

Tolvaptan bei ADPKD:

Kritische Beurteilung der Studien

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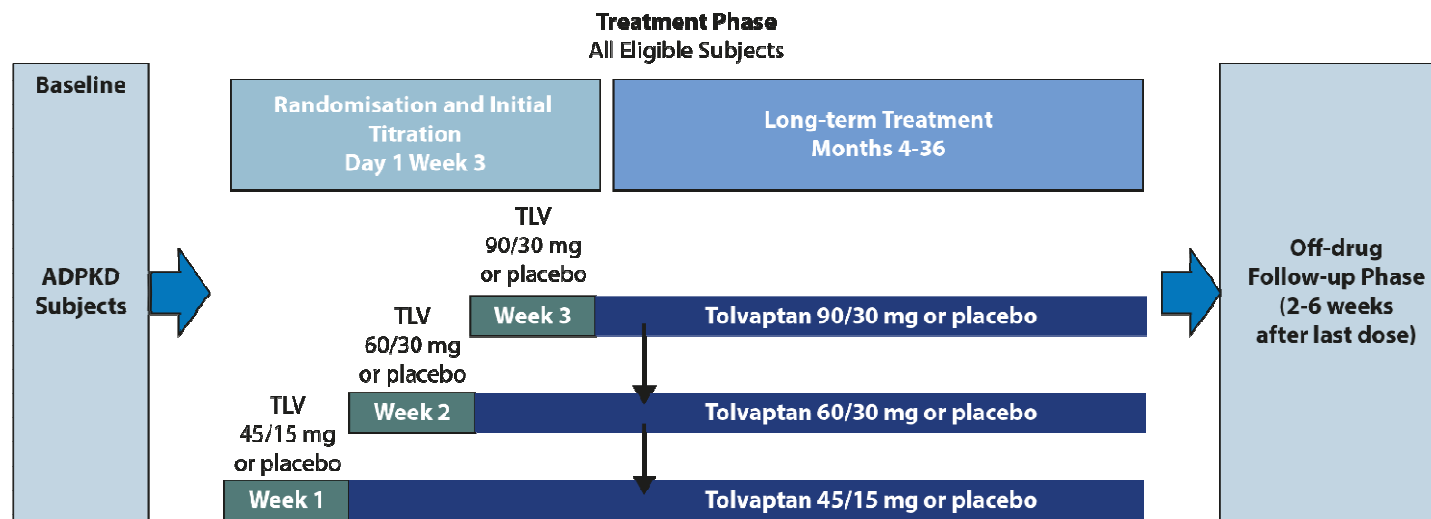
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TEMPO 3:4 study design: patients randomised to tolvaptan or placebo over a 3-year period



- In TEMPO 3:4, 1,445 patients were randomised (2:1) to tolvaptan (at the highest of three twice-daily dose regimens that the patient found tolerable) or placebo

ADPKD: autosomal dominant polycystic kidney disease; TLV: tolvaptan.

Torres VE, et al. *N Engl J Med* 2012; 367: 2407-2418.



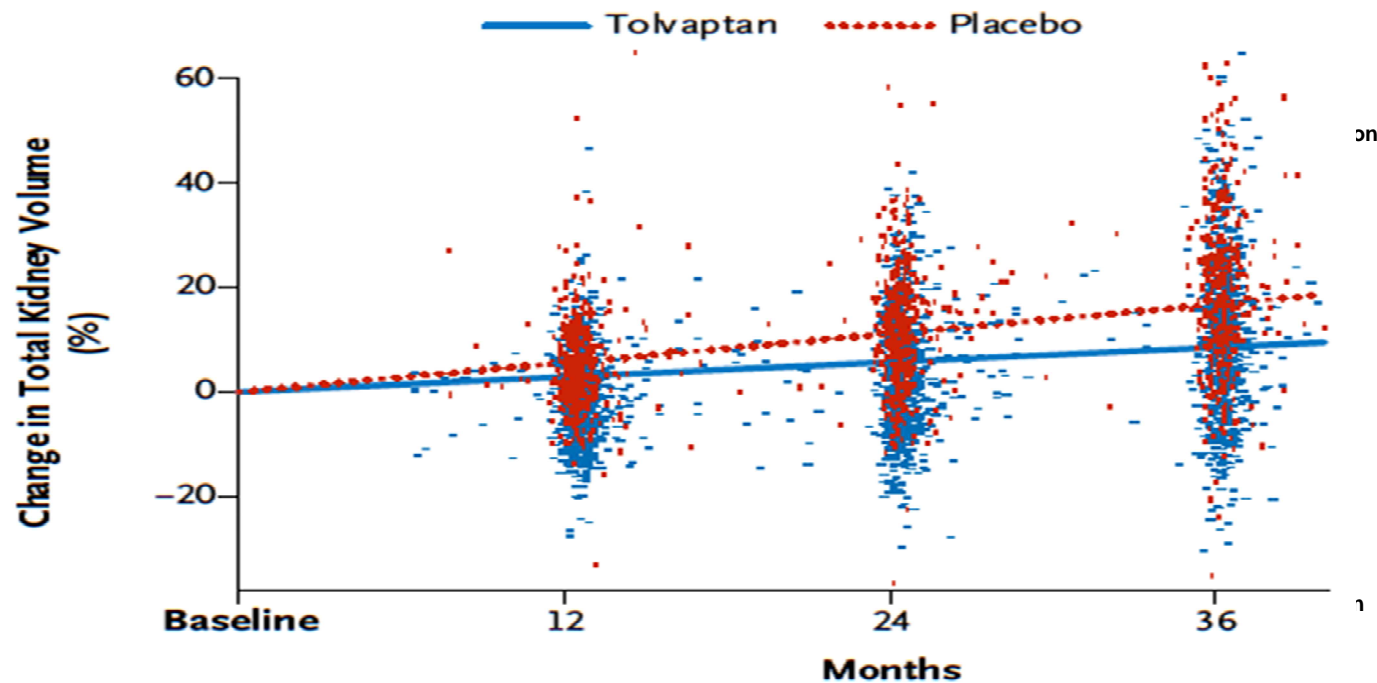
TEMPO 3:4 key entry criteria: subjects had large kidney volumes and preserved kidney function

•Inclusion criteria

- 18–50 years, with diagnosis of ADPKD by Ravine criteria
 - eCrCl ≥ 60 mL/min (by Cockcroft-Gault)
 - Total kidney volume (TKV) ≥ 750 ml by MRI (as indicator of rapid progression)



TEMPO 3:4: TKV increased 2.8%/year with tolvaptan (N=961), 5.5% with placebo (N= 484)

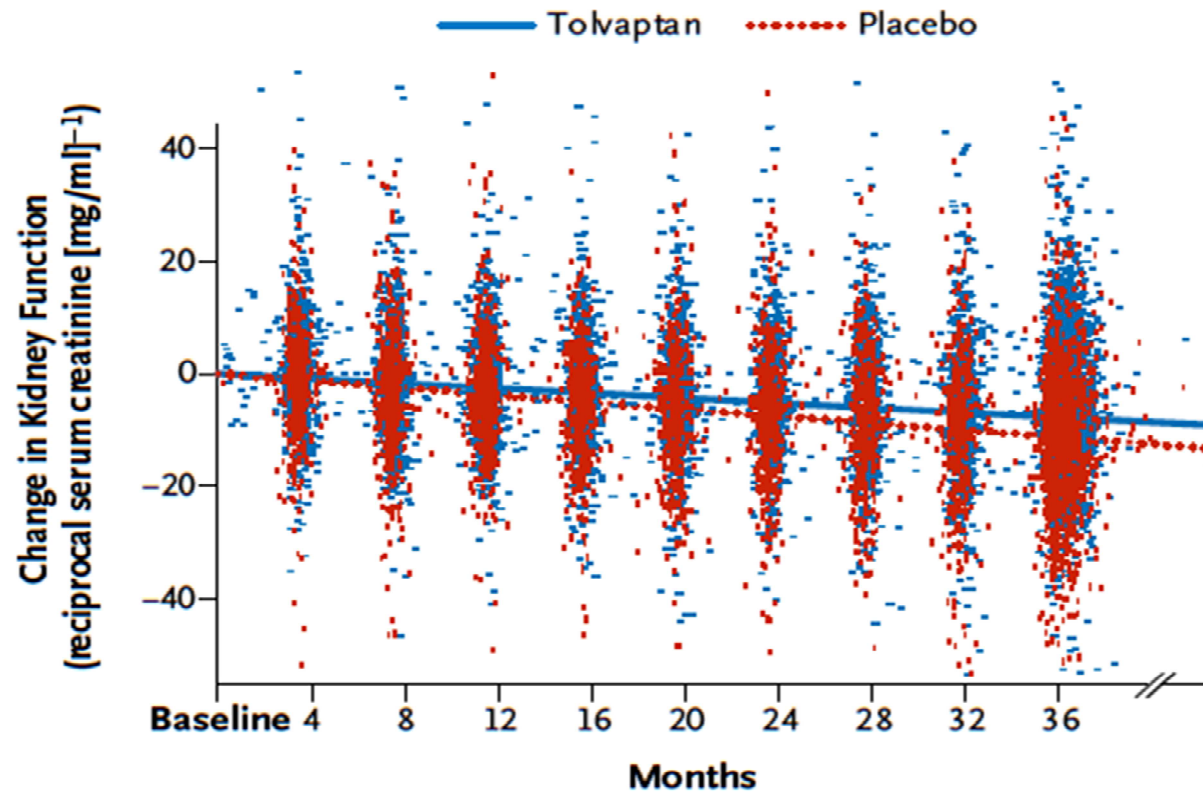


Torres VE, et al. *N Engl J Med* 2012; 367: 2407-2418.

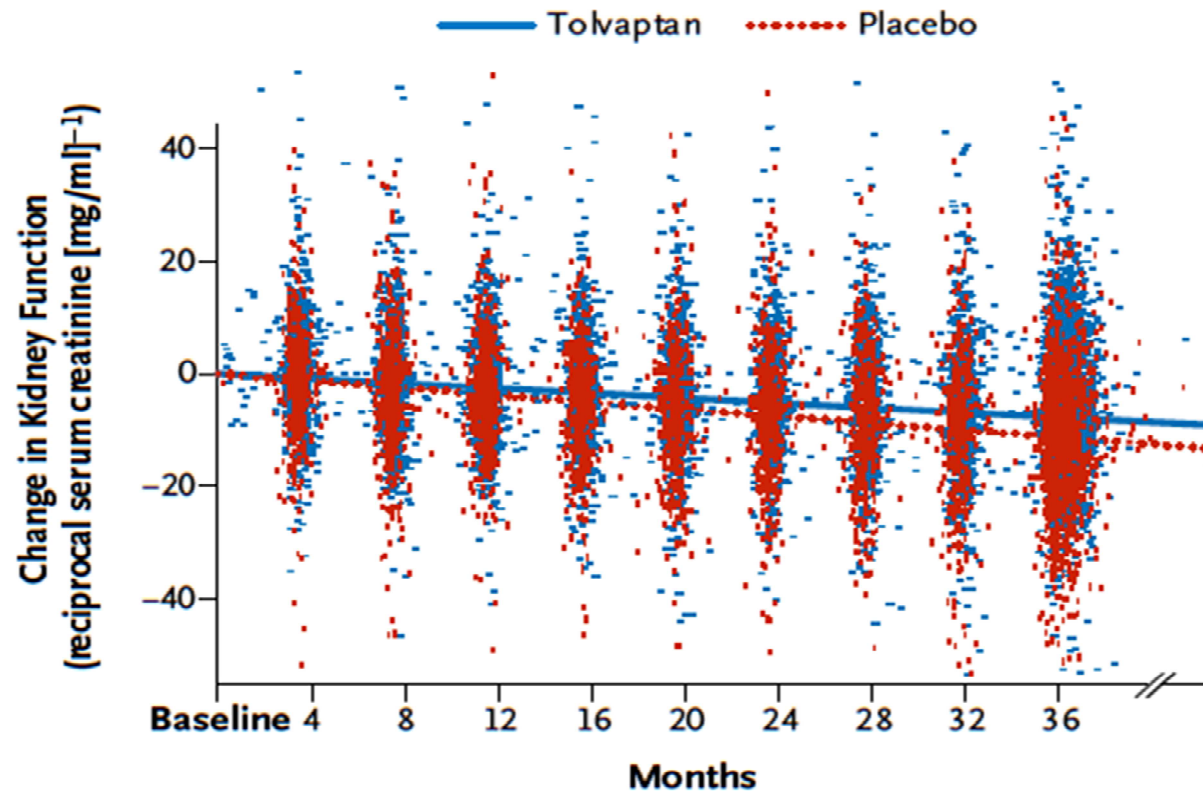
Nürnberg



TEMPO 3:4: eGFR loss with with tolvaptan (- 2.72 ml/year), more with placebo (-3.70 ml/year)



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Delta serum-creatinine per 3 years:

Tolvaptan:

1.05 to 1.21 mg/dl

Placebo:

1.04 to 1.27 mg/dl



The problem of surrogate markers

- eGFR

eGFR over 3 years

Tolvaptan: 81.4 to 73.3 ml/min (Delta 8.3)

Placebo: 82.1 to 71.0 ml/min (Delta 11.1)



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- eGFR

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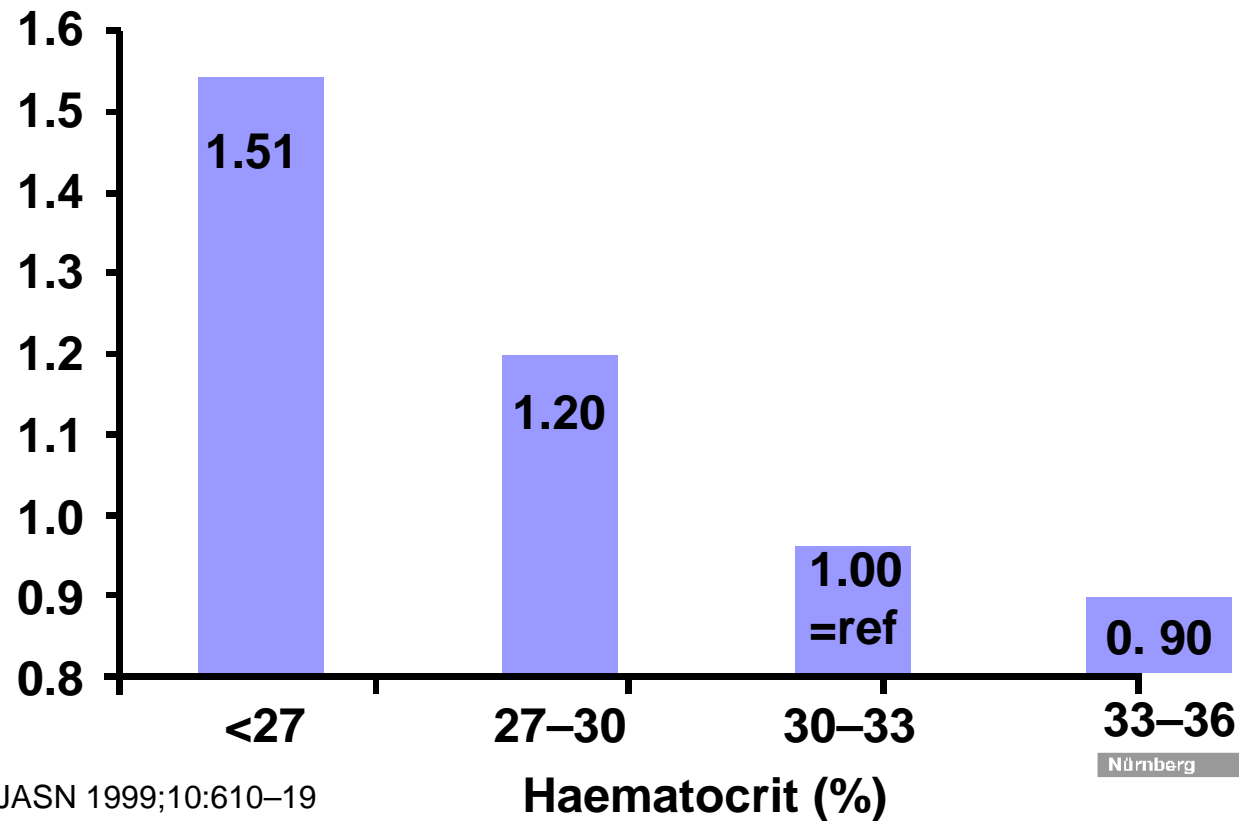
How confident can we possibly be to project those 3-year data to ESRD in a 15 - >30 year future ??



The problem of surrogate markers

- Hemoglobin: Higher CV mortality with low Hb

Relative risk for death

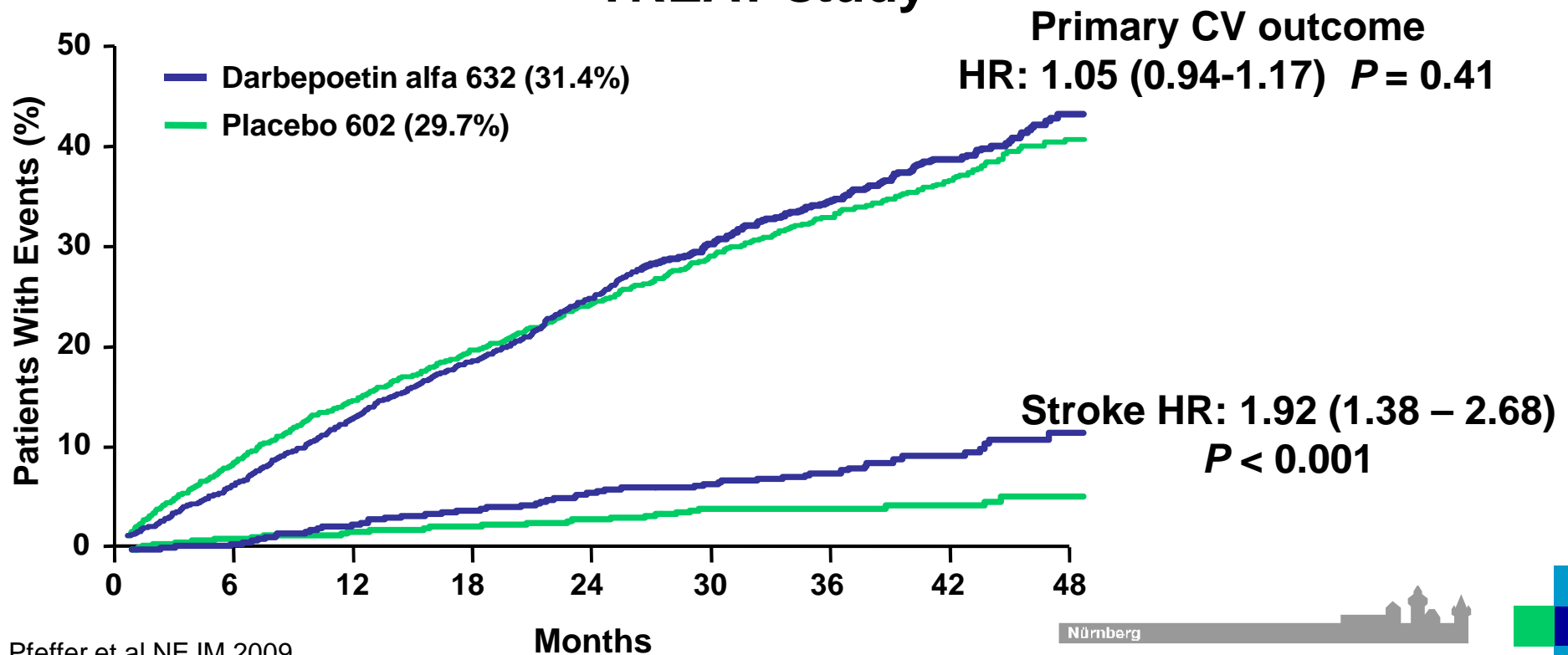


Ma JZ et al. JASN 1999;10:610-19

The problem of surrogate markers

- Hemoglobin: no benefit in treating low Hb

TREAT study



Pfeffer et al NEJM 2009

The problem of surrogate markers

- Failed RCTS on positive surrogates

- Hemoglobin: TREAT, BESARAB, CHOIR, CREATE
- Arrhythmias: CASS
- Vitamin E: HOPE
- Homocystein: HOPE-2
- HbA1c: ORIGIN, TECOS, EXAMINE, ELIXA, SAVOR
- HDL: Many failed drugs
- Positive inotropics all failed
- Weight loss most drugs failed



There is no surrogate for safety: Adverse events

	Tolvaptan (%)	Placebo (%)
Thirst	55.3	20.5
Polyuria	38.3	17.2
Fatigue	13.6	9.7
<i>Hypertension</i>	<i>32.2</i>	<i>36.0</i>
<i>Renal pain</i>	<i>27.0</i>	<i>35.0</i>
<i>Urin. infection</i>	<i>8.3</i>	<i>12.6</i>
Liver tests	1.8	0.8



There is no surrogate for safety: Adverse events

	Tolvaptan (%)	Placebo (%)
GPT 3x > upper limit	4.4	1.0
GPT 3x > and bilirubin 2x > upper limit	0.2	0
Drop-out	23.0	13.8
Drop-out after adverse event	15.4	5.0



Finally: blood pressure

Mean BP in TEMPO: 129 / 83 mmHg

Mean BP in HALT-PKD: 109 / 71 mmHg

Conclusions

Wie sicher können wir sein, dass Unterschiede im Delta-Serumkreatinin von 0,07 mg/dl pro 3 Jahre sich übersetzen lassen in eine Verlängerung der Zeit bis zur Dialyse/Transplanta?

Wie sicher sind wir, dass sich die Nebenwirkungen in 3 Jahren übersetzen lassen auf z.B. 30 Jahre.

EMA, EDTA, NICE, FDA etc beurteilen die Tolvaptan Daten bei ADPKD massiv unterschiedlich



What to do? Guidance from....

Licence (EMA, FDA)

ERA-EDTA guidance

NICE



What to do? Guidance from....

Tolvaptan licence

Therapeutic Indications

Tolvaptan is indicated...

- in adults
- with CKD stage 1 to 3 at initiation of treatment
- with evidence of rapidly progressing disease



What to do? Guidance from.... NICE

1.1 Tolvaptan is recommended as an option....only if:

- **CKD stage 2 or 3** at the start of treatment
- **Evidence of rapidly progressing disease** and
- The company provides it with the **discount** agreed in the patient access scheme.



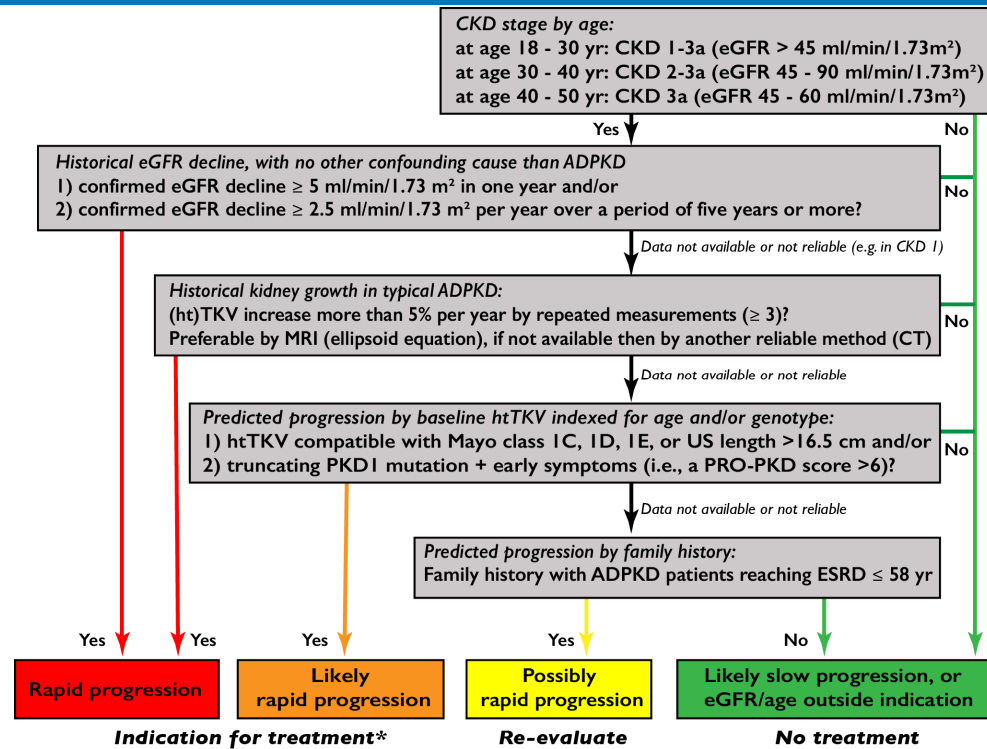
What to do? Guidance from.... EDTA working group on inherited diseases

Tolvaptan is recommended

- **CKD stage 1 to 3a**
 - (more restrictive than the licensed indication by **excluding stage 3b patients**)
 - less restrictive than NICE by **including CKD stage 1 patients**)
- **Excludes patients >50 years**



What to do? Guidance from.... EDTA working group on inherited diseases



What to do? Guidance from.... EDTA working group on inherited diseases

"... translate into every 4 years of Tolvaptan treatment delaying the incidence of ESRD by approximately 1 additional year"

"Tolvaptan **slowed the rate of eGFR loss by 26%** from 3.70 to 2.72 ml/min/1.73m²/year ..."2

In the RENAAL study **losartan was associated with 15% reduction in eGFR decline** vs placebo (5.2 vs 4.4 ml/min/1.73m² per year)³

In the IDNT study **irbesartan was associated with a 15% reduction in CrCl decline** vs placebo (5.5 vs 6.5 ml/min/1.73m²/year, respectively)⁴

1. Gansevoort RT, et al. *Nephrol Dial Transpl* 2016; (Epub Ahead of Print);



“Rapid progressing disease”

Deteriorating eGFR

-5 ml/min over 1 year or -2.5 ml/min/year over 5 years

Large kidneys MR or U/S, volume or length

- For age
- Absolute size

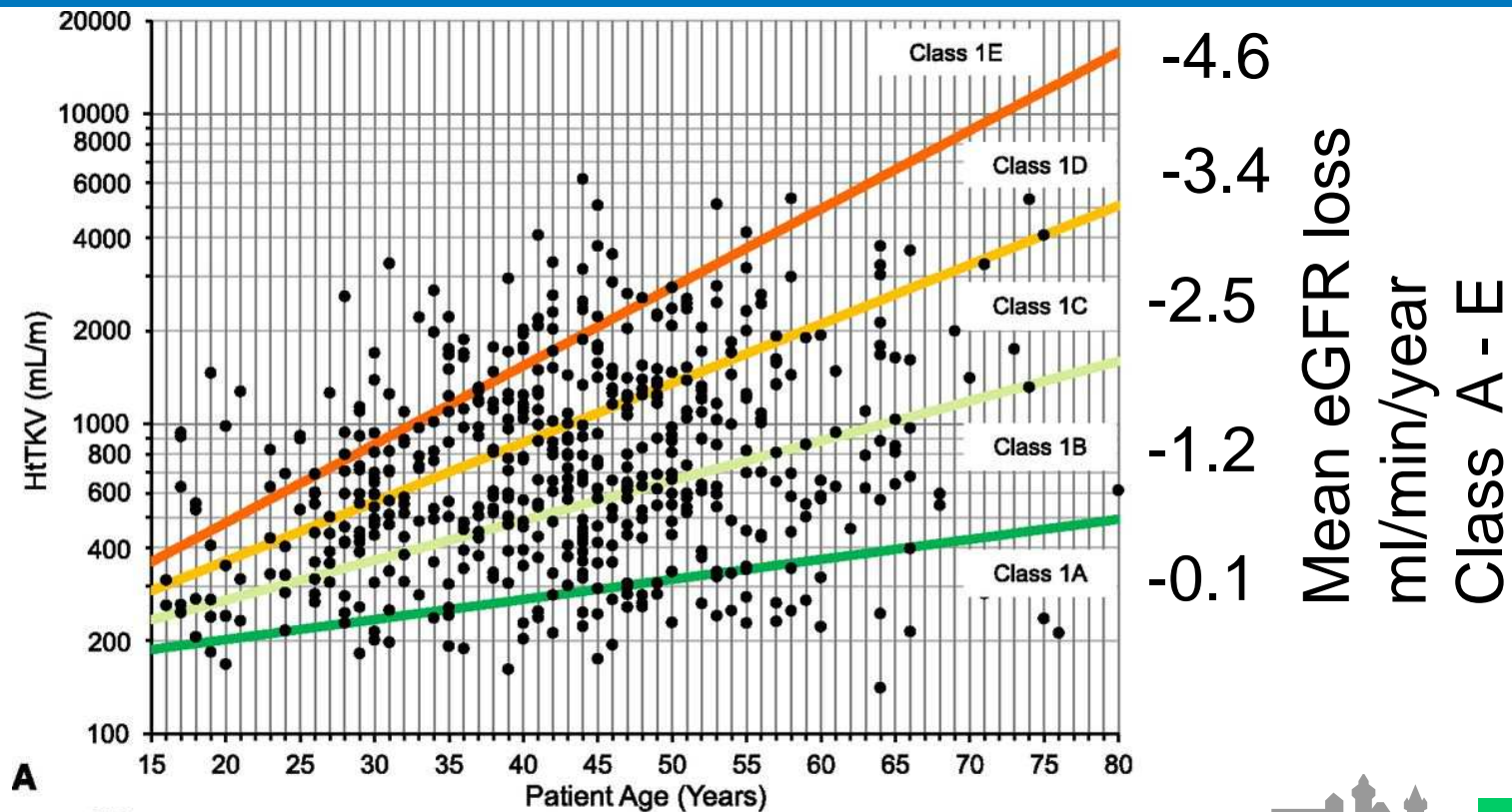
Age/anticipated date of ESRD/projected lifespan

Other markers:

- FH of age at ESRD
- Genotype
- Early Hypertension/symptoms



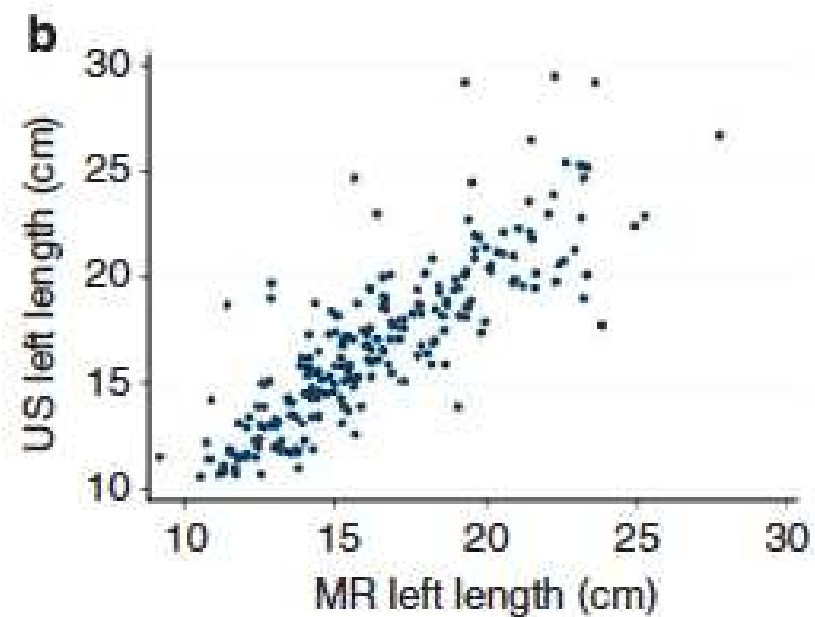
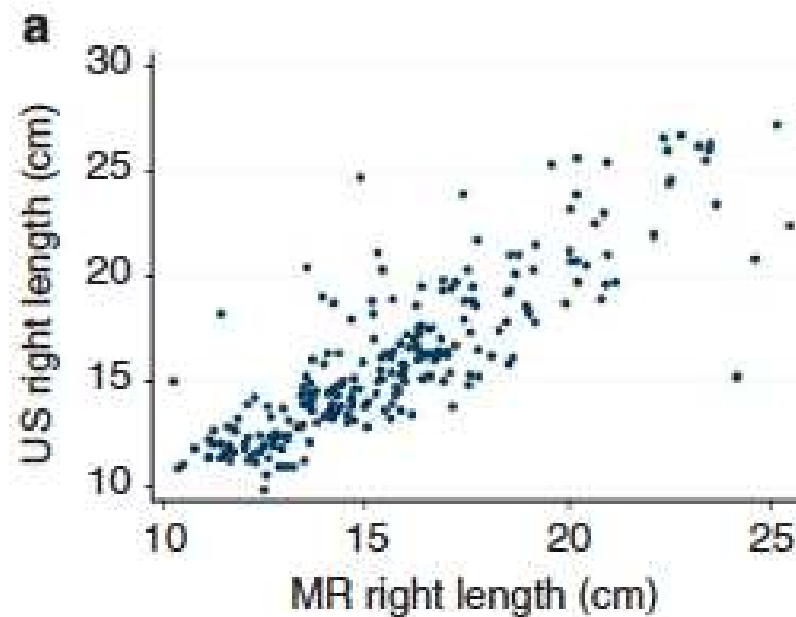
Ht-TKV and age predict the change in eGFR in ADPKD type 1 patients.



Irazabal MV et al. JASN 2015;26:160-172

Nürnberg

High correlation of kidney length by MRI and ultrasound (US)



Case 2

Mrs SP, age 42

- ADPKD discovered aged 41 during investigation for right upper quadrant pain

Family History

- No family history of ADPKD

Past Medical History

- Hypertension treated with ACEi
- Miscarriages x 2
- Hypothyroidism
- Urinary tract infections

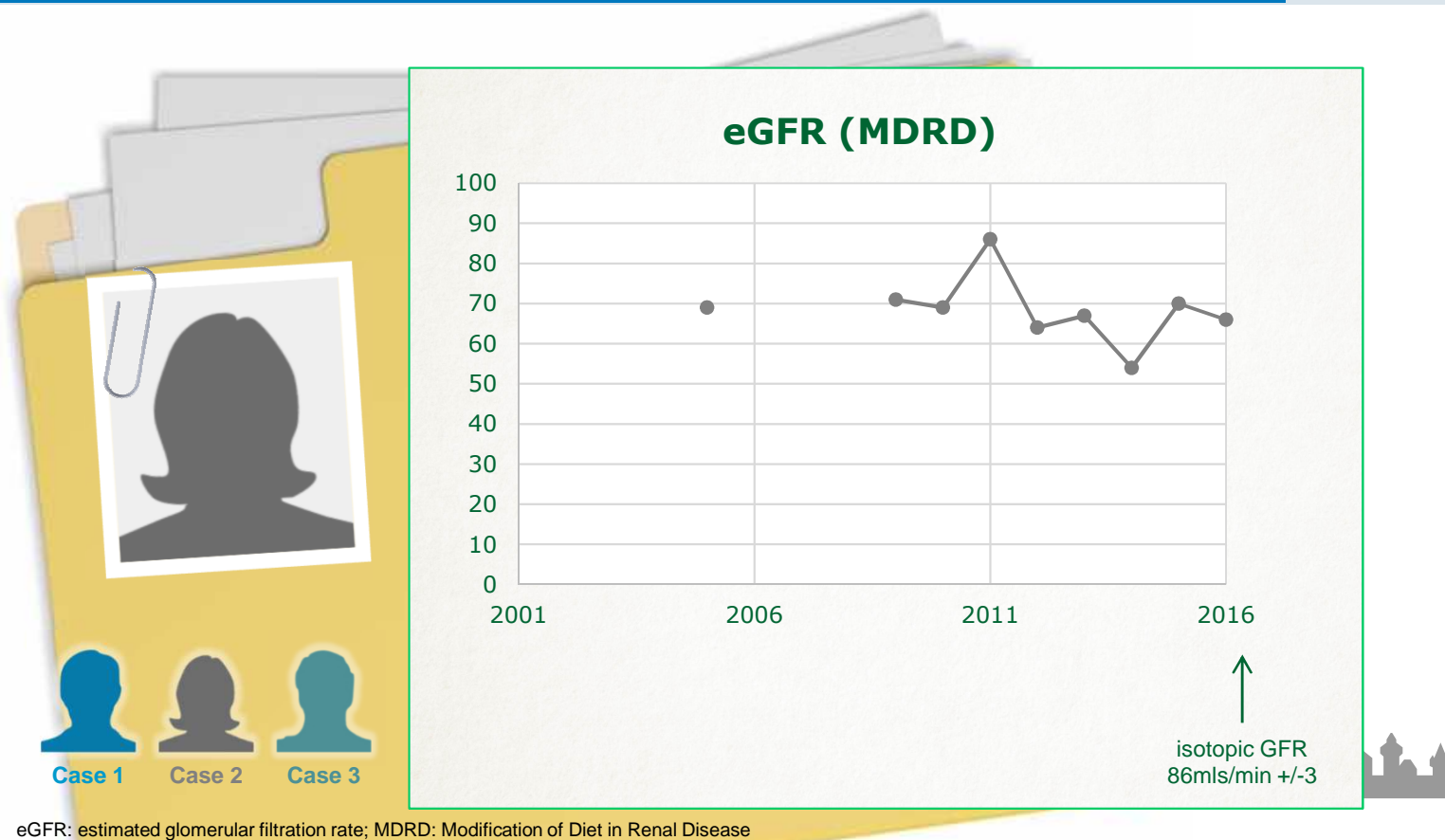
Imaging

- Abdominal ultrasound 2015
- 'Left kidney contains at least 8 cysts, largest 3cm. Renal length 13cm'
- 'Right kidney contains multiple small cysts, renal length 13cm'
- 'Multiple cysts are seen throughout the liver which is enlarged'

Genotyping Confirmed mutation in PKD1 (Deletion exon 27)



Case 2



Case 2



Case 3

Mr MM, age 33

- South African. Moved to the UK in 2013
- ADPKD diagnosed on screening ultrasound as teenager

Family history

- Mother had renal transplant in South Africa
- Daughter aged 10 has renal cysts but normal renal function

Past Medical History

- Hypertension treated with ARB
- Hospital admission with infected cyst in 2010

Imaging

- Renal ultrasound 2013
- 'Both kidneys contain multiple cysts of up to 5cm in size' (no measurements taken)
- Renal ultrasound 2016
- 'Right kidney 15cm, Left kidney 17cm'

Genotyping Confirmed pathogenic mutation in PKD2 gene



Case 1



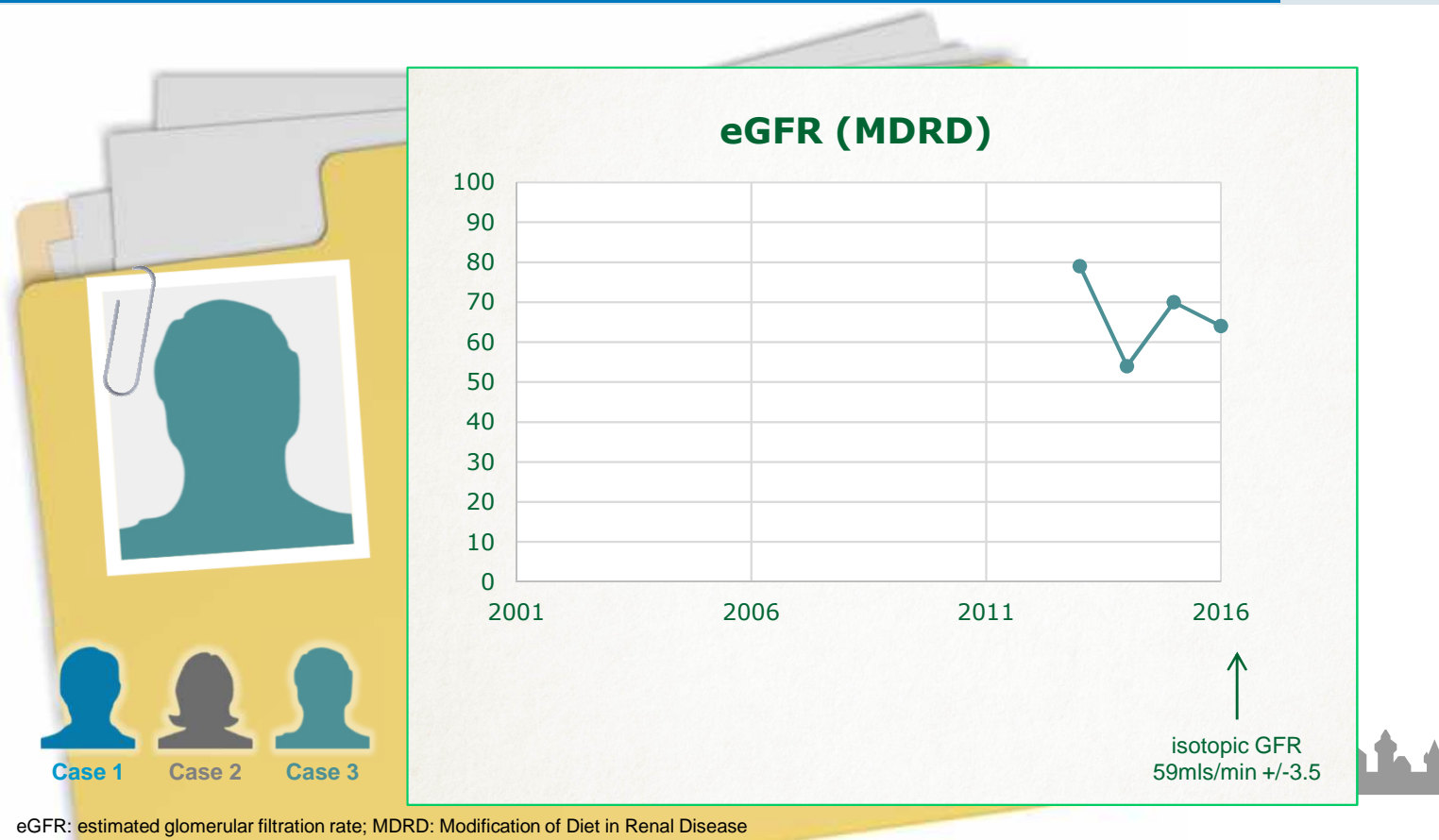
Case 2



Case 3



Case 3



eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease