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Optimal Management of ADPKD Patients Prior to Dialysis

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December 7, 2018

Potential conflicts of interest declaration

The content of the following speech is the result of efforts to achieve the maximum degree of impartiality and independence.

As a speaker, I wish to point out that there are **personal connections** to companies whose products are of interest within the context of the following speech. The companies concerned and connections are listed below:

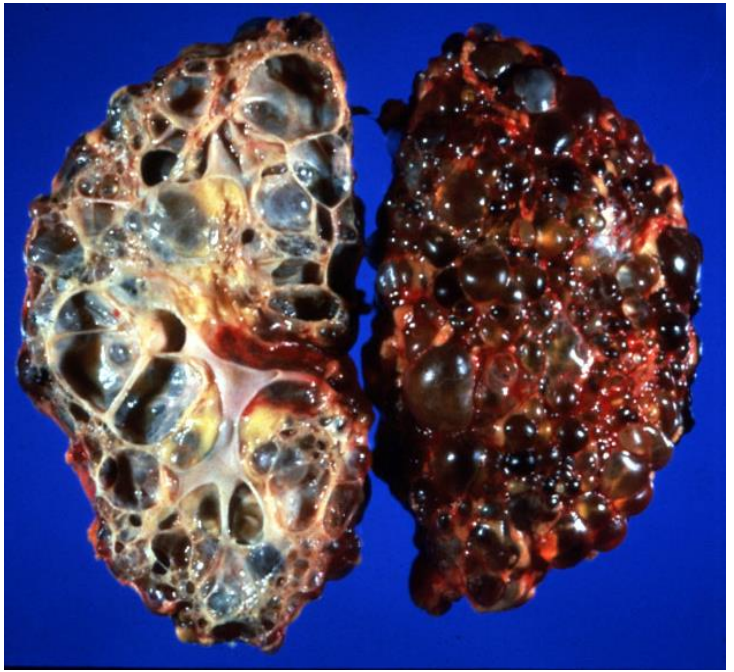
Companies	Connections
Otsuka, US Dept. of Defense, Kadmon, Sanofi-Genzyme	Research Support
Otsuka, Sanofi-Genzyme, Palladiobio, Vertex	Consultant
Otsuka Canada, Otsuka Spain	Speaker

Goals and Objectives

- Review clinical issues and management at stage 4 CKD
  - progressive loss of GFR
  - enlarged total kidney volume (TKV)
- Discuss current pharmacological therapies including tolvaptan, lanreotide and octreotide
- Discuss interventions to reduce cyst/kidney size and pain including cyst aspiration/sclerosis, fenestration, embolization, nephrectomy

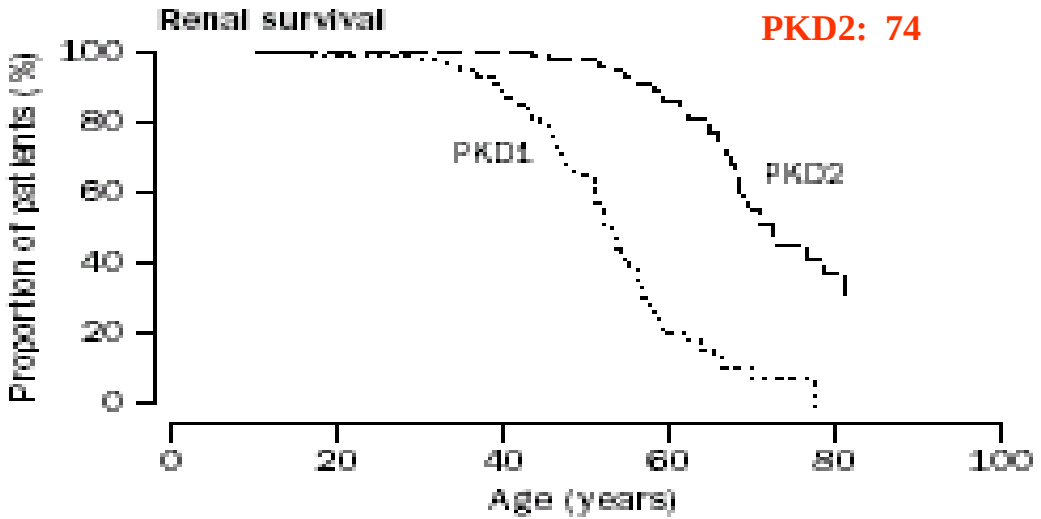
Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- Hereditary systemic disorder
- Bilateral kidney cysts
- Progressive decline in GFR leading to kidney failure in ~50% of patients by 6th decade
- Extrarenal manifestations
  - Cysts
  - Extracellular matrix abnormalities
- All of the issues associated with chronic kidney disease
  - Anemia, metabolic bone disease, nutrition, increased CV risk



Progressive Loss of Kidney Function

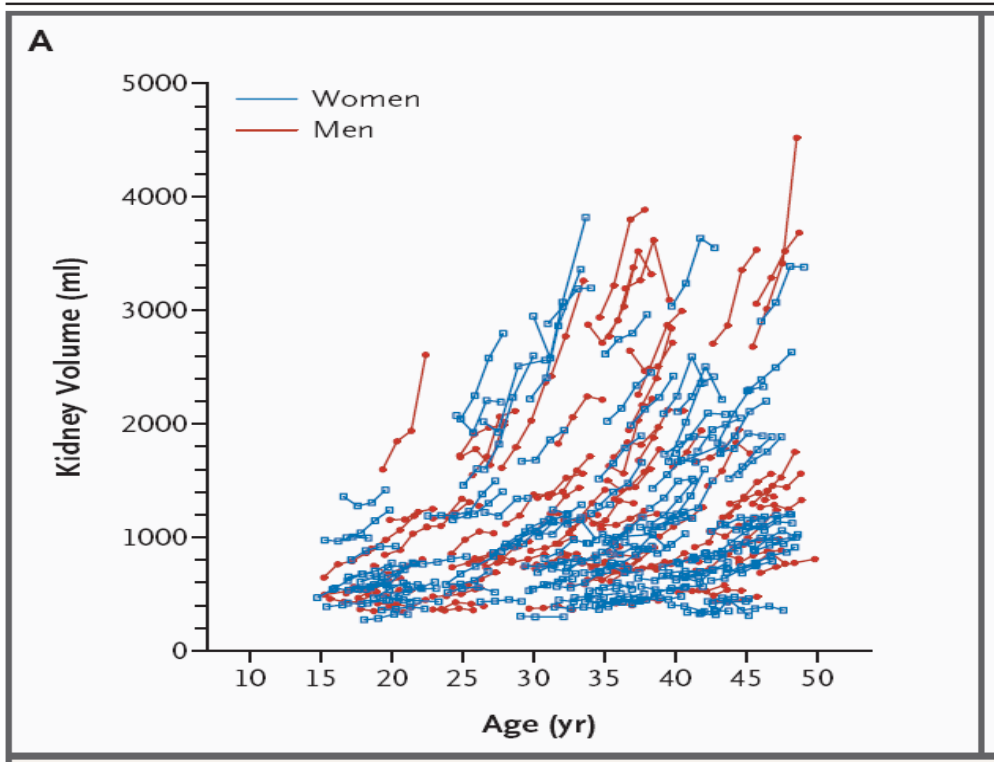
Median age of ESRD:
PKD1: 54
PKD2: 74



Hateboer et al, THE LANCET 353:103, 1999

Kidney Manifestations of ADPKD

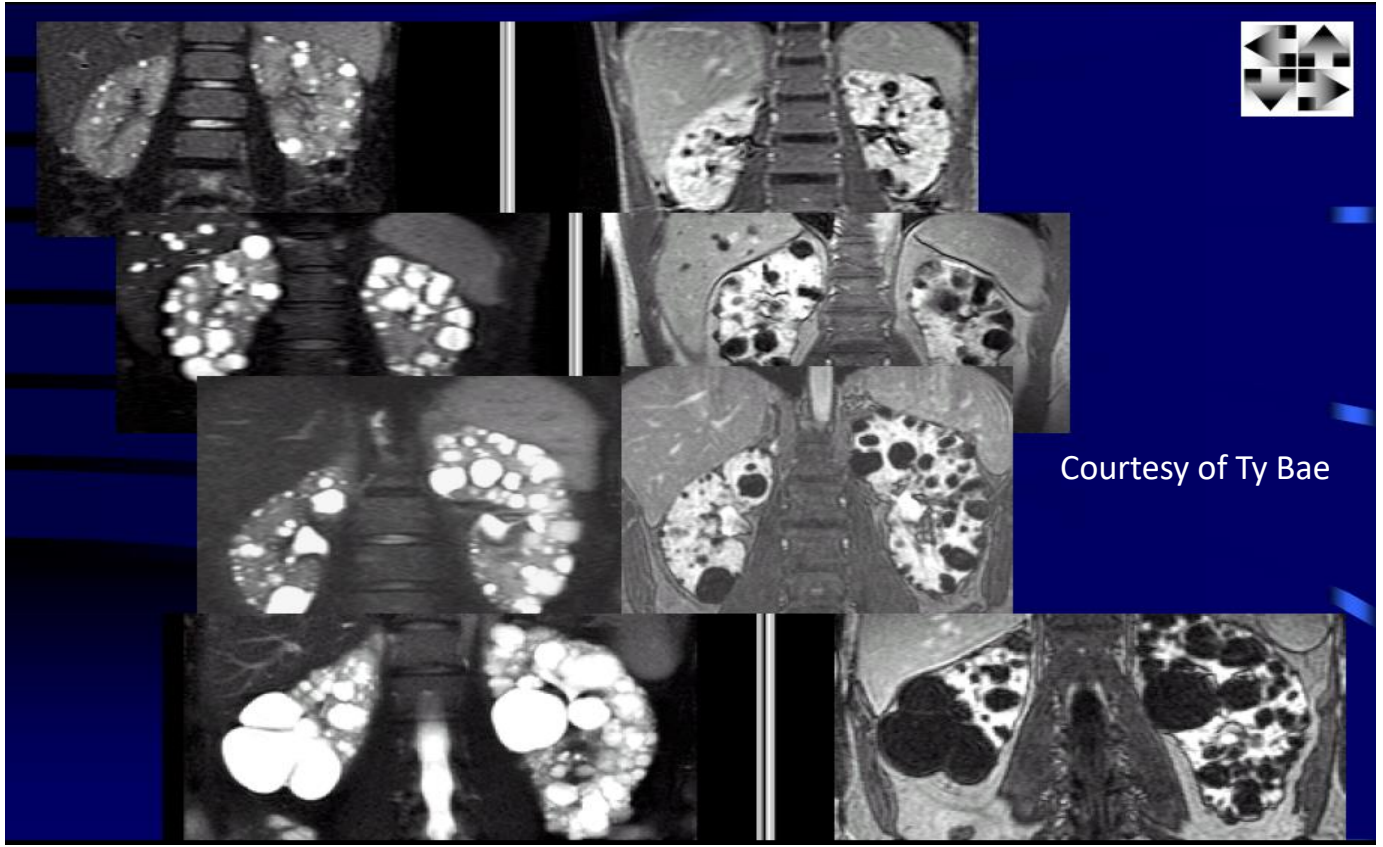
- Cysts throughout both kidneys
- Inexorable increase in total kidney volume
  - Acute and chronic pain, palpable kidneys
  - Progressive loss of kidney function
  - Hypertension
  - Intermittent hematuria
  - Cyst infection; pyelonephritis
  - Nephrolithiasis
  - Impaired concentrating ability



GFR declined 4.3 ml/min/1.73 m^2 only in those with TKV>1500 ml

CRISP Cohort

NEJM 354:2122-30, 2006


Courtesy of Ty Bae

Rates of GFR decline 3-6 ml/min/1.73 m^2/year

Study	Starting GFR (ml/min/1.73m^2)	GFR decline (ml/min/1.73m^2/yr)
MDRD Study A	25 - 55	-5.8/5.9
MDRD Study B	13 - 24	-4/4.9
HALT PKD Study A	> 60	-2.9/3.0
HALT PKD Study B	25 – 60	-3.91/3.87
TEMPO 3:4 control	> 60 (Ccr)	-3.7
ALADIN1 control	> 40	-4.95
DIPAK1 control	30-60	-3.46
CRISP 1	> 70	-4.3 (TKV>1500)
REPRISE	25-65	-3.61
SUISSE control	> 70 (Ccr)	-2.3
Everolimus (Walz)	30 - 89	-3.85

Estimated Time to ESRD From CKD4

- ESRD: eGFR $\leq$ 15 ml/min/1.73 m^2
- Starting at eGFR 30 ml/min/1.73 m^2:
  - Rate -5 ml/min/1.73 m^2/year: 3 years
  - Rate -3 ml/min/1.73 m^2/year: 5 years

Optimal Management in CKD4

- Optimize cardiovascular and overall health
- Prepare for kidney replacement therapy
- Manage Complications
- Preferred modality for ESRD would be pre-emptive live donor transplant-appropriate preparation in anticipation of such

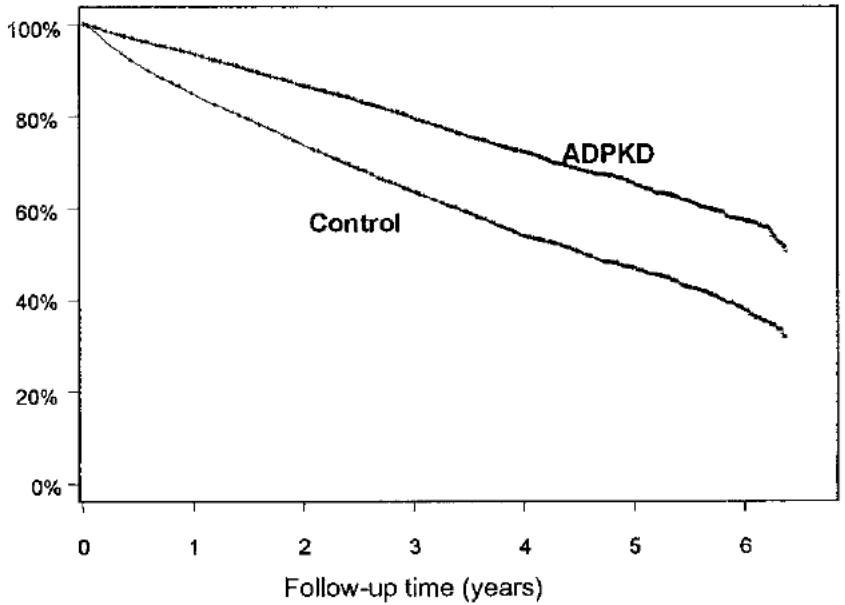


Fig 1. ESRD survival of ADPKD and nondiabetic control patients. Follow-up of 9,435 ADPKD patients and nondiabetic controls matched for age, gender, and year of ESRD continued until death or end of study. Survival in ADPKD significantly exceeded that in nondiabetic controls ($P = 0.0001$, log-rank test).

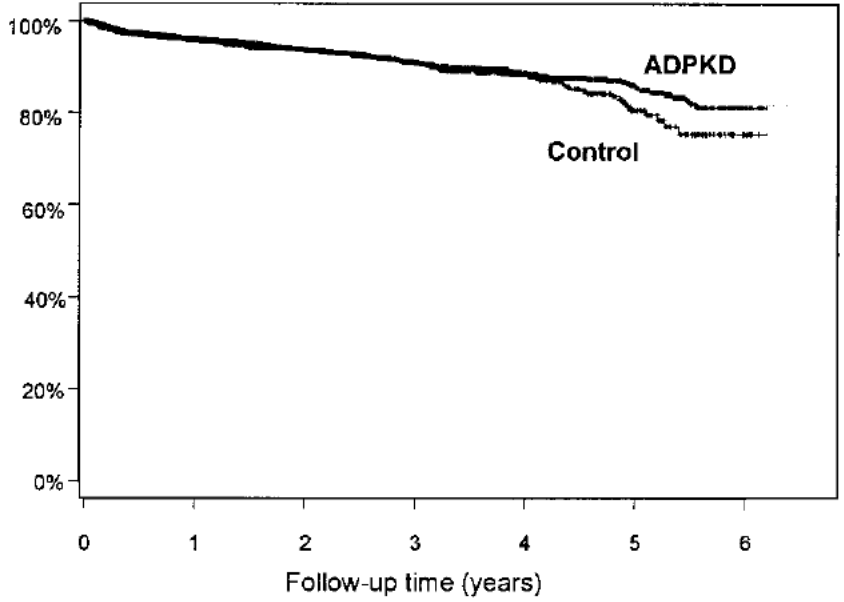


Fig 2. ESRD survival after transplant. Follow-up after transplant of 1,554 nondiabetic control and 3,170 ADPKD patients continued until death or end of study. Transplant status was based on intent to treat: When transplanted, a person is considered as a transplant patient until death or end of follow-up. Survival after transplant did not significantly differ between ADPKD and nondiabetic controls ($P = 0.23$, log-rank test).

AJKD 38: 774, 2001

General management of ADPKD

- Blood pressure control (Goal ≤ 110/75 mmHg if 18-50 y.o. and eGFR > 60 ml/min; otherwise ≤ 130/85 mmHg)
- Moderate sodium restriction (2.3- 3 g/day)
- Increased hydration (UOsm ≤ 280 mOsm/Kg) ***With caution!***
- Maintain normal BMI; moderate caloric restriction
- Cholesterol: LDL<100, HDL>50mg/dL ; low threshold for statins

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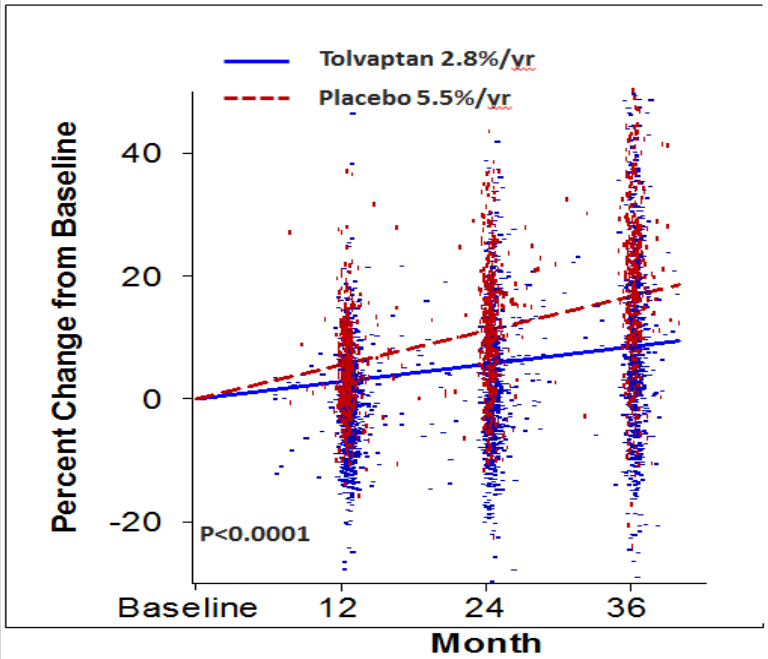
- Moderate protein and phosphorus restriction
- Maintain serum bicarbonate ≥ 22 mEq/L

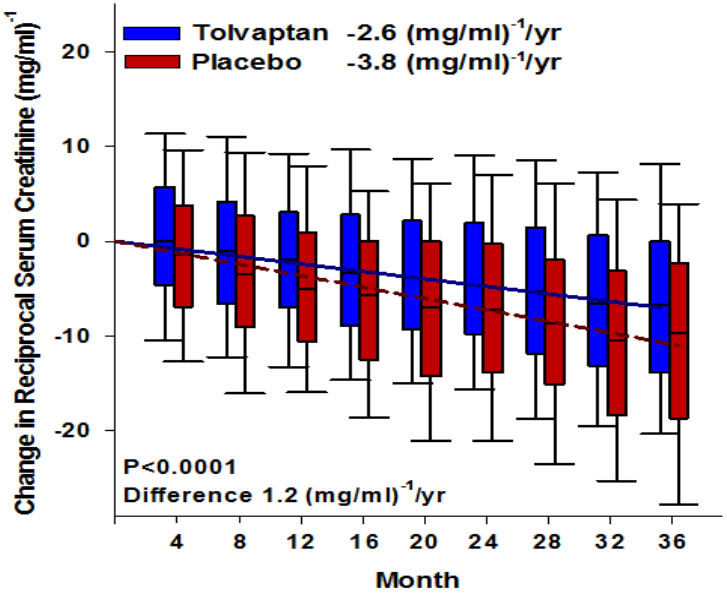
Chebib and Torres, JASN 2018

Can We Slow GFR Progression?

- Tolvaptan (Jinarc): yes; also slows TKV expansion
- Octreotide: maybe; slows TKV expansion year 1
- Lanreotide: no; slows TKV expansion

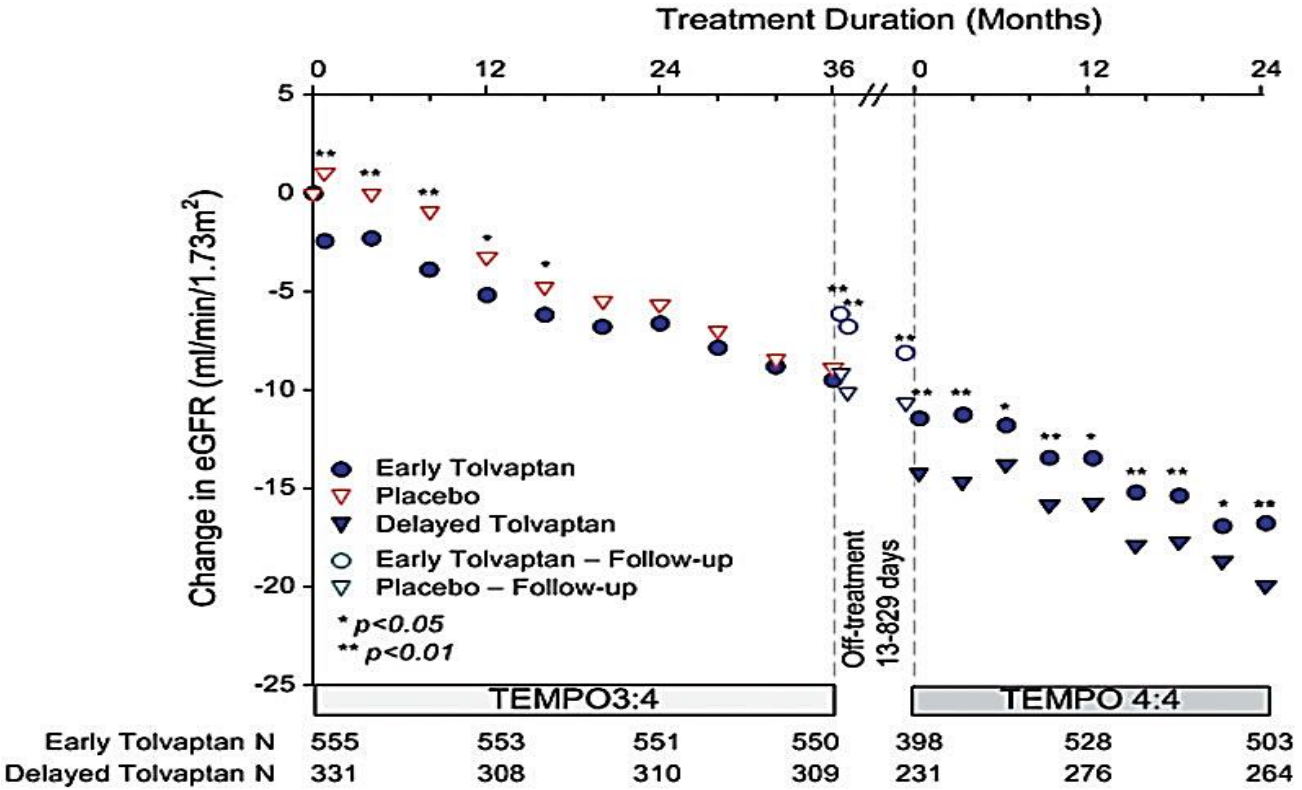
TEMPO 3:4 Results: Percent Change in TKV and Change in 1/Serum Creatinine: entry Ccr ≥ 60ml/min





Torres et al NEJM 367: 2407, 2012

Change in eGFR From TEMPO 3:4 baseline to End of TEMPO 4:4—Key Secondary Endpoint



Torres et al NDT 32:1262, 2017.

Objectives of the REPRISE Study

To ascertain:

The effect of tolvaptan to slow eGFR decline

- Its overall and hepatic safety with monthly monitoring
- Age: 18 to 55 years eGFR: ≥25 and ≤65 mL/min/1.73m^2
- Age: 56 to 65 years eGFR: ≥25 and ≤44 mL/min/1.73 m^2
  - (Past evidence of decline of >2.0 mL/min/1.73 m^2 per year)

Torres et al. NEJM 377:1930-1942, 2017.

REPRISE Study Population

Demographic Characteristic	Tolvaptan (N=683)	Placebo (N=687)
Age, years *	47 ± 8	47 ± 8
Male, %	51	49
Caucasian, %	92	92
Hypertension, %	93	93
ACEIs and/or ARBs, %	87	85
eGFR (CKD-EPI), ml/min/1.73m² *	41 ± 11	41 ± 11
CKD 2, %	5	6
CKD 3a, %	31	29
CKD 3b, %	44	46
CKD 4, %	20	19

* mean ± SD

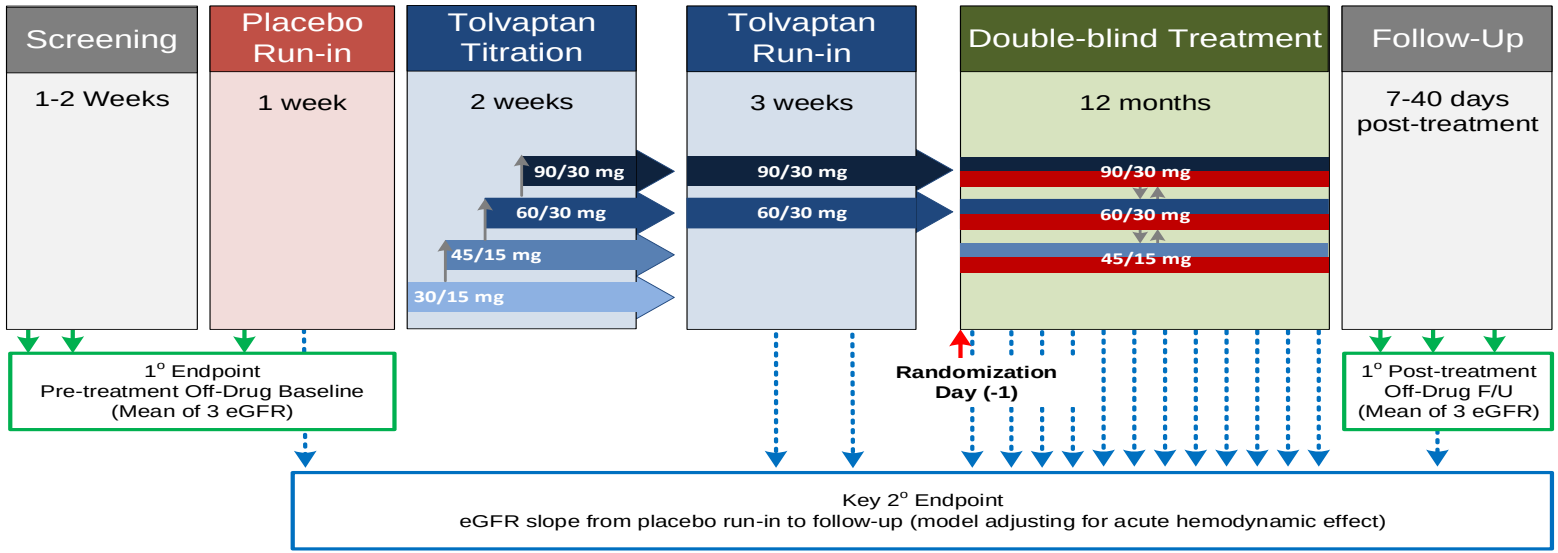
TEMPO 3:4 patients were younger (age 39 y) and in earlier CKD stages (eGFR 81)

NEJM Nov 4, 2017 (online)

Torres et al. NEJM 377:1930-1942, 2017

TRIAL DESIGN AND ENDPOINTS

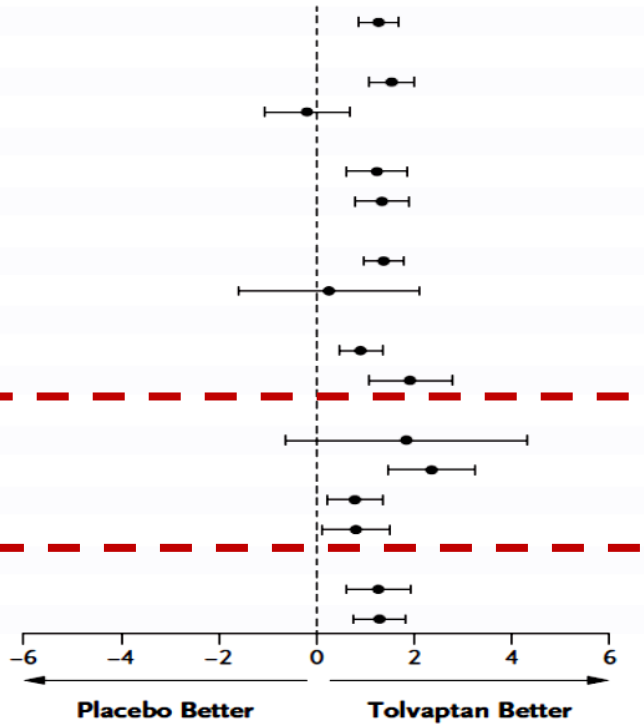
Randomized-withdrawal, Placebo-controlled, Double-blind



Torres et al. NEJM 377:1930-1942, 2017

A Subgroup Analyses

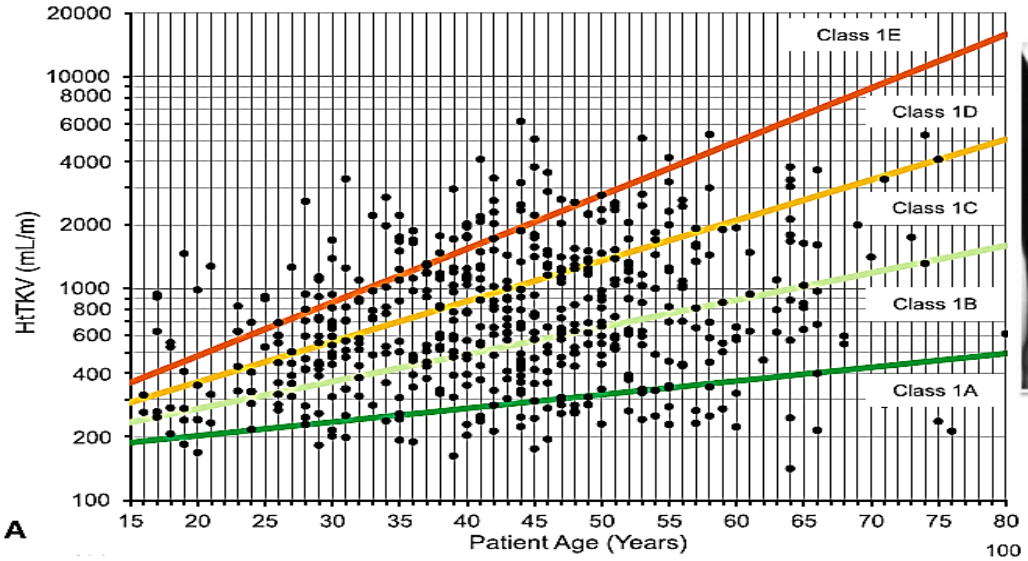
Subgroup	Tolvaptan	Placebo	Mean Estimated GFR Change (95% CI)	Tolvaptan	Placebo	Difference	P Value
	no. of patients			*ml/min/1.73 m²*			
All patients	668	663		−2.34	−3.61	1.27	<0.001
Age							
≤55 yr	572	569		−3.07	−4.60	1.54	<0.001
>55 yr	96	94		−2.54	−2.34	−0.20	0.65
Sex							
Female	327	341		−2.89	−4.13	1.23	<0.001
Male	341	322		−3.09	−4.43	1.34	<0.001
Race							
White	614	610		−2.97	−4.34	1.37	<0.001
Nonwhite	54	53		−3.29	−3.54	0.25	0.79
Baseline estimated GFR							
≤45 ml/min/1.73 m²	432	423		−3.45	−4.35	0.90	<0.001
>45 ml/min/1.73 m²	236	240		−2.20	−4.11	1.91	<0.001
Chronic kidney disease stage							
2	31	38		−2.81	−4.65	1.84	0.14
3a	206	196		−2.13	−4.49	2.36	<0.001
3b	294	304		−3.20	−3.99	0.78	0.008
4	137	125		−3.80	−4.60	0.81	0.02
Geographic region							
United States	286	282		−2.88	−4.14	1.26	<0.001
Other	382	381		−3.09	−4.38	1.29	<0.001



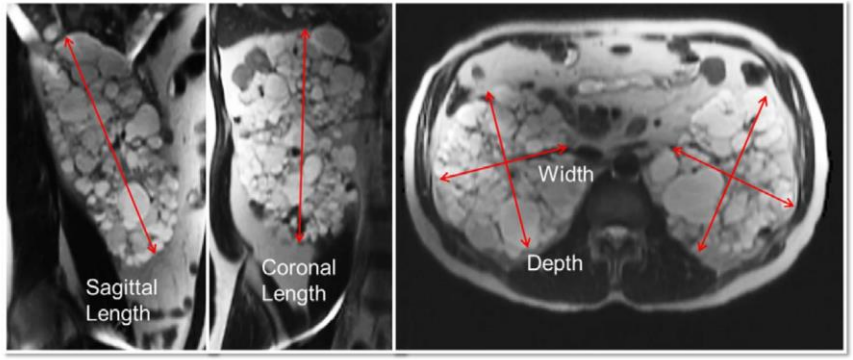
REPRISE Torres et al. NEJM 377:1930-1942, 2017.

What is Risk of Rapidly Progressing ADPKD? (Not defined by regulators in US and Europe)

- **Large kidneys at a young age**
  - **Mayo Imaging classification (1C, 1D, and 1E) is a predictive biomarker, in secondary analyses of HALT Study A and TEMPO 3:4**
  - Average kidney length greater than 16.5 cm; age less than 45
  - TEMPO 3:4 criteria: TKV>750, 18-50, cCr >60
- **REPRISE criteria**
  - 18 to 55 years eGFR: ≥25 and ≤65 mL/min/1.73m^2
  - Not clear if high risk 56 to 65 years eGFR: ≥25 and ≤44 mL/min/1.73 m^2; Past evidence of decline of >2.0 mL/min/1.73 m^2 per year
- **DNA Mutation analysis**
  - Genotype: *PKD1* vs *PKD2;* protein truncating or not
  - PROPKD score $\geq$ 6
  - ESRD in first degree relative before age 55
  - Male gender, pain issues, kidney bleeds



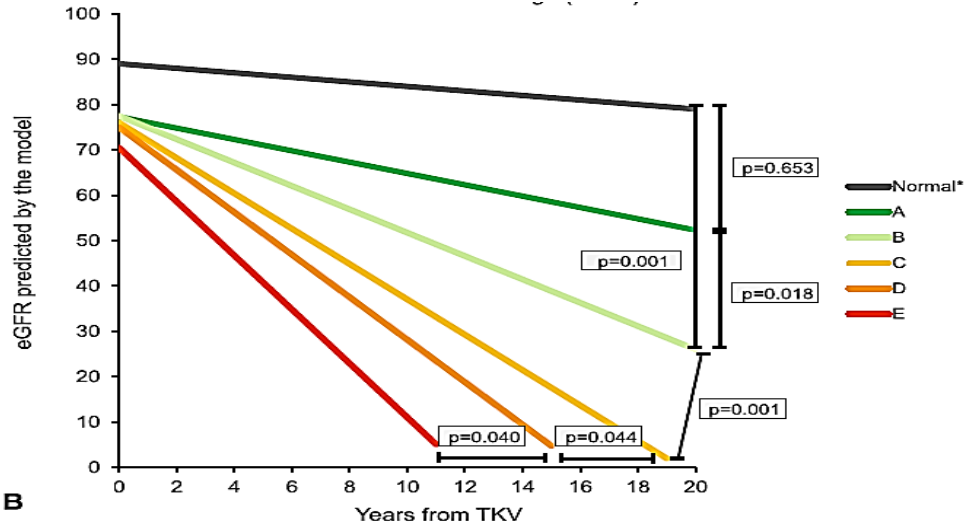
Irazabal et al JASN, 2015



Only applies to "typical" ADPKD

Rate of htTKV expansion from theoretical starting htTKV of 150 ml/m:

≤1.5%	**(1A)**
>1.5%–3%	**(1B)**
>3%–4.5%	**(1C)**
>4.5%–6%	**(1D)**
>6%	**(1E)**



Nephrol Dial Transplant (2016) 0: 1–12
doi: 10.1093/ndt/gfv456

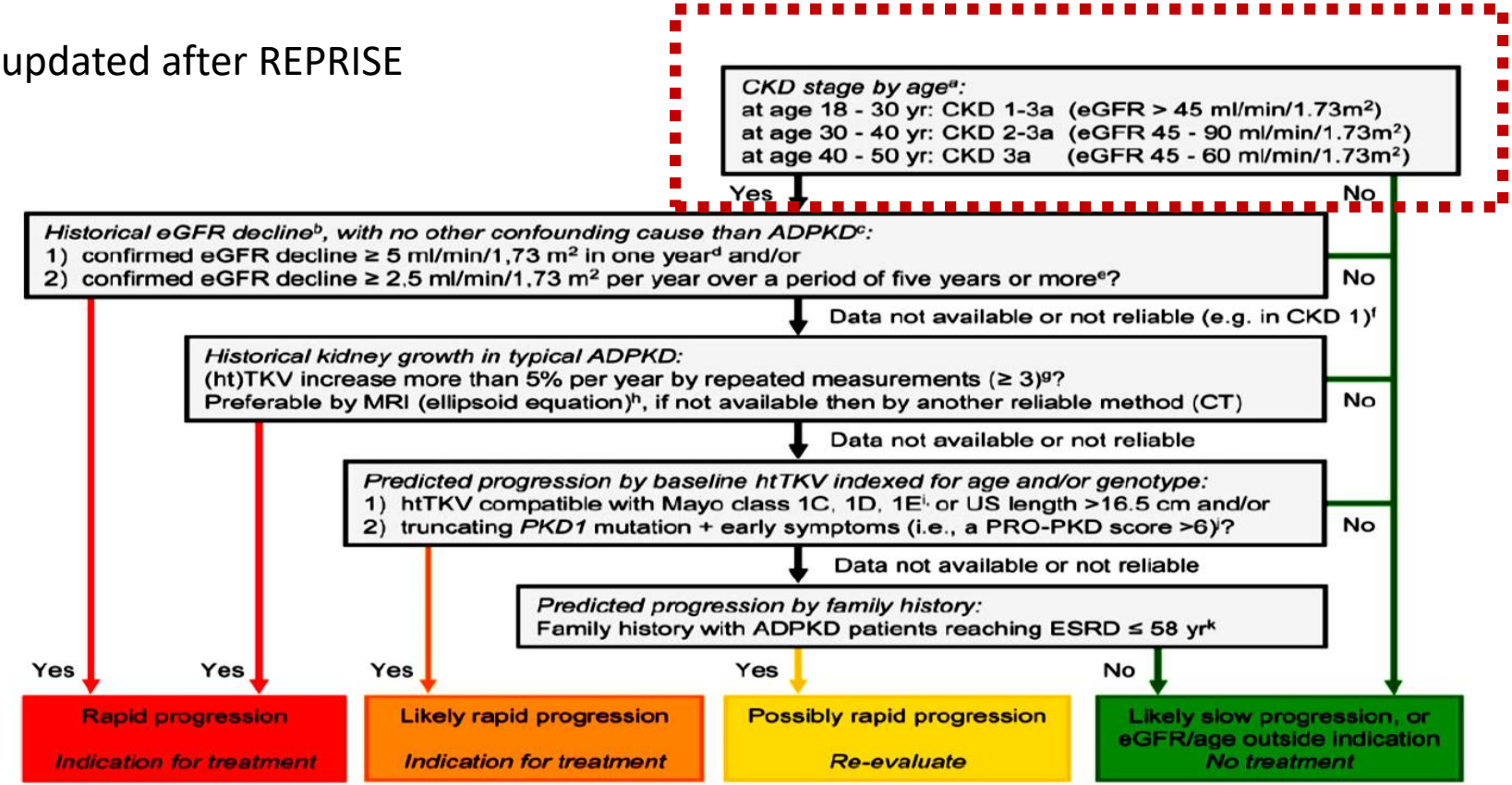
ndt
Nephrology Dialysis Transplantation

NDT Perspectives

Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice

Ron T. Gansevoort[1], Mustafa Arici[2], Thomas Benzing[3], Henrik Birn[4,5], Giovambattista Capasso[6], Adrian Covic[7], Olivier Devuyst[8,9], Christiane Drechsler[10], Kai-Uwe Eckardt[11], Francesco Emma[12], Bertrand Knebelmann[13], Yannick Le Meur[14], Ziad A. Massy[15,16,17], Albert C.M. Ong[18], Alberto Ortiz[19], Franz Schaefer[20], Roser Torra[21,22], Raymond Vanholder[23], Andrzej Więcek[24], Carmine Zoccali[25] and Wim Van Biesen[23]

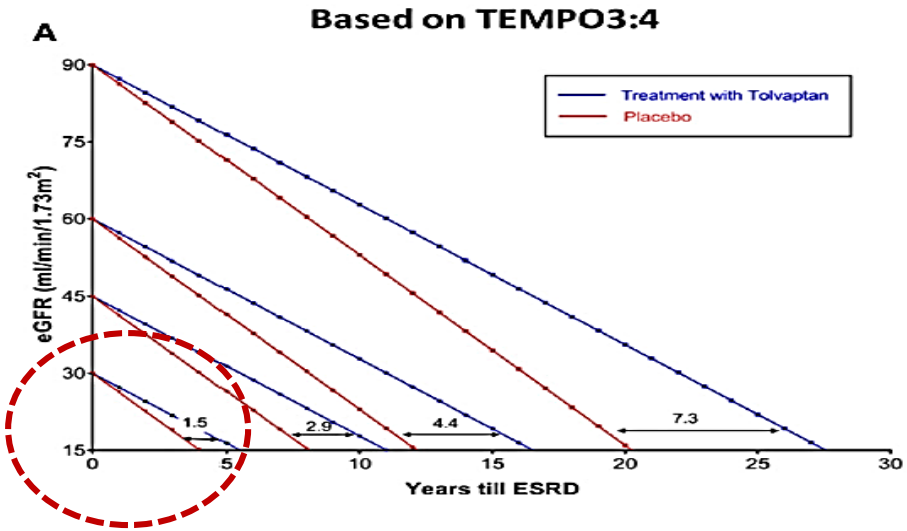
Not updated after REPRISE

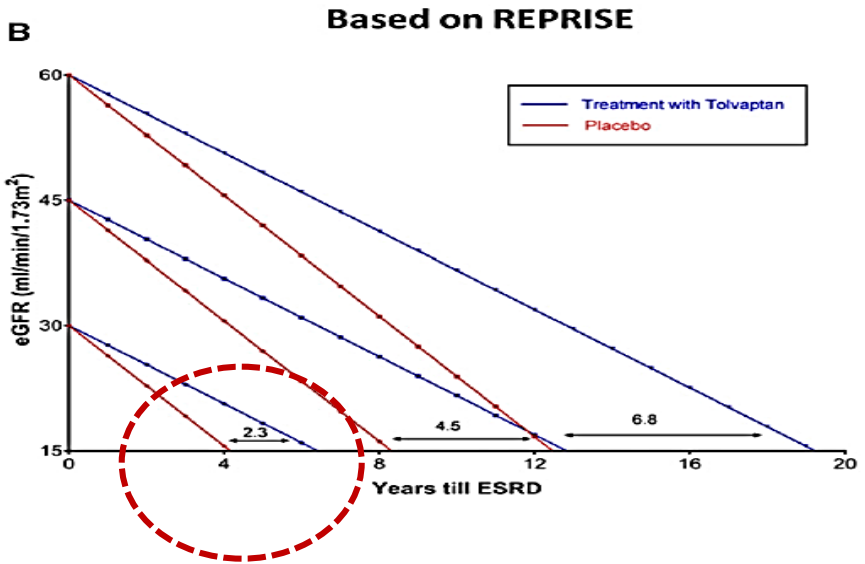


Jinarc Approved for CKD4 in ADPKD

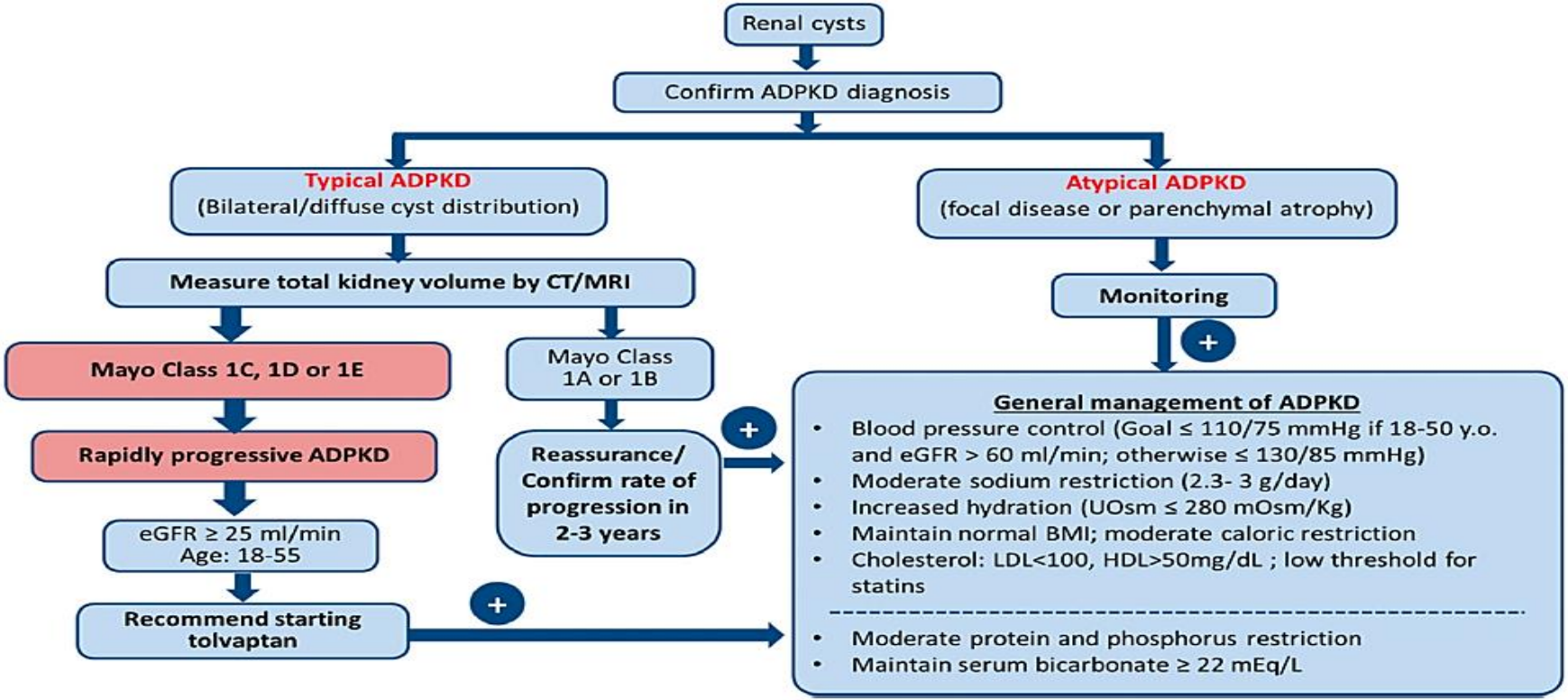
- On 28 June 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted an extension to the existing indication as follows:
  - "Jinarc is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease (see section 5.1)."
- 2 August, 2018, European Commission has approved an extension of indication for JINARC (tolvaptan) to include adult patients with CKD stage 4 ADPKD
- Monthly monitoring of liver function tests for 18 months; every 3 months thereafter

Theoretical Benefit from Tolvaptan



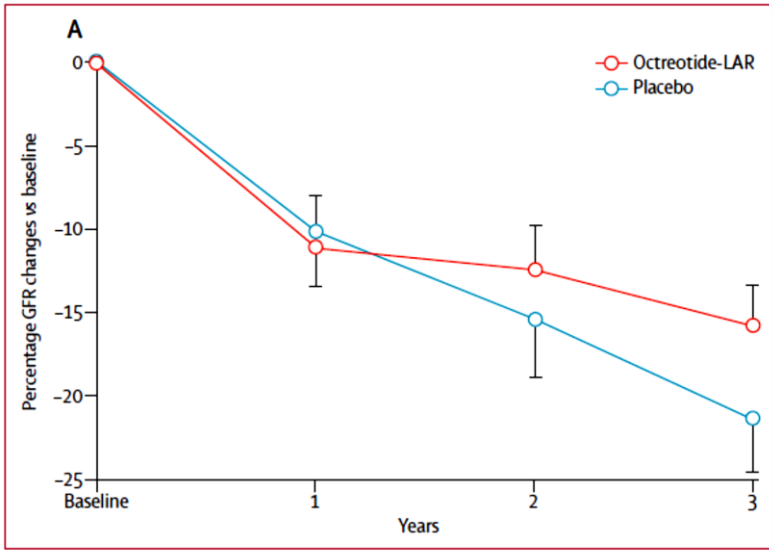


Consensus Criteria to Use Tolvaptan in the US



Chebib and Torres. JASN, 2018

ALADIN1



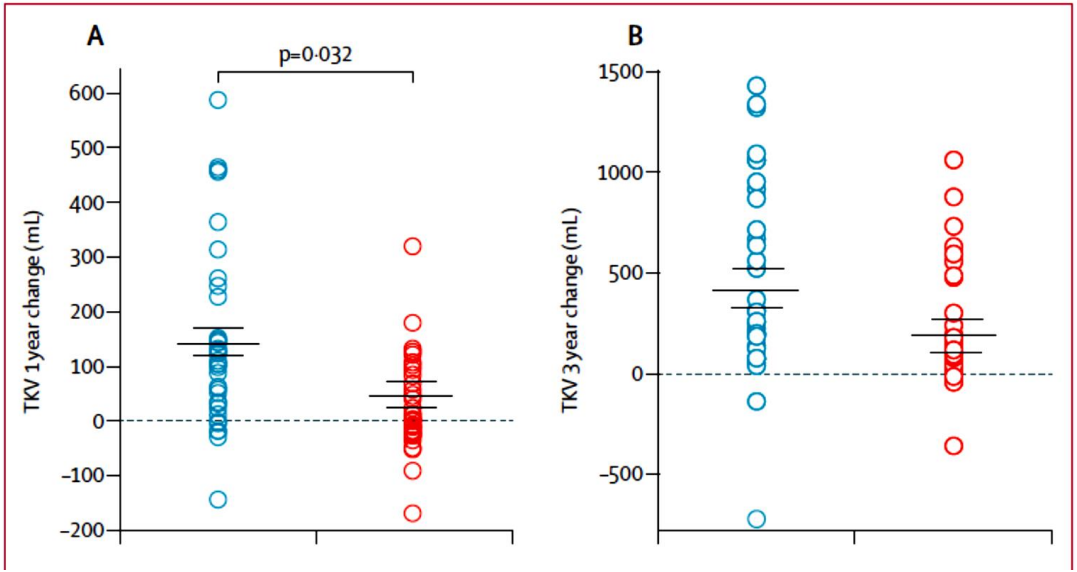
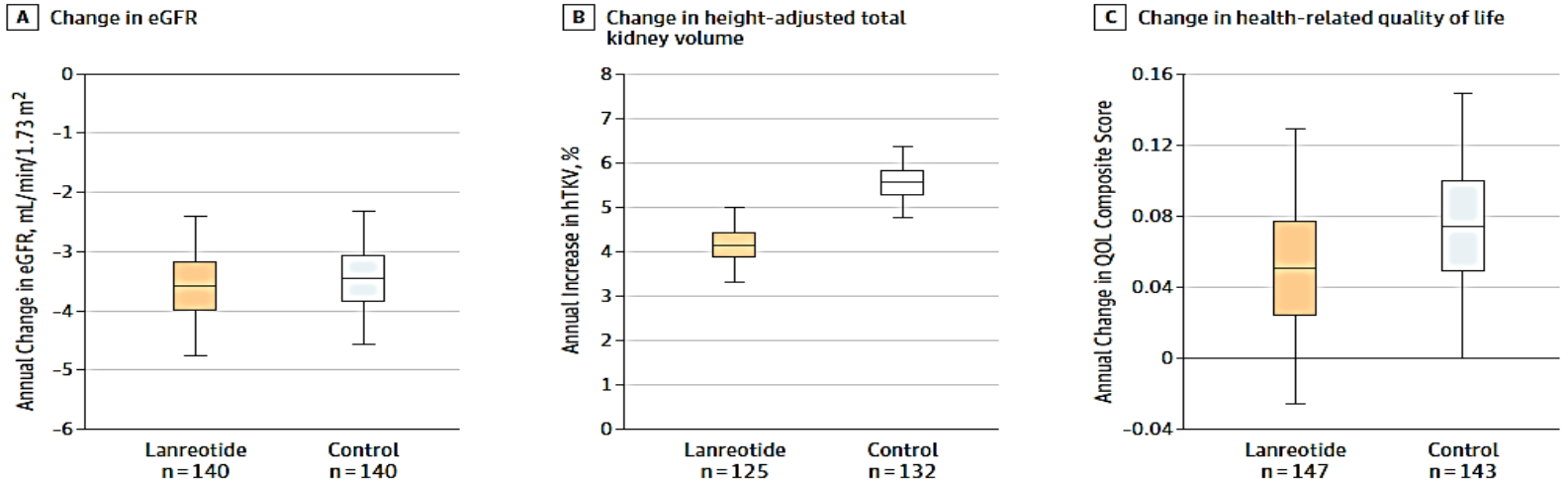


Figure 5: **Effect of placebo or Octreotide-LAR treatment on kidney function**

Lancet 382:1485, 2013, NCT00309283

Figure 4. Effect of Lanreotide and Standard Care Compared With Standard Care Only on Secondary Outcomes



A, Change in kidney function, calculated as change in estimated glomerular filtration rate (eGFR) measured 12 weeks after the end of treatment visit (ie, at the posttreatment visit) compared with the pretreatment value (difference, −0.13 mL/min/1.73 m^2 per year [95% CI, −1.76 to 1.50]; $P = .88$). B, Change in height-adjusted total kidney volume (htTKV; difference, −1.33% per year [95% CI, −2.41 to −0.24]; $P = .02$). C, Change in health-related quality of life (QOL; difference −0.03 units per year [95% CI, −0.13 to 0.08]; $P = .67$). QOL is measured on a scale ranging from 1 (not bothered) to 5 (extremely bothered). For all panels, boxplots show predicted mean and 25th and 75th percentile, and lower and upper ends of the error bars show predicted 2.5th and 97.5th percentile, respectively, as derived from the mixed model analyses.

DIPAK 1, JAMA, 2018

Measures to Address Kidney/Cyst Size

- Chronic pain
- Volume effects
  - Single vs multiple cysts
- Native Nephrectomy
- Embolization

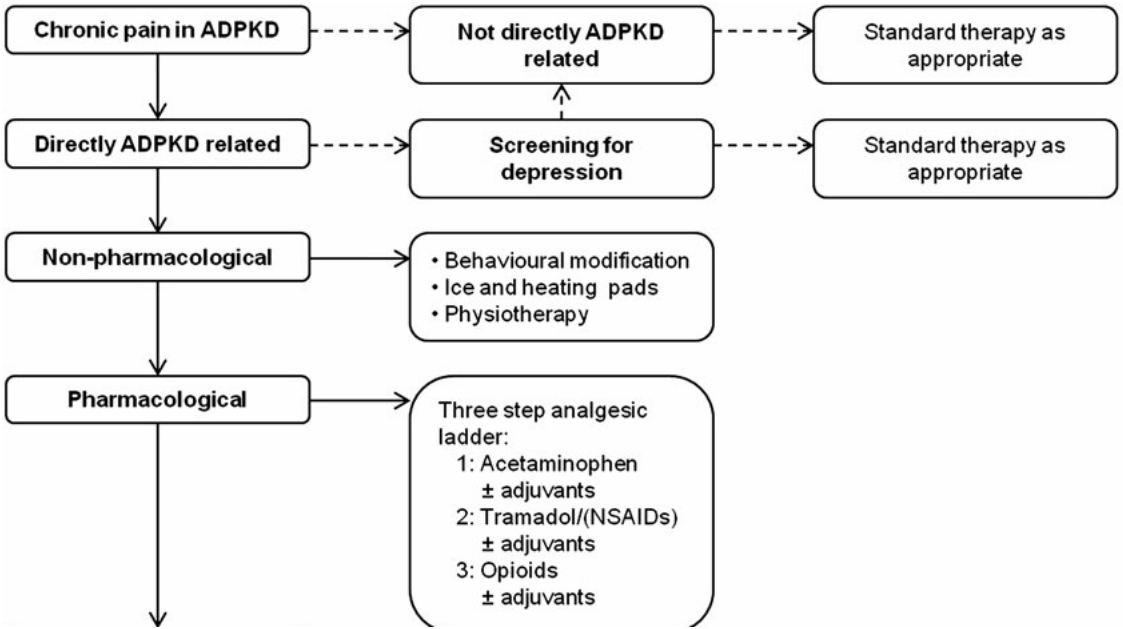
Nephrol Dial Transplant (2014) 29: iv142–iv153
doi: 10.1093/ndt/gfu073

ndt
Nephrology Dialysis Transplantation

Full Review

A stepwise approach for effective management of chronic pain in autosomal-dominant polycystic kidney disease

Niek F. Casteleijn[1], Folkert W. Visser[1], Joost P.H. Drenth[2], Tom J.G. Gevers[2], Gerbrand J. Groen[3], Marie C. Hogan[4] and Ron T. Gansevoort[1], on behalf of the DIPAK Consortium



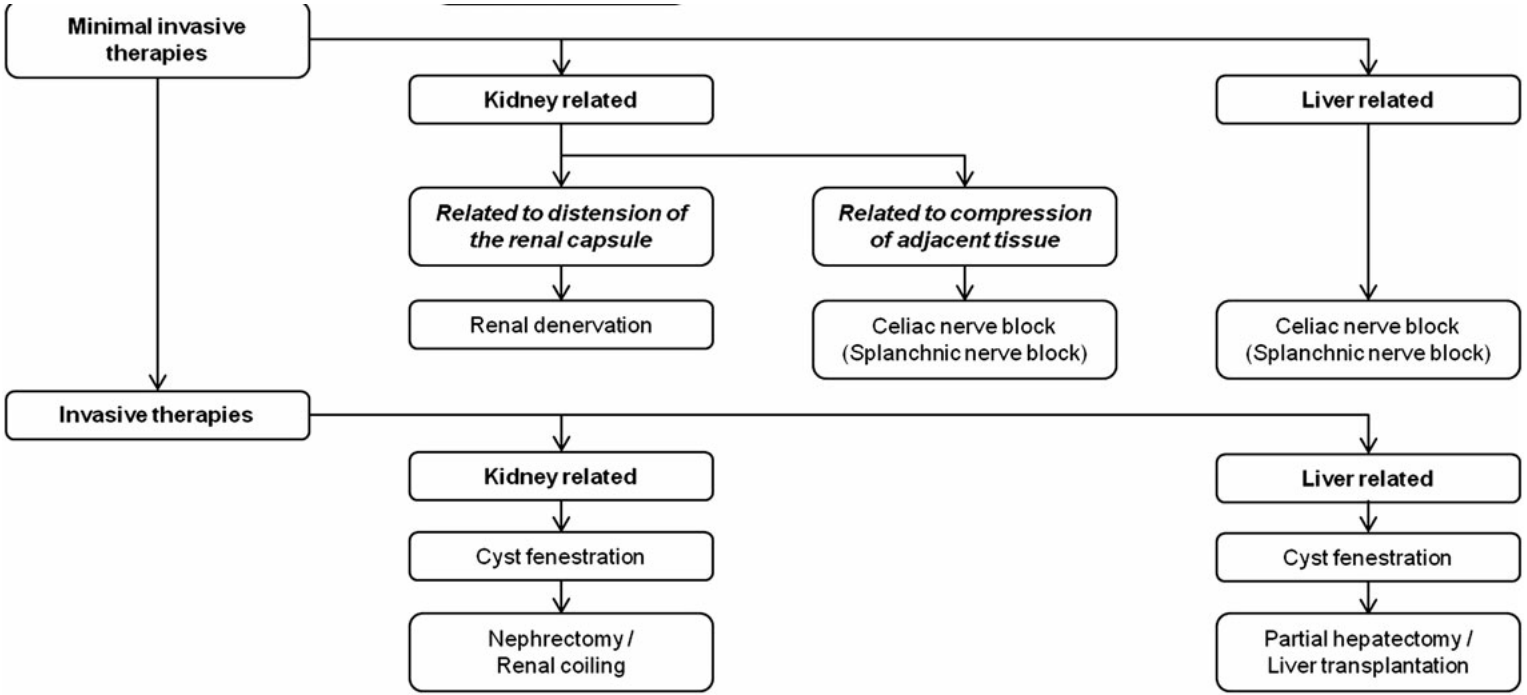


Table 1. Summary of reports describing renal denervation in ADPKD patients for chronic kidney pain related to polycystic disease

Author	Year	Technique	Patient (*N*)	Location	Pain outcome	Follow-up (months)	Complications
Renal denervation							
Valente	2001	Laparoscopic	1	Bilateral	90% Pain free	Unknown	Blood pressure unchanged
Chapuis	2004	Thoracoscopic	1	Unilateral	80% Pain free	24	None
Resnick	2006	Laparoscopic	4	Unilateral (one patient bilateral)	100% Pain free	6–16	None
Casteleijn	2014	Radio frequency ablation	1	Bilateral	100% Pain free	4	Blood pressure decreased

Table 2. Summary of reports describing cyst fenestration, cyst aspiration and sclerotherapy in ADPKD patients for chronic kidney pain related to polycystic disease

Author	Year	Technique	Patient (*N*)	Location	Pain outcome	Follow-up (months)	Complications
Cyst aspiration and cyst sclerotherapy							
Bennett	1987	Percutaneous cyst aspiration	11	Unilateral	33% Had some pain relief	18	None, part of the patients needed open cyst aspiration
Uemasu	1993	Cyst aspiration and sclerotherapy with minocycline hydrochloride	3	Unilateral	66% Had some pain relief	8	None
Uemasu	1996	Cyst aspiration and sclerotherapy with minocycline hydrochloride	10	Bilateral	20% Had some pain relief	12	Cyst volume did not differ statistically after sclerotherapy
Kim	2003	Cyst ablation with *N*-butyl cyanoacrylate and iodized oil	21	Unilateral	80% Had some pain relief	54	None
Lee	2003	Cyst ablation with absolute ethanol	11	Unilateral. One bilateral	64% Had some pain relief	12	Four patients had increased perception of pain
Singh	2006	Cyst ablation with absolute ethanol	15	Unilateral. Two bilateral	Mean pain relief of 66%	7 days	One patient had worsening pain and one patient developed a nephrocutaneous fistula
Kim	2009	Cyst ablation with *N*-butyl cyanoacrylate and iodized oil	21	Unilateral	76% Had some pain relief	36–90	ESRD in six patients, 22% of the cysts reappeared

Nephrol Dial Transplant (2014) 29: iv142–iv153
doi: 10.1093/ndt/gfu073

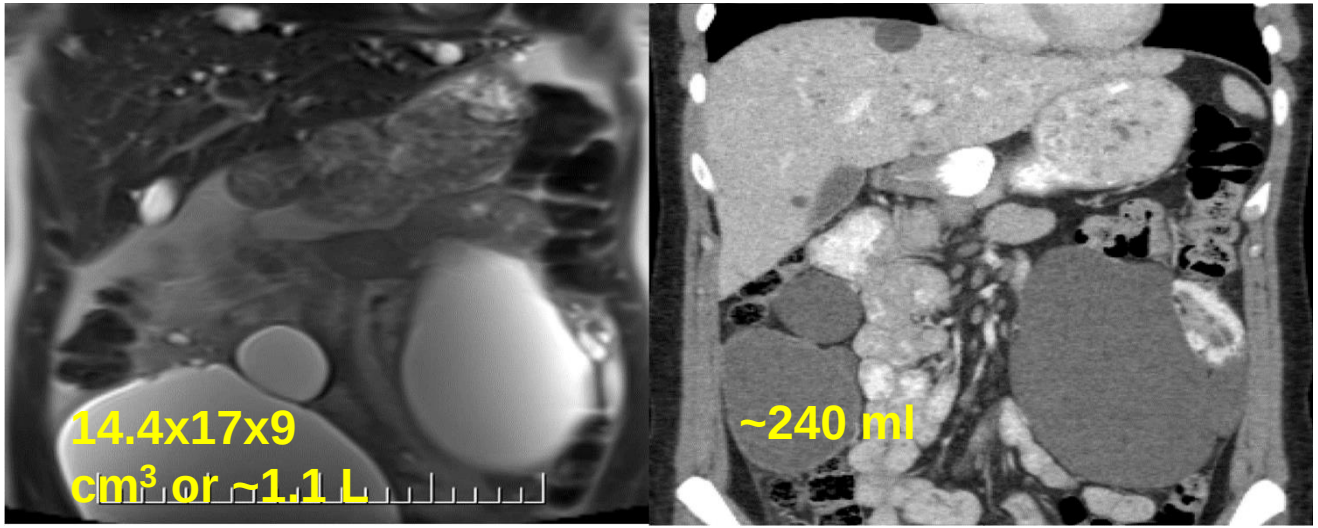
Table 2. Summary of reports describing cyst fenestration, cyst aspiration and sclerotherapy in ADPKD patients for chronic kidney pain related to polycystic disease

Author	Year	Technique	Patient (*N*)	Location	Pain outcome	Follow-up (months)	Complications
Cyst fenestration							
Elzinga	1992	Open	30	19 unilateral, 11 bilateral	63% Pain free	21	Two patients needed a second procedure
Brown	1996	Laparoscopic	8	Unilateral	80–100% Pain reduction	12–28	Two patients had persistent pain
Lifson	1998	Laparoscopic	8	Unilateral	25% Pain reduction	36	One patient had retroperitoneal bleeding, ileus and chemical peritonitis
Dunn	2001	Laparoscopic	15	9 unilateral, 6 bilateral	62% Pain reduction	26	Three patients had urinoma, two had perforations of collecting system
Lee	2003	Laparoscopic	29	23 unilateral, 6 bilateral	81% Had some pain relief	36	Three patients had urinoma
Fryczkowski	2007	Laparoscopic	15	Unilateral, 2 bilateral)	23% Pain free	24	Mean hospitalization of 10 days
Haseebuddin	2012	Laparoscopic	18	Unknown	67% Pain reduction	130	Three patients needed nephrectomy

Nephrol Dial Transplant (2014) 29: iv142–iv153
doi: 10.1093/ndt/gfu073

Foam Sclerotherapy

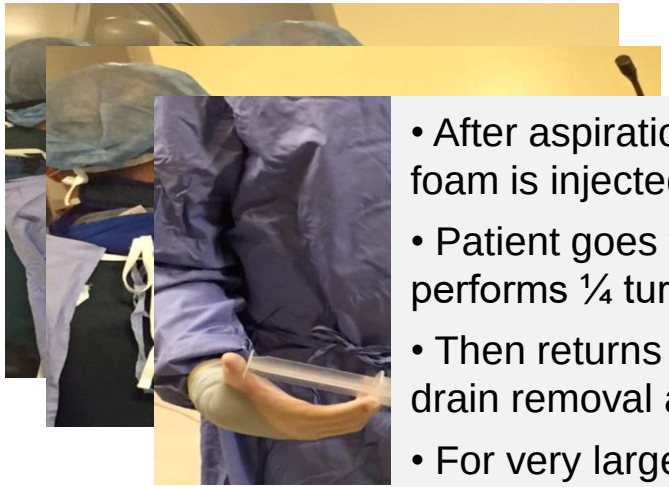
Next slides courtesy of Drs. Y. Pei and E. Shlomovitz; University Health Network, Toronto



- **before Rx** **1 month after**

36 yo F with ADPKD

STS Foam Sclerotherapy for Cystic Kidney Volume Reduction

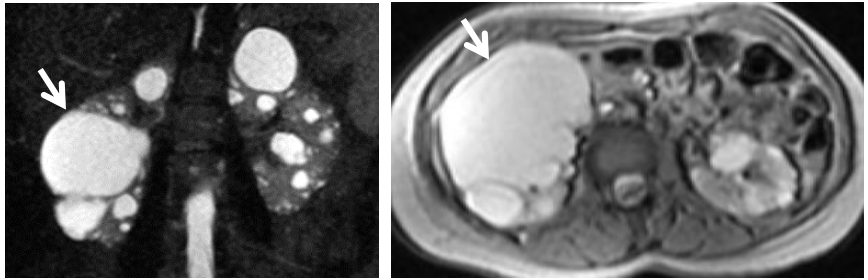


- After aspiration of cyst fluid, 3% STS foam is injected into each cyst
- Patient goes to Recovery Room and performs ¼ turn q15’ for one hour
- Then returns to radiology suite for drain removal and discharged
- For very large (>8 cm) cyst, drain will stay until 2nd session one week later

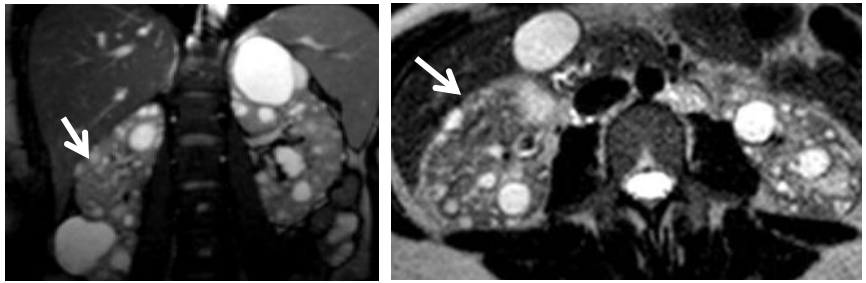
Improvement of CrCl Post-Foam Sclerotherapy

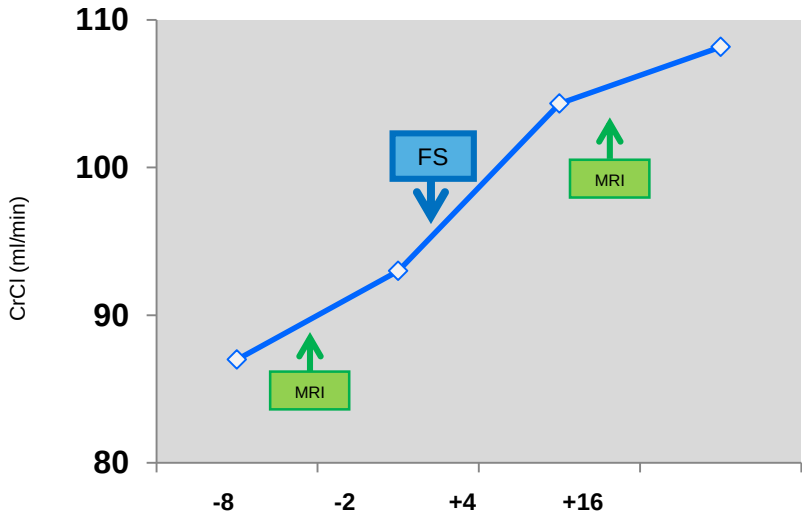
33 yr old female with a *PKD1* PT mutation

Pre-TKV: 1071 mL



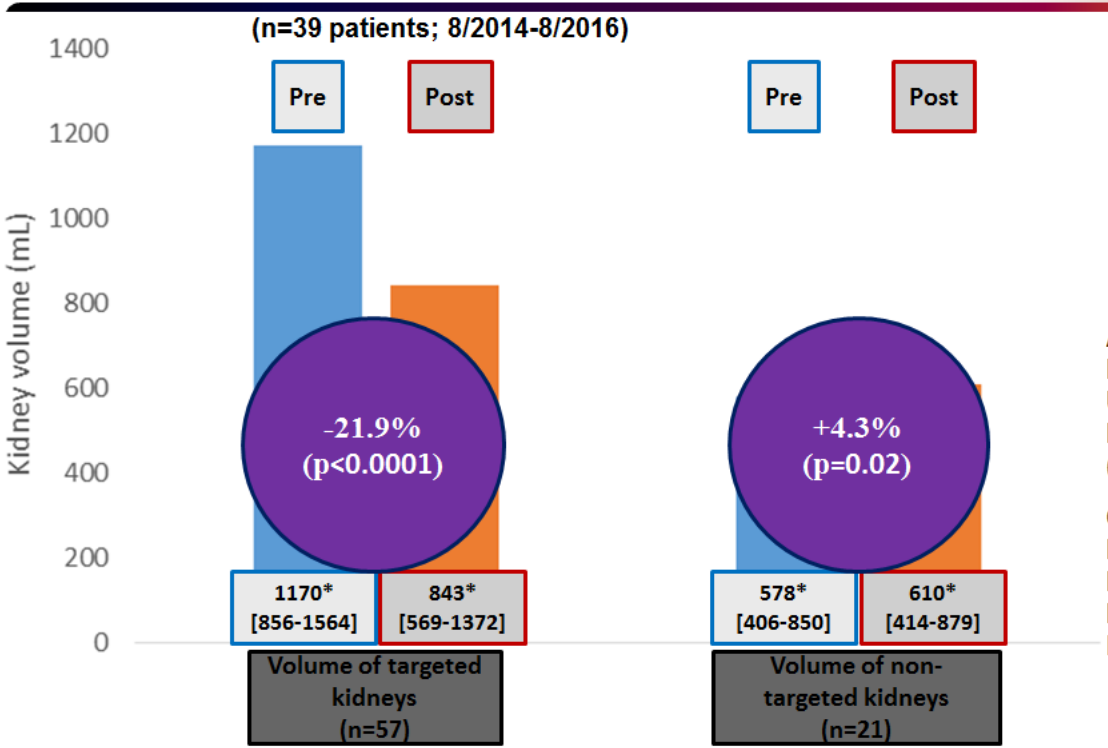
Post-TKV: 755 mL ↓ 29.5%





?resolution of obstruction of upstream nephrons and vasculature

Cyst Ablation by Foam Sclerotherapy
An Experimental Rx



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Collaborators:
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Lily Shi, MD

*Median [IQ range]; mean interval between MRI/CT = 14.5 months

Safety and Tolerability (n~120)

- Well tolerated in majority of patients
- Significant but self-limiting pain (i.e. moderate to severe in intensity for >24 hrs. requiring analgesic Rx) in ~15% of patients
- Cyst infection requiring antibiotic Rx in ~1% of patients
- Impact on preservation or improvement of GFR to be determined

http://www.kidney-international.org meeting report

Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

Arlene B. Chapman[1], Olivier Devuyst[2], Kai-Uwe Eckardt[3], Ron T. Gansevoort[4], Tess Harris[5], Shigeo Horie[6], Bertram L. Kasiske[7], Dwight Odland[8], York Pei[9], Ronald D. Perrone[10], Yves Pirson[11], Robert W. Schrier[12], Roser Torra[13], Vicente E. Torres[14], Terry Watnick[15] and David C. Wheeler[16] for Conference Participants[17]

Preparation for transplantation

Kidneys should not be routinely removed prior to transplantation, as nephrectomy in ADPKD patients is associated with significant morbidity and mortality.[87–90] Indications for nephrectomy include recurrent and/or severe infection, symptomatic nephrolithiasis, recurrent and/or severe bleeding, intractable pain, suspicion of renal cancer, and space restrictions prior to transplantation, taking into account that kidney size typically declines after transplantation.[91] Hand-assisted laparoscopic nephrectomy is better tolerated.[92–94] Although practices vary widely, on average less than one-third of patients in published series undergo pretransplant nephrectomy.[87,95–97] Experience with prior and simultaneous nephrectomy has been reported,[96,98] but both practices have not been directly compared. Transcatheter artery

Nephrectomy of Polycystic Kidneys

- Pre-transplant (bilateral) nephrectomy
  - Precludes pre-emptive transplantation - loss of GFR
  - For recurrent infection, bleeding, malignancy
- Simultaneous nephrectomy
  - Longer and more complicated procedure; prolongs cold-ischemia time in deceased donor transplant
  - Higher transfusion requirements
  - No difference in allograft function
  - Higher patient satisfaction (1 procedure) and shorter cumulative length of hospital stay
- Deferred or 'staged' or 'sandwich' nephrectomy
  - Wait until successful transplant performed
  - Allows stabilization/reduction of immunosuppression
  - Additional surgery

Martin et al. BJUI 2012; E1003
Lucas et al. J Urology 2010; 184:2054
Neef et al. Nephrol Dial Transplant 2013; 28:466
Dinckan, AnnTransplant, 2013; 18:697-704
Williamson et al. J Endourol. 2014; 28: 1268-1277
Bansal et al. Can Urol Assoc J. 2014; 8: 341-5

Embolization of Renal Arteries

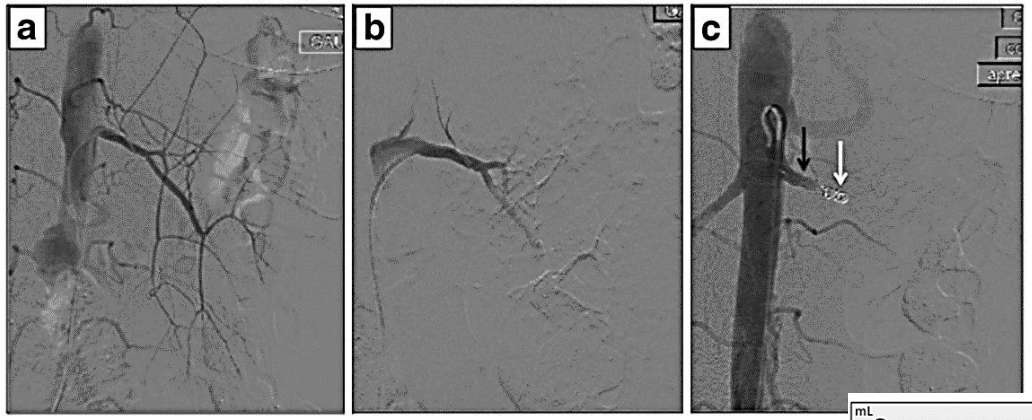

Fig. 2 Embolization procedure. **a** Renal artery angiogram showing enlarged kidney with thin arteries and no parenchymography. Note the absence of polar artery. **b** Complete artery occlusion after slow absolute ethanol injection. **c** Final angiogram control after coils and plug delivery shows complete proximal renal artery occlusion

- N=73 patients, 76 kidneys
- Proceeded to KT in 89.5%
- Technical failure rate 7.9%
- Post-embolization syndrome (fever/pain) 18.3%
- Severe complications 4.9% (pseudoaneurysm, vein thrombosis, PE)
  - Comparable to surgery
- Good allograft function

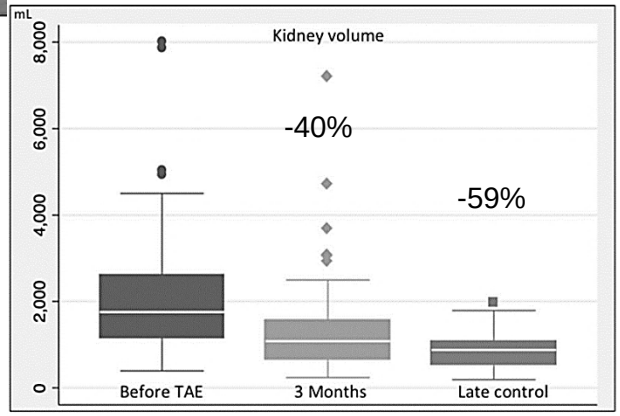

Fig. 3 Volume decrease before ERA, at 3 months, and belatedly after trans-arterial embolization

Petitpeirre et al. Eur Radiol 2015; 25:3262-3271

Meta-analysis of Transcatheter Arterial Embolization

Table 1 Summary of studies examined in systematic review

Investigators	Study type	Patients (*n*)	Embolization agent (*n*)	Outcome measure	Starting volume (mL)	% Reduction in renal volume (± SD)				
						3 months	6 months	12 months	18 months	24 months
Cornelis et al. [16]	Prospective	25	PVA	Transplant contraindication	2314 ± 1898	42 ± 18	54 ± 17	NA	NA	NA
Petitpierre et al. [17]	Retrospective	73	PVA (33) Ethanol (42) PVA and ethanol (7)	Transplant contraindication	2141 ± 1439	40 ± 14	NA	NA	NA	NA
Ubara et al. [18]	Retrospective	64	Stainless steel coil (12) Platinum microcoil (10) Microcoil and gelatin sponge (42)	Compression symptoms	2068 ± 1972	73.8 ± 12	61.7 ± 14.7	53.4 ± 11.6	NA	NA
Suwabe et al. [19]	Retrospective	400	Platinum microcoil	Compression symptoms	2529 ± 1016.72	31.4	38.2	46.5	NA	NA
Sakuhara et al. [20]	Prospective	15	Ethanol	Compression symptoms	2850 (1946–5253)	60.9 ± 6.2	47.3 ± 7.7	38.8 ± 7.5	35.1 ± 7	32.1 ± 6.9
Yamakoshi et al. [21]	Retrospective	28	NA	Pulmonary function	6330.5 ± 3126.5 (both kidneys)	NA	NA	45.6 ± 14.6	NA	NA

Ye et al. Cardiovasc Intervent Radiol. 2018; 41: 828-834

Cyst and Kidney Interventions

- Single center studies
- Small number of patients
- Lack of controlled trials
- Publication bias of “good” outcomes

- Must rely on clinical judgement and recognize potential harm of invasive interventions

Thanks for your Attention!