontinuation due to aquaresis-related events	8.3%	4.6% - *2.1%* *(versus 0.1%)*
Fatigue	13.6% *(versus 9.7%)*	4.3% - 6.8% *(versus 3.5%)*
Liver: ALT>3N	4.4% *(versus 1%)*	5.6% *(versus 1.2%)*

Risk factors of discontinuation:
- Younger age
- Preserved renal function
- High fasting urine osmolality

Torres VE et al., N Engl J Med. 2017, 377(20):1930-1942
Torres VE et al.,N Eng J Med 2012;367:2407-18– Devuyst et al, Kidney Int Rep. 2017 Jul 21;2(6):1132-40

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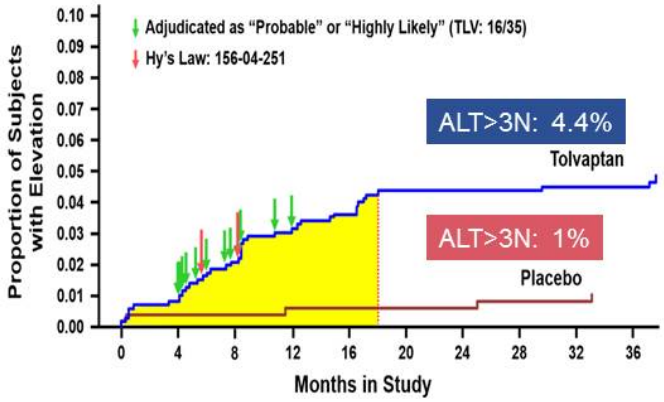
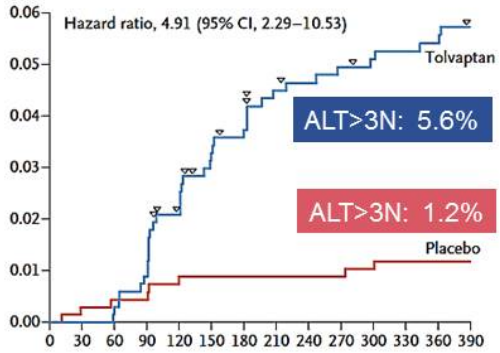
Liver enzyme elevation and Tolvaptan

TEMPO 3:4



REPRISE



Hy's law (ALT>3N and Bili>2N): **2 cases**
(+1 in the open label extension study)

No case meeting **Hy's law**

Watkins et al, Drug Saf., 2015, 38(11):1103-13 - Torres VE et al., N Engl J Med. 2017, 377(20):1930-1942

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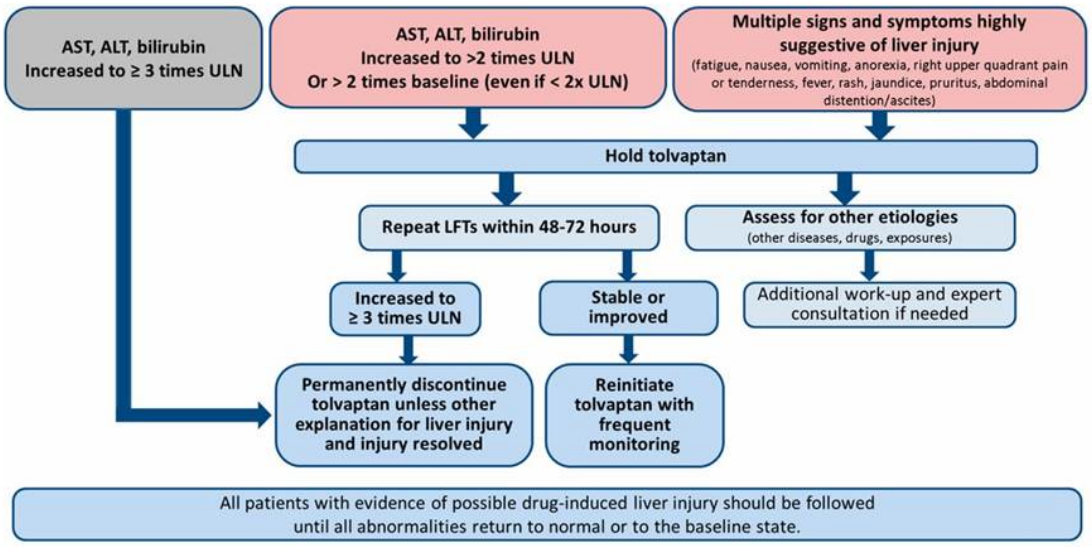
Tolvaptan: Liver enzyme monitoring

REMS (Risk Elevation Mitigation Strategy)
ALAT ASAT Bilirubin week 2 and 4, then monthly until M18, then every 3 months



Chebib F et al., J Am Soc Nephrol. 2018 Oct;29(10):2458-2470

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European Medical Agency Therapeutic indication of Tolvaptan

Tolvaptan 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 4** at initiation of treatment **with evidence of rapidly progressing disease**

Evidence of rapidly progressing disease?

Mayo Imaging classification 1C, 1D, 1E
Or PROPKD High Risk (+ intermediate?)
Or history of decline of eGFR >5ml/min in 1 year, or >2.5ml/min/y during 5y

https://www.ema.europa.eu

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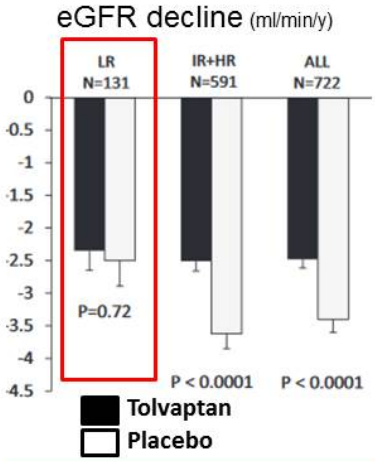
No apparent benefice of Tolvaptan in PROPKD Low-risk patients

	Tolvaptan	Placebo
Low-Risk (n=132)	79	53
Intermediate Risk (n=344)	226	118
High Risk (n=273)	167	106

81.8% classified as Intermediate or High risk

Placebo group	Age at baseline	TKV growth %/y	eGFR decline ml/min/y
Low-Risk	43.6	5.11	2.58
Intermediate	39.5	4.72	3.53
High Risk	**36.3**	**6.75**	**4.11**



No benefit of Tolvaptan on eGFR decline in the PROPKD Low-Risk Group

Cornec-Le Gall E et al., NDT 2018, 33: 645–652

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Somatostatin analogs (SSA) in ADPKD

Study	SSA	eGFR	Nb of patients	TKV	eGFR
ALADIN (Italy)	Octreotide	>40	40/39	TKV growth at 3y: **negative**	eGFR decline at 3y: **negative**
DIPAK1 (NL)	Lanreotide	30-60	154/155	TKV growth at 2.5y: **positive**	eGFR decline 2.5y: **negative**
ALADIN2 (Italy)	Octreotide	15-40	51/49	TKV change at 1y: **positive**	eGFR decline at 3y: **negative**
LIPS (France)	Lanreotide	30-89	*90/90*	*Ongoing*	

Caroli et al., Lancet. 2013, 382:1485-95 - Perico et al., PLoS Med. 2019, 5;16(4)
Meijer et al., JAMA. 2018, 320:2010-2019 - https://clinicaltrials.gov/

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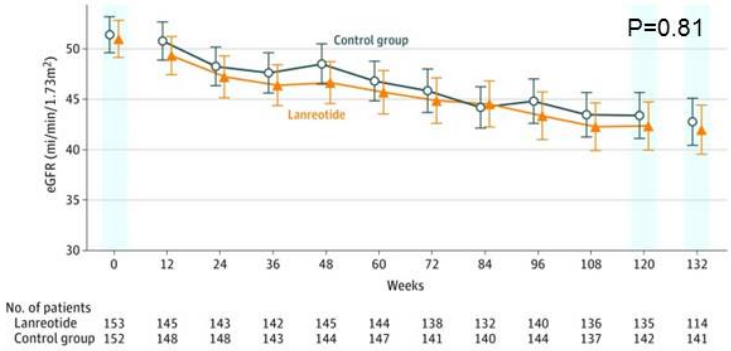
DIPAK: Lanreotide in late stage ADPKD

18-60 years
eGFR 30-60 ml/min/1.73m²

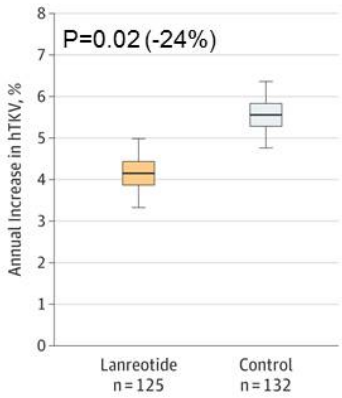
→

Open label study
309 subjects, randomization 1:1
30 months

Primary outcome on treatment: Change in eGFR



Secondary outcome: Change in HtTKV before vs after treatment



Meijer et al, JAMA. 2018, 320:2010-2019

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DIPAK: Tolerability

	Lanreotide (n=153)	**Control** (n=152)
Abnormal feces	91%	6.6%
Abdominal disconfort	79%	20%
Fatigue	42%	21%
Injection site disconfort	32%	0.7%
Nausea	29%	4.6%
Dizziness	20%	7.9%
Flatulence	18%	0%
Bradycardia	15%	10.7%
Chest pain	7.8%	1.3%
HbA1c increased	5.2%	0.7%
Serious adverse event	28% *(2.6% withdrawal)*	12.5% *(1.3% withdrawal)*
Hepatic cyst infection	5.2%	0%

Meijer et al, JAMA. 2018, 320:2010-2019

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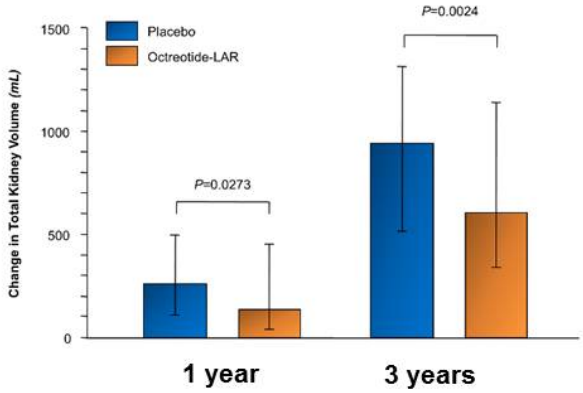
ALADIN2: Octreotide in late stage ADPKD

>18 years
eGFR 15-40 ml/min/1.73m²

→

Placebo-control
100 subjects, randomization 1:1
36 months

Primary outcome : change of TKV



Perico et al., PLoS Med. 2019, 5;16(4)

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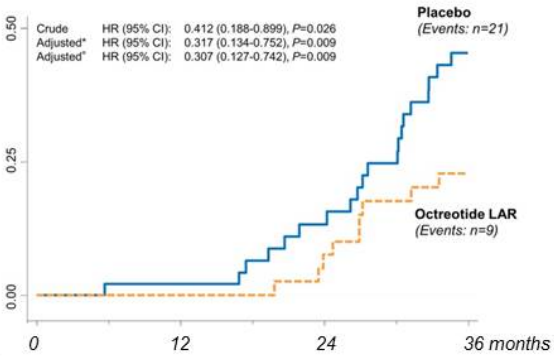
ALADIN2: Octreotide in late stage ADPKD

Co-primary outcome: eGFR decline during follow-up

	Placebo	Octreotide-LAR
Baseline eGFR	25.8 ml/min/1.73m²	27.9 ml/min/1.73m²
eGFR decline	- 3.97 ml/min/y	- 3.76 ml/min/y

Secondary composite endpoint of doubling SCr or ESRD



Patients at risk	0	12	24	36 months
Placebo	49	46	38	20
Octreotide-LAR	51	45	37	23

Perico et al., PLoS Med. 2019, 5;16(4)

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Ongoing Phase 3 trials

(ongoing or starting in 2020)

Study name	PA-ADPKD-301	STAGED-PKD	FALCON	KD019-2011	METROPOLIS
Class	V2RA	GSC inhibitor	Nrf2 activator (NF-kB inhibitor)	EGFR inhibitor	Stimulation of AMPk
Molecule	Lixivaptan (palladio)	Venglustat (Sanofi)	Bardoxolone (Reata)	Tesavatinib (Kadmon)	Metformin (Bari, Italy)
Number of participants	1200 (2:1)	560 (1:1:1)	300 (1:1)	100 (1:1)	150 (1:1)
Control group	Placebo	Placebo	Placebo	Placebo	Tolvaptan
Inclusion	18-60 y eGFR>30 BMI 18-35 Min Osm >300	18-50 y eGFR 45-90 Mayo 1C/D/E	18-70 y eGFR 30-90 (30-44 if >56y)	18-60y eGFR>25 Mayo 1C/D/E	18-50 y eGFR>45 *PKD1* trunc
Primary outcome(s)	eGFR at 1y	TKV at 18m eGFR at 2y	eGFR at 1y Safety	TKV at 1y TKV at 18m TKV at 2y	eGFR at 2y
Duration	1 year	2 years	2 years	2 years	2 years

https://clinicaltrials.gov

Cornec-Le Gall E, Alam A, Perrone RD, Lancet, 2019, 393: 920

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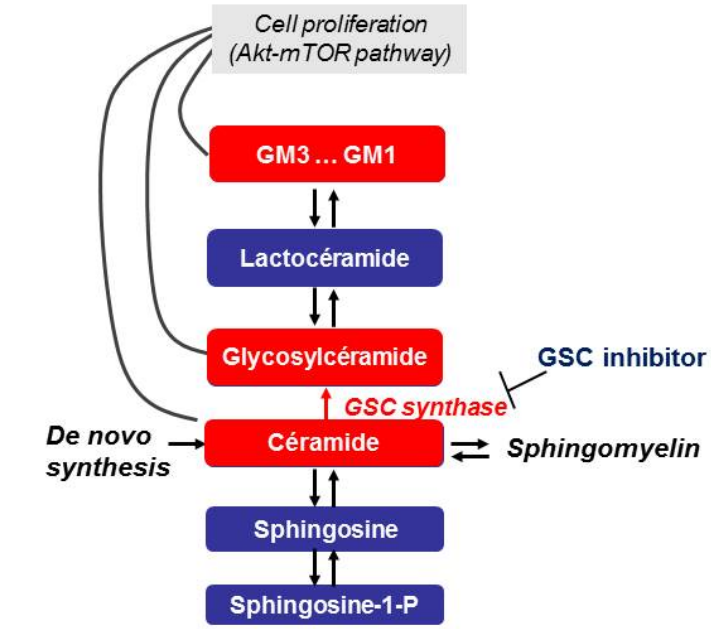
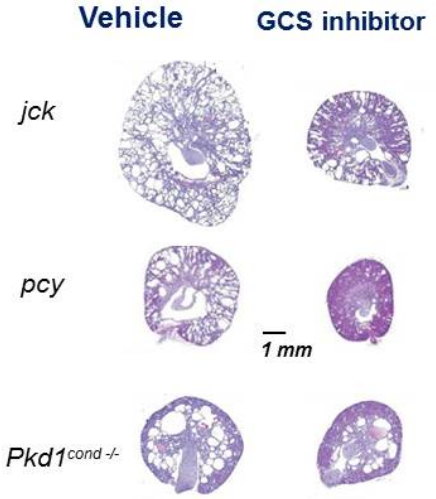
Emerging treatments: Venglustat





Increased in PKD

Natoli et al., Nature Med 2010, 16:788-792

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Take-Home Message

- Importance of blood pressure monitoring, preferably using RAAS blockers
- Tolvaptan is effective in reducing kidney growth and preventing decline of renal function and presumably delaying the need for renal replacement therapy. Selection of rapidely progressive patients can be made based on age, eGFR, HtTKV, and genetic information.
- Trials testing somatostatin analogs did not demonstrate a significant effect on reducing eGFR decline (to date), and showed that SSA are associated with higher incidence of adverse events.
- Other molecules are under clinical or preclinical trials. Stay tunned!

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