# ADPKD and Clinical Trials: Progress and future directions

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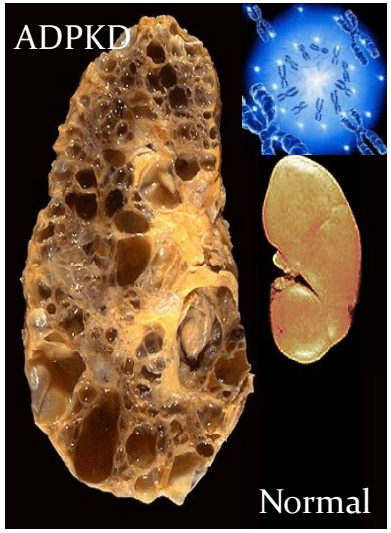
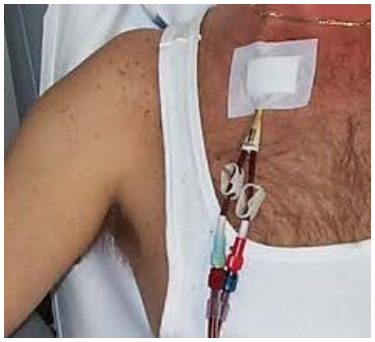
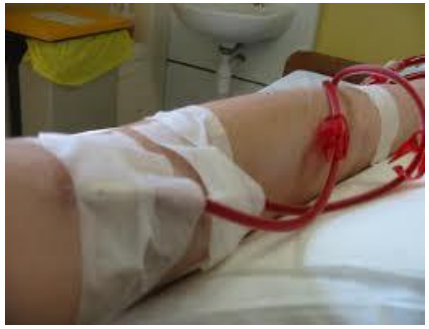
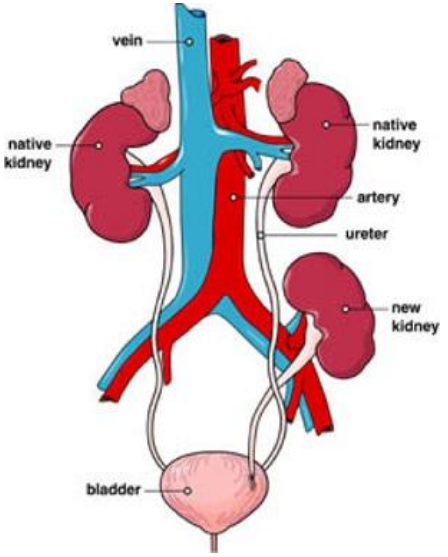
# Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- Commonest inherited kidney disease
- Progressive cyst development & growth
- 3rd commonest cause of **renal failure** (UK)

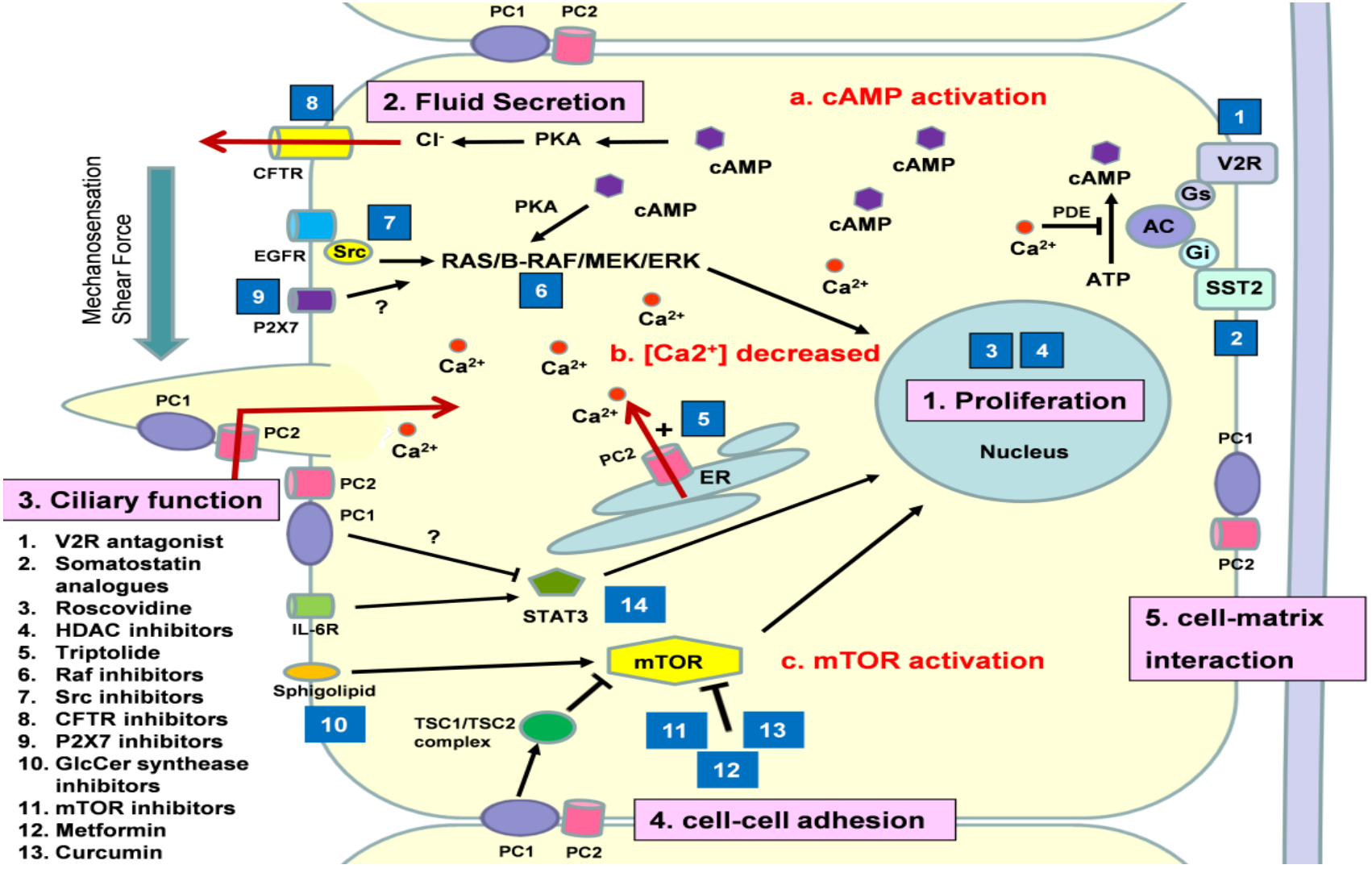






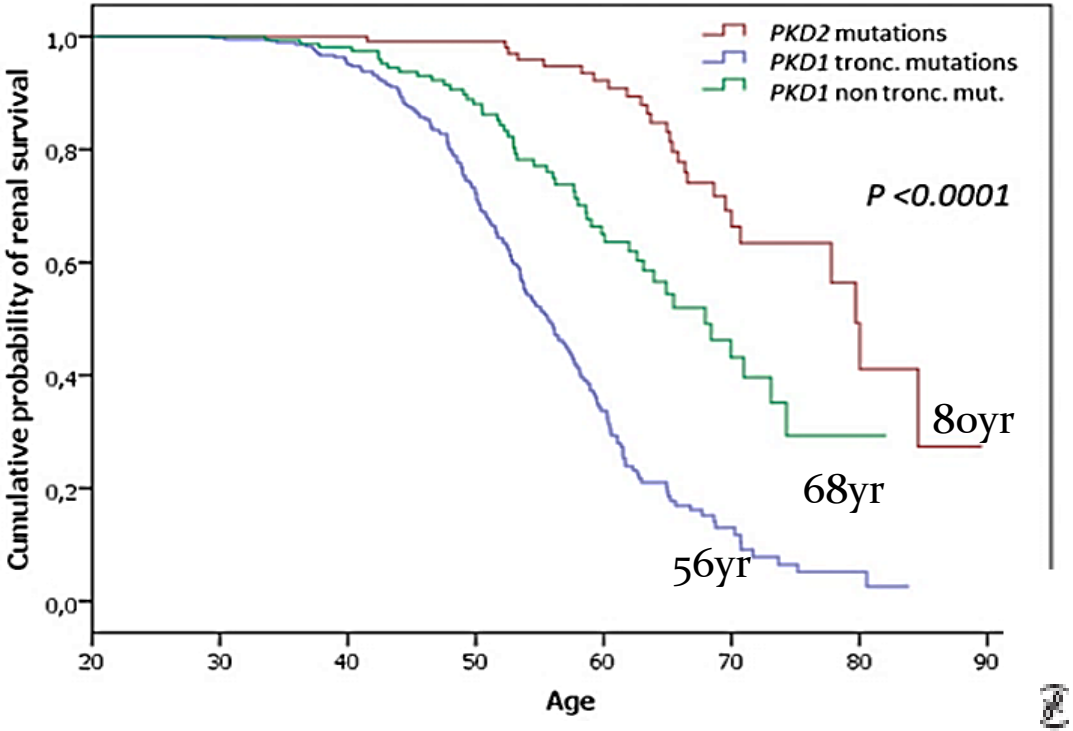
# Pathogenesis of ADPKD




Chang, BJCP 2013

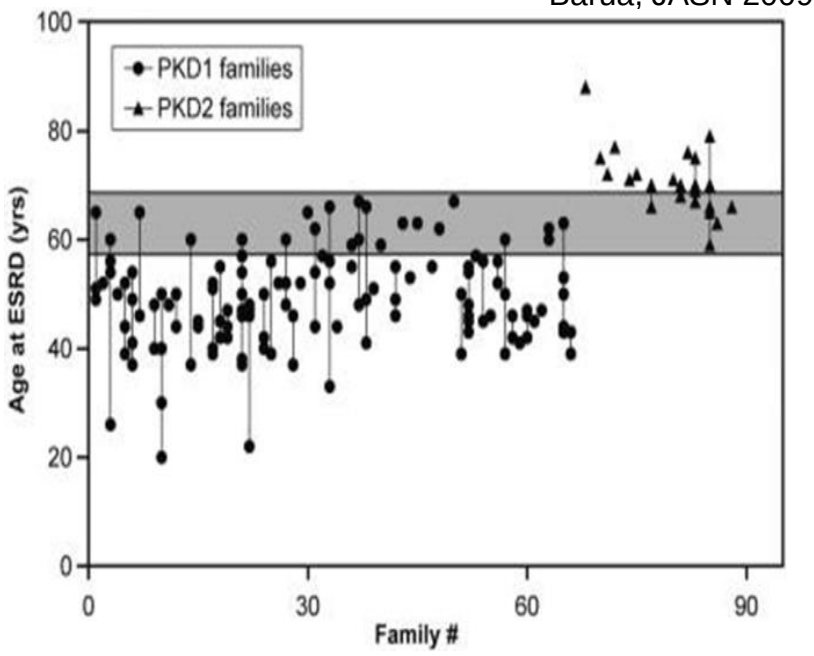
# Challenges of clinical trials in ADPKD

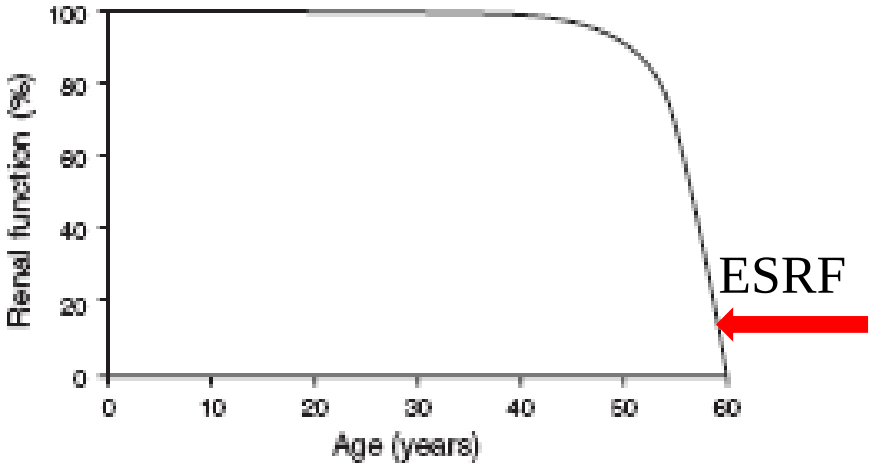
- Progression highly variable




Cornec-Le Gall JASN 2013

Barua, JASN 2009

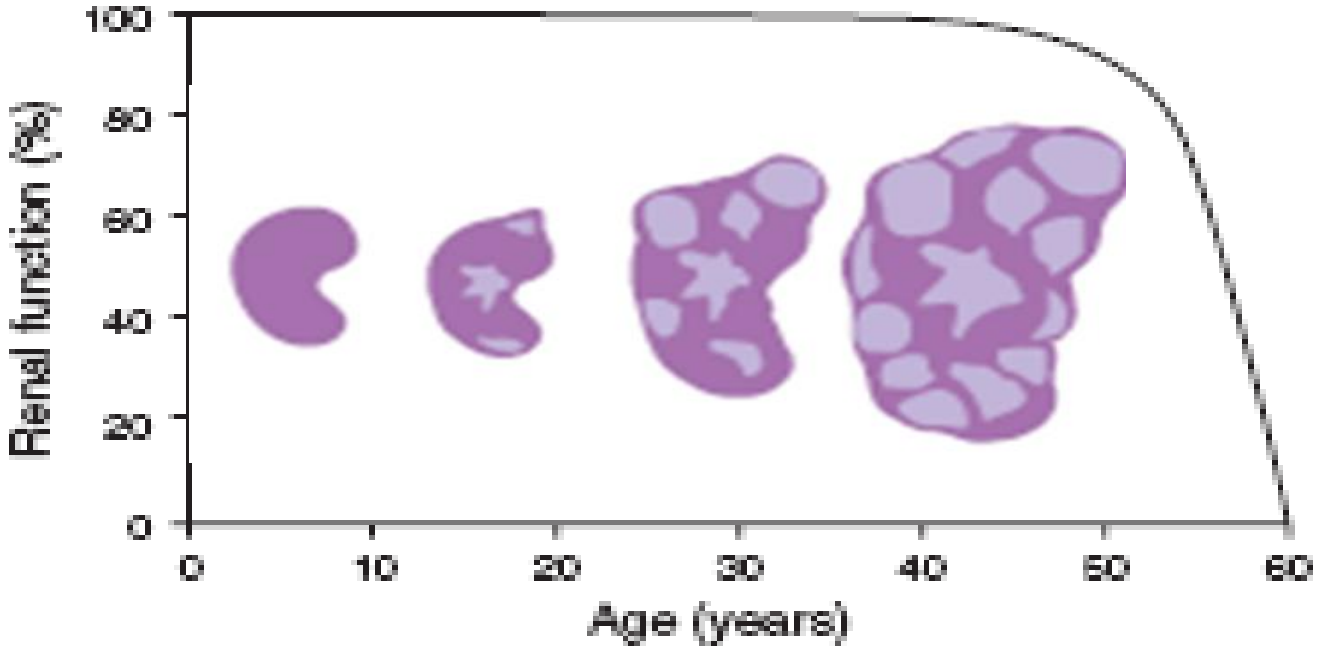


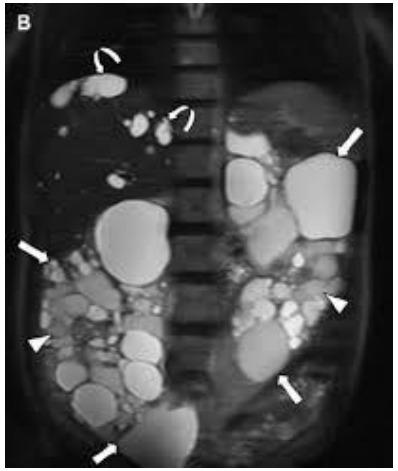




- Monitoring progression:

  **eGFR late marker**

# Total kidney volume (TKV) in ADPKD




- Gradual cyst development/years → ↑TKV
- **TKV clinically relevant,** marker of **progression**:

1981: 1st (n43, CT) correlated **1/CrCl** (Thomsen)

# Consortium for Radiologic Imaging Studies of PKD

**CRISP**: (multicentre, central analysis) NIDDK funded

Annual MRI, 241 patients, 16-45yrs, eGFR>70ml/min

Aim - reliably & accurately measure TKV and TCV

- detect change (sequential scans)
- is TKV, TCV associated with ↓GFR

**CRISP1**(Chapman 2003):

TKV measurement reliability 99.9% (phantoms) 0.998 (pts)

TKV **greater** with age, hypertension, UAE

TKV **inversely correlated** with GFR (iothalamate)

# Total Kidney Volume (TKV) as an endpoint?

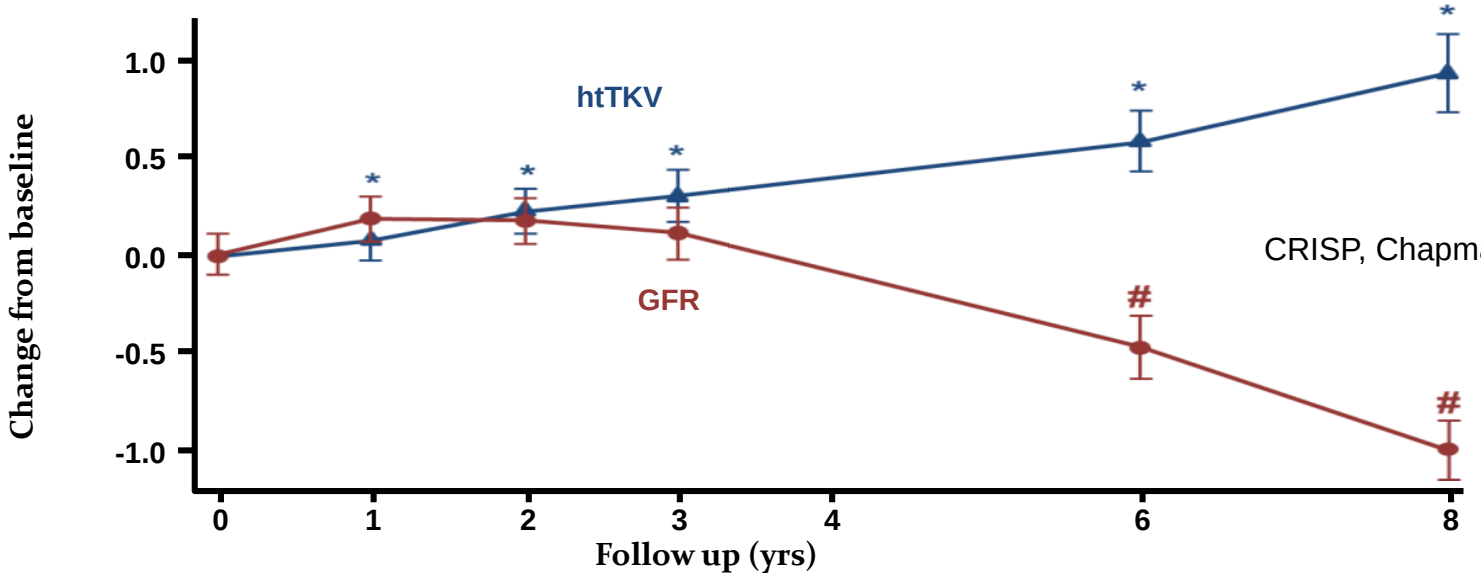
CRISP after 3yrs

- Baseline TKV predicts future rate of increase
- TKV increased: 5.3%/year, greater if ***PKD1***

CRISP, Grantham, NEJM 2006

CRISP after 8yrs

- Increasing TKV **precedes** change in eGFR




CRISP, Chapman, CJASN 2012

# Trials in ADPKD involving TKV

**2007:** PKD Foundation & FDA:

**Accept** kidney growth as 1° outcome to encourage industry for PKD drug development

**2009:** Database and data standards to build evidence

The HALT Polycystic Kidney Disease Trials: Design and Implementation

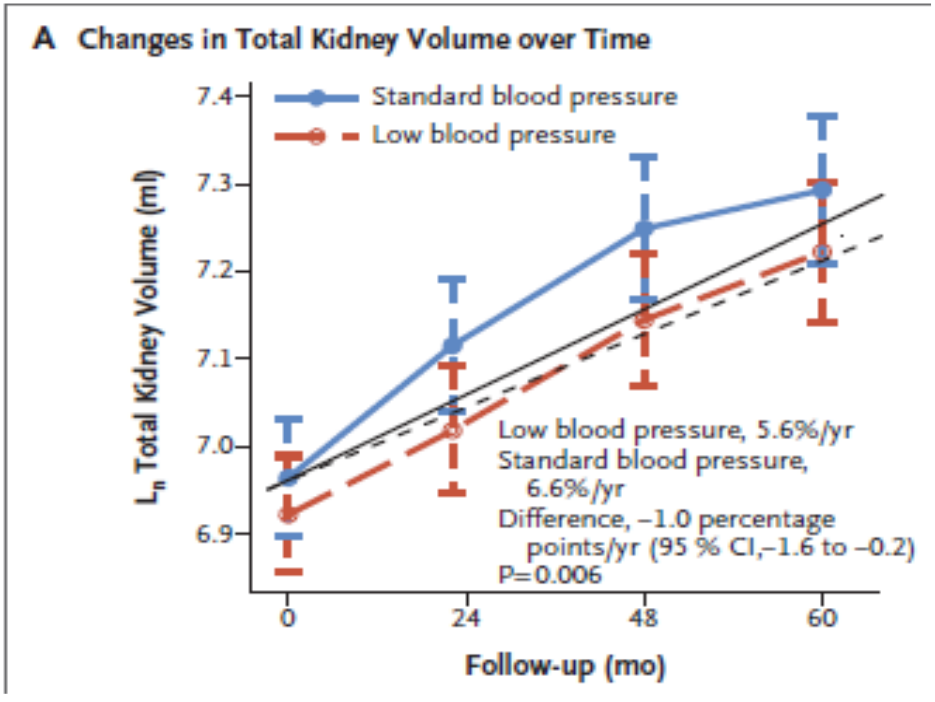
Chapman, HALT CJASN 2010

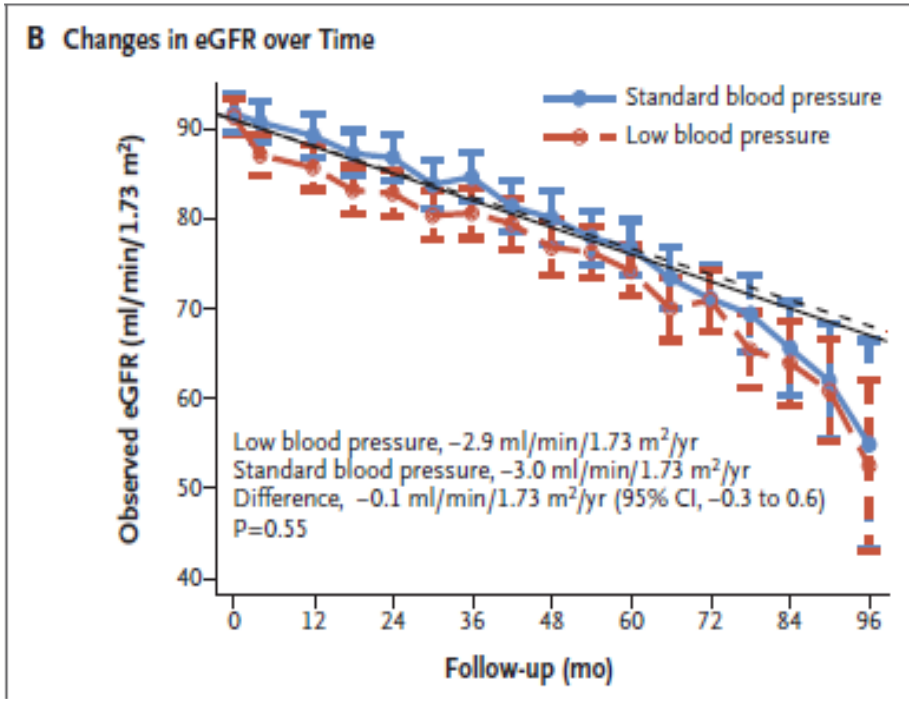
- Target hypertension (NIH/NIDDK)
- RAAS blockade: Dual vs mono ACEi/ARB
- **Early:** <50yrs, eGFR>60ml/min
- 2 BP targets, 1º: annual % change in TKV
- 5yrs (MRI: 0, 1, 2, 5yrs)

# HALT PKD results

- 553 patients completed trial

Schrier, NEJM 2014




- Benefit of change in TKV did not translate to eGFR
- Time lag? Haemodynamic?

# TEMPO 3:4 1st effective (specific) therapy in ADPKD

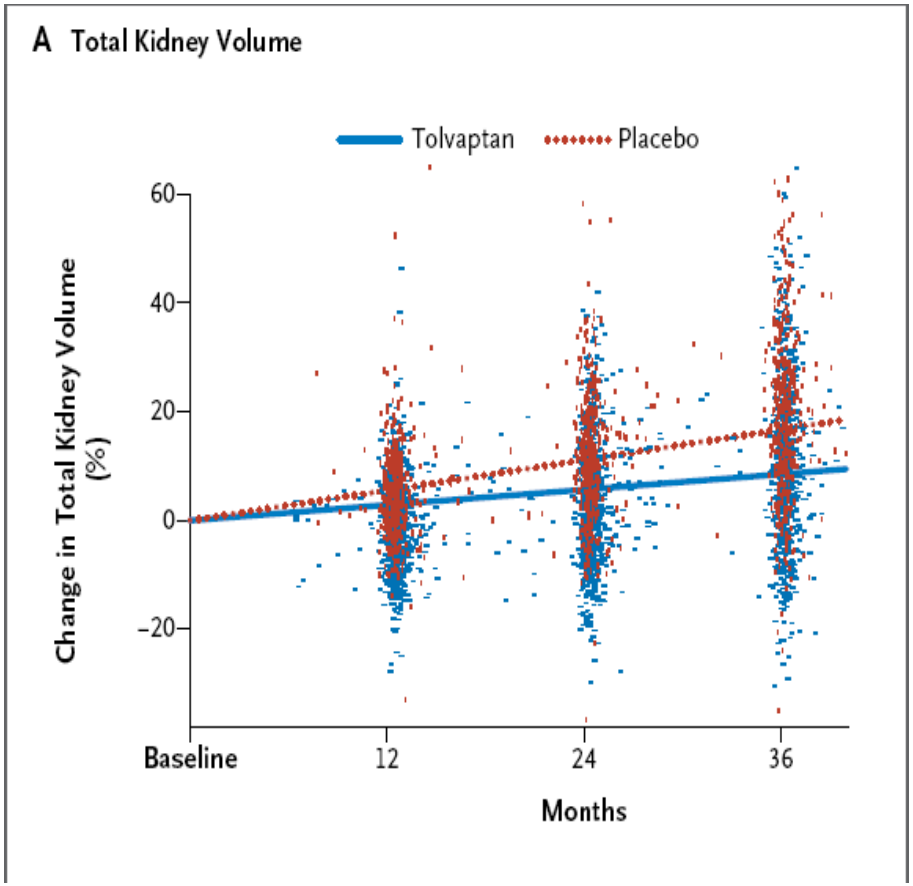
## Tolvaptan Efficacy and safety in Management of PKD and Outcomes

- Tolvaptan/Placebo for 3yrs (double blind)
- 1445 patients, 18-50yrs
- Normal kidney function (>60ml/min/1.73m$^2$)
- TKV>750mL/m (**burden of disease**)
- 1°: **Change in kidney volume (0, 1, 2, 3yrs)**

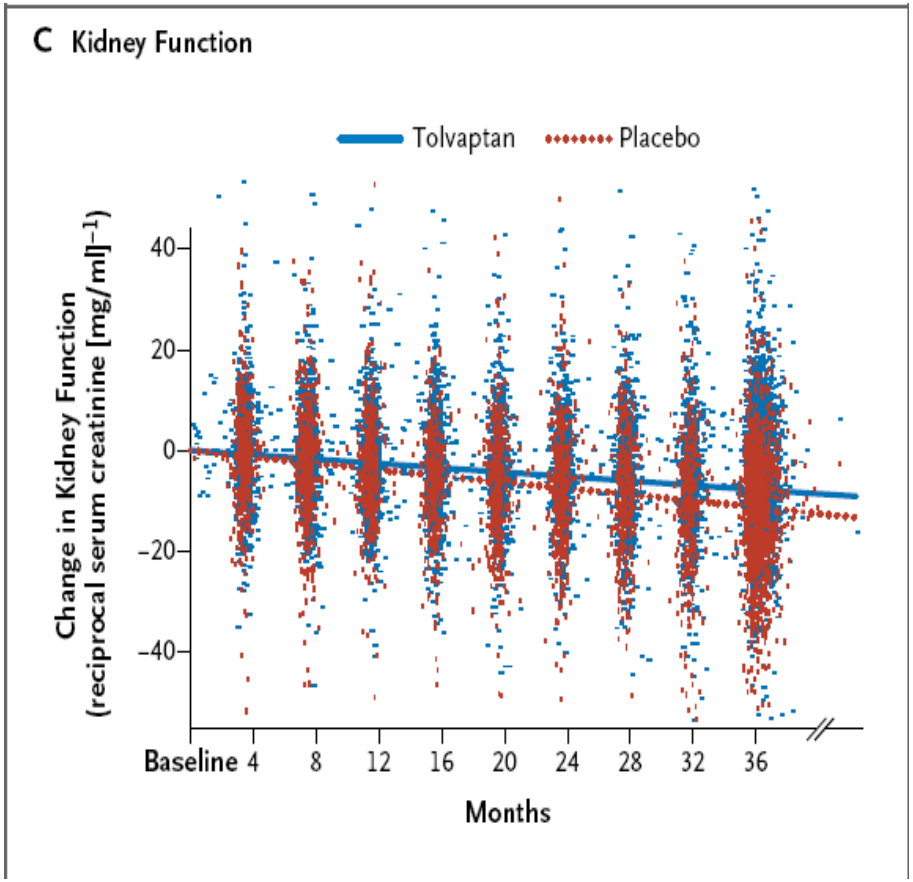
  2°: Change in eGFR, renal pain, hypertension
- Completed Jan 2011

# TEMPO 3:4 RCT: 1st effective therapy in ADPKD

Tolvaptan: 2.8%pa
Placebo: 5.5%pa




Tolvaptan: -2.7ml/min/pa
Placebo: -3.7ml/min/pa




**50% slower ↑TKV**

**30% slower ↓eGFR**

Torres NEJM 2012

# Eligibility for Tolvaptan in ADPKD

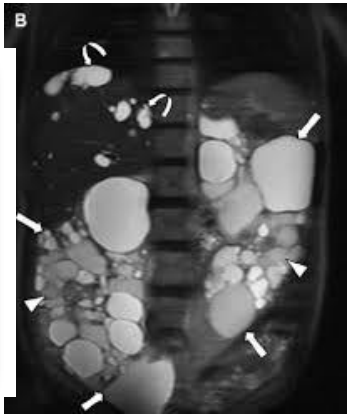
NICE
National Institute for Health and Care Excellence

NICE, Oct. 2015

- Stage 2-3 CKD (eGFR 30-89ml/min)
- Evidence of "rapid disease progression"

ΔeGFR >2.5ml/min/pa
(5 points over 5 years)
ΔeGFR >5ml/min over 12 mths

ΔTKV >5% pa (MR or CT)
(3 measurements over 2-3 yrs)




- **Biomarker Qualification:**
- **EMA:** Nov. 2015 and **FDA:** Sept. 2016
- **COU:** baseline TKV predicts pts at high risk of progression (+age, eGFR)

# US Regulations for Drug Approval

Traditional

- Endpoints: ESRF, survival,

**Accelerated** – used in ADPKD

- For drugs treating serious/life threatening disease
- Surrogate endpoint
- Requires additional post marketing confirmatory trial

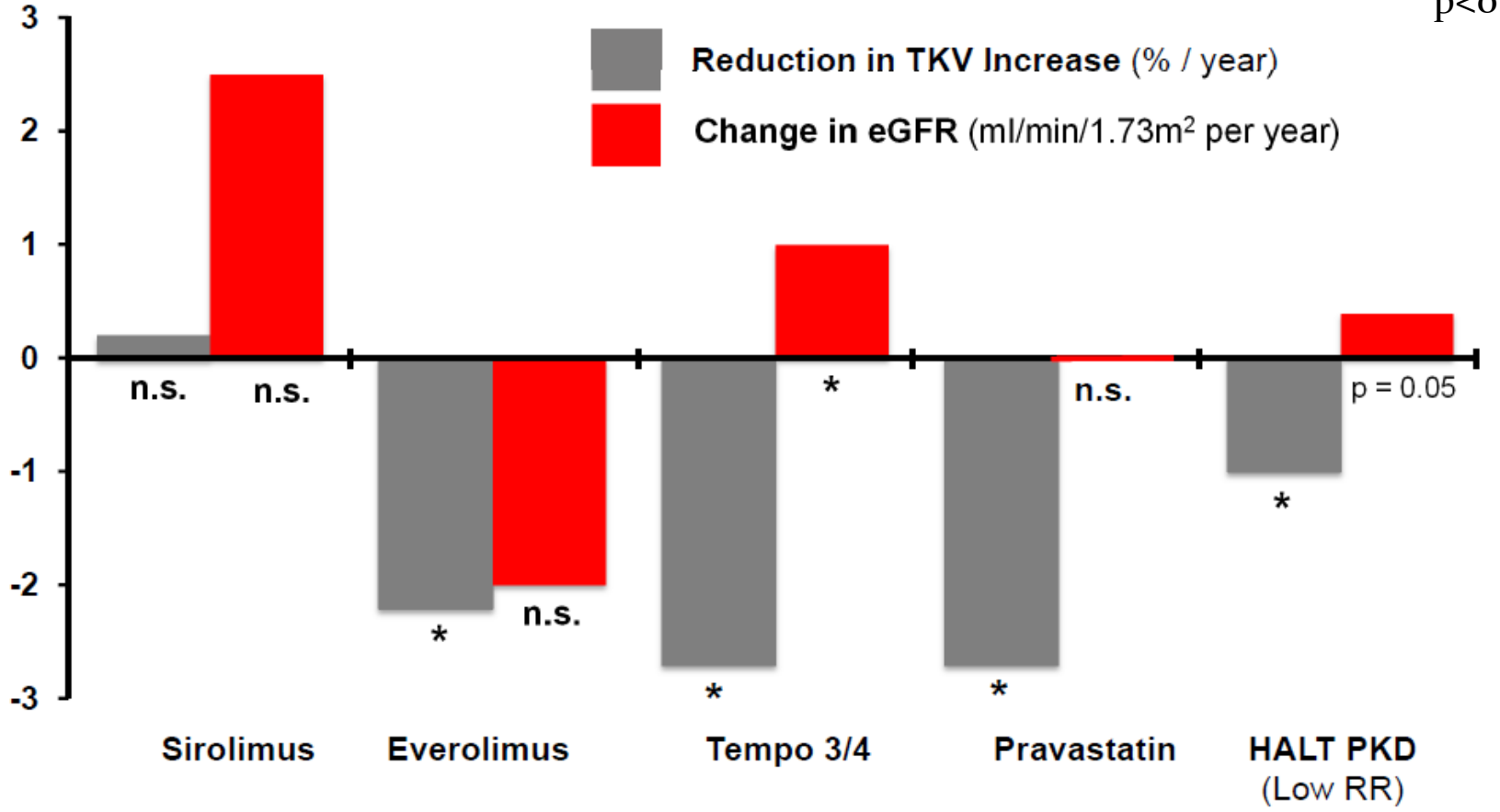
**REPRISE:** Replicating evidence of preserved renal function: an investigation of Tolvaptan's safety & efficacy

RCT, eGFR 25-65 (<55yrs) or 25-44 (56-66yrs), No MRI

Torres, NEJM, 2017

# Summary of recent trials in ADPKD using TKV

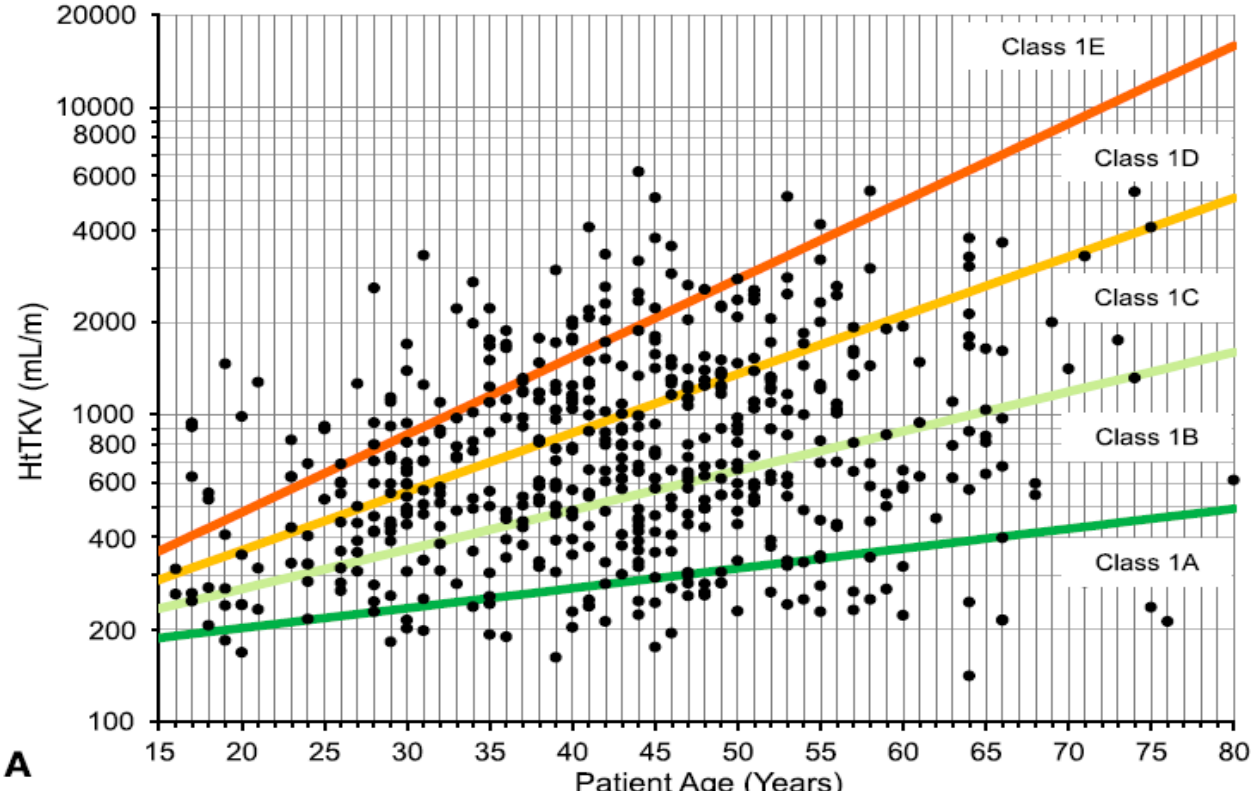
N>100
*p<0.05




Ong et al, Lancet 2015

# Future Trials in ADPKD

- Enrich trial population for “an event” (timescale)
- Mayo Imaging Classification: baseline TKV predicts progression




1A: <1.5%
1B: 1.5-3%
1C: 3-4.5%
1D: 4.5-6%
1E: >6%

Irazabal, JASN 2014

# Future Trials in ADPKD - outcomes

- Ensure high performance, standardised methods for measuring **serial TKV**
- Automated quantification of TKV

**Automatic Measurement of Kidney and Liver Volumes from MR Images of Patients Affected by Autosomal Dominant Polycystic Kidney Disease**

Maatje D.A. van Gastel,[1,2] Marie E. Edwards,[1] Vicente E. Torres,[1] Bradley J. Erickson,[3] Ron T. Gansevoort,[2] and Timothy L. Kline[1,3]

Deep learning network, n=500.

TKV: Bias <0.1% Precision 2.7 95% CI -5.4-5.4

# Future Directions

- Target earlier stage ADPKD, trial populations with preserved eGFR
- Identify complimentary early surrogate endpoints eg functional MRI techniques
- Collaborative multicentre funding (especially if absence of pharmaceutical sponsor)

# Summary

- Variability in progression of ADPKD requires risk stratification of patients to enrich clinical trial populations, optimising events during a trial

- Extensive evidence supports increased TKV is clinically relevant and currently the earliest prognostic biomarker in ADPKD approved by the EMA and FDA

- There is scope for the development of additional early surrogate functional MRI biomarkers in ADPKD

# Acknowledgements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Polycystic Kidney Disease

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Funding research to save lives

Thank you