Spital Thurgau

Insights into the clinical evidence for Tolvaptan and treatment decisions

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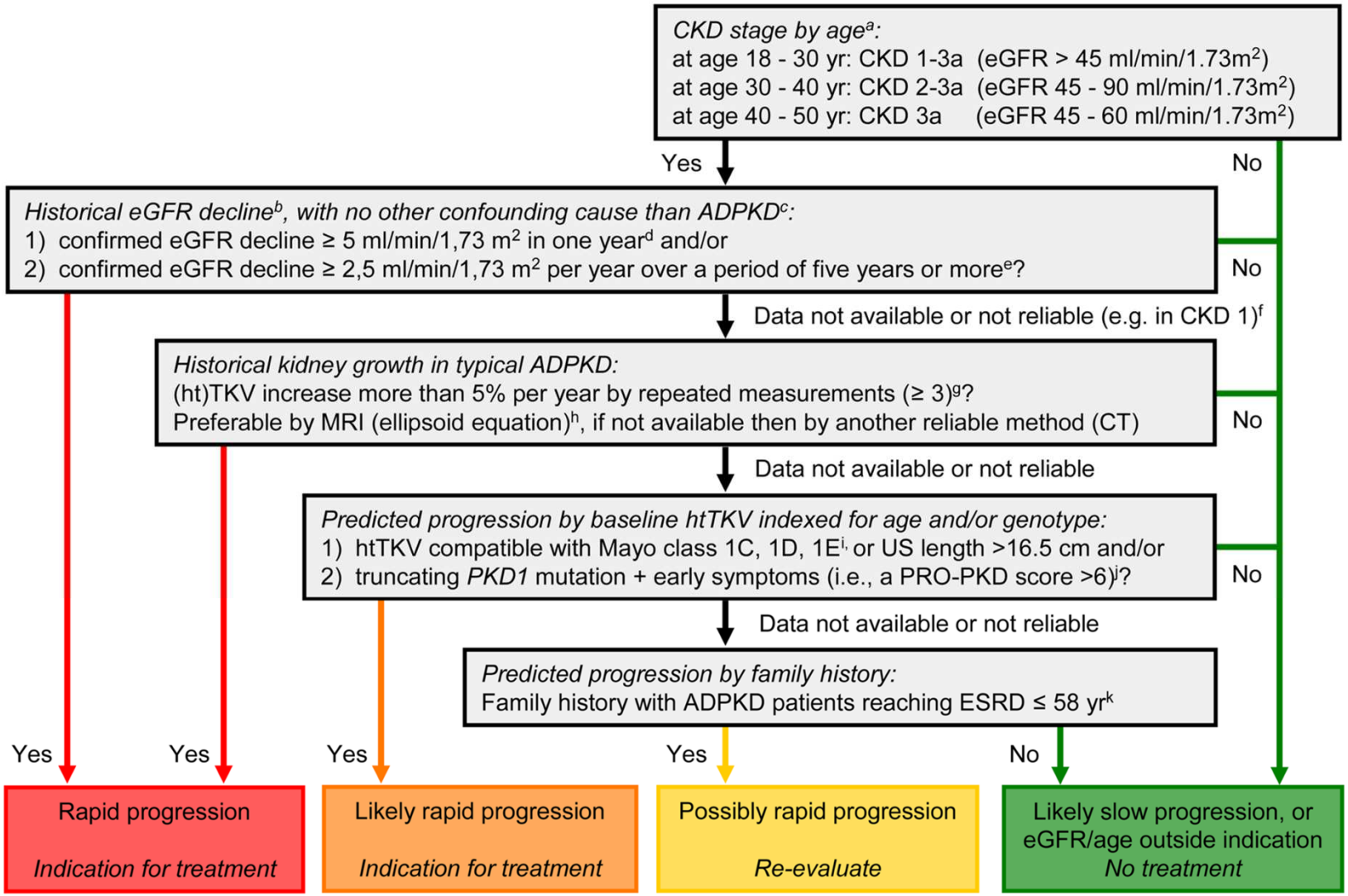
www.nephrologie-thurgau.ch



ERA-EDTA recommendations, Gansevoort et al., NDT 2016

Criteria for the prescription of Tolvaptan (List of Pharmaceutical Specialties)

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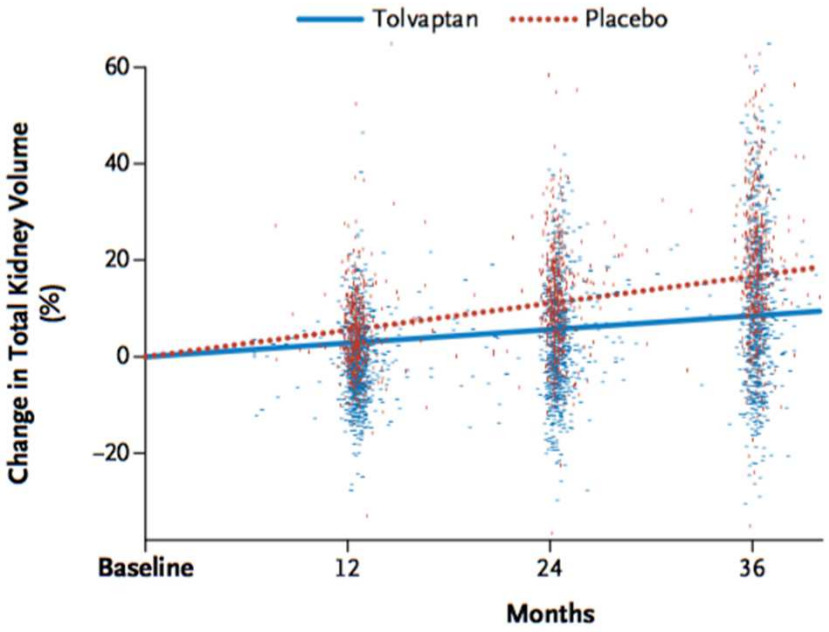
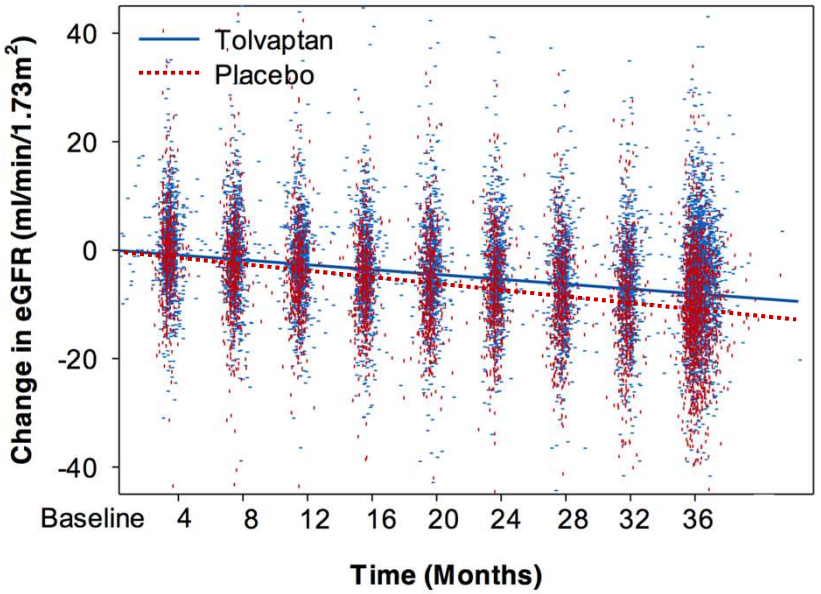
  - Mayo class 1 C, 1D or 1E based on age and (ht)TKV
  - Truncating PKD1 mutation and PRO-PKD-score >6

Outline of the talk

- Summary of the clinical data on Tolvaptan
  - with a focus on recent data
- Guidance on the application of the LS criteria
  - taking into consideration the new clinical data
  - with an emphasis on imaging methods

Tempo 3:4





2.8% vs. **5.5%**

TKV increase per year

-50%

-2.72 vs. **-3.70**

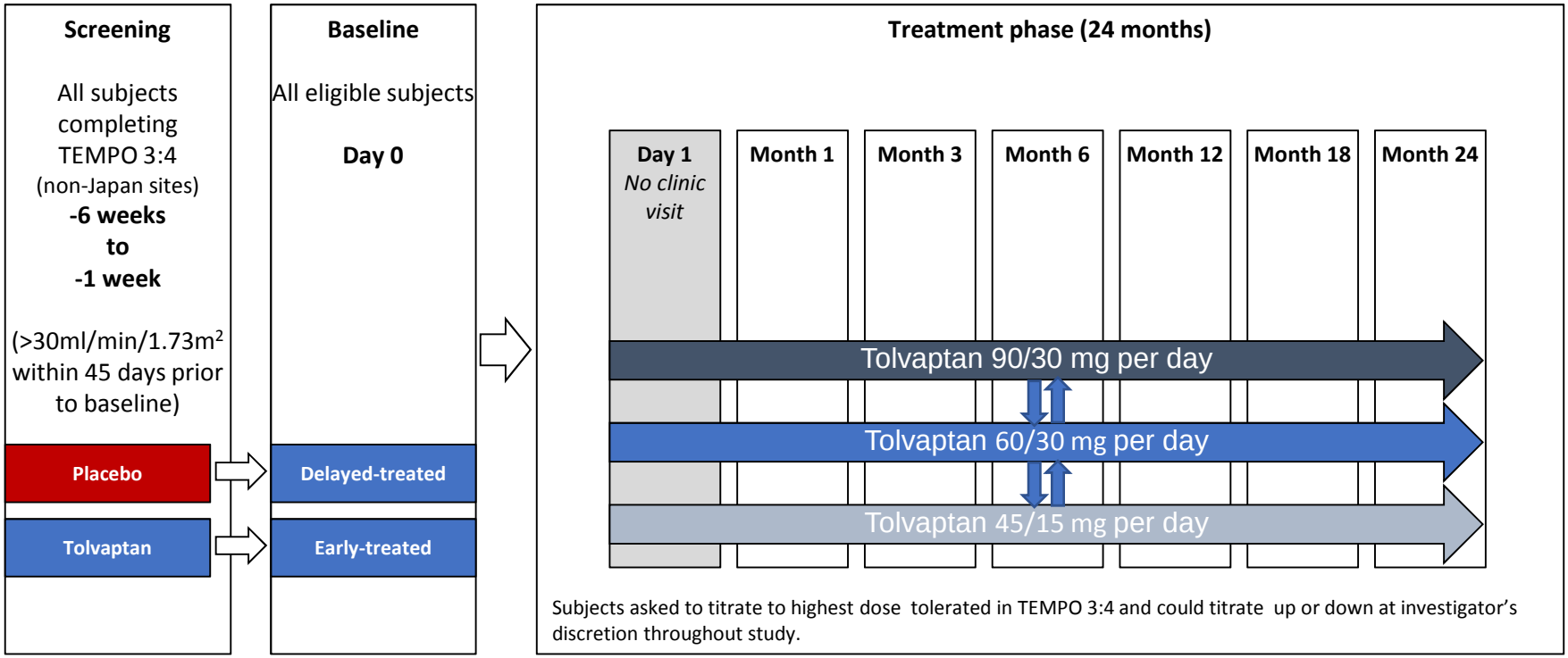
ml/min/1.73m²

annual decrease in eGFR

-26%

Torres VE et al. NEJM 2012;367:2407

TEMPO 4:4 study design



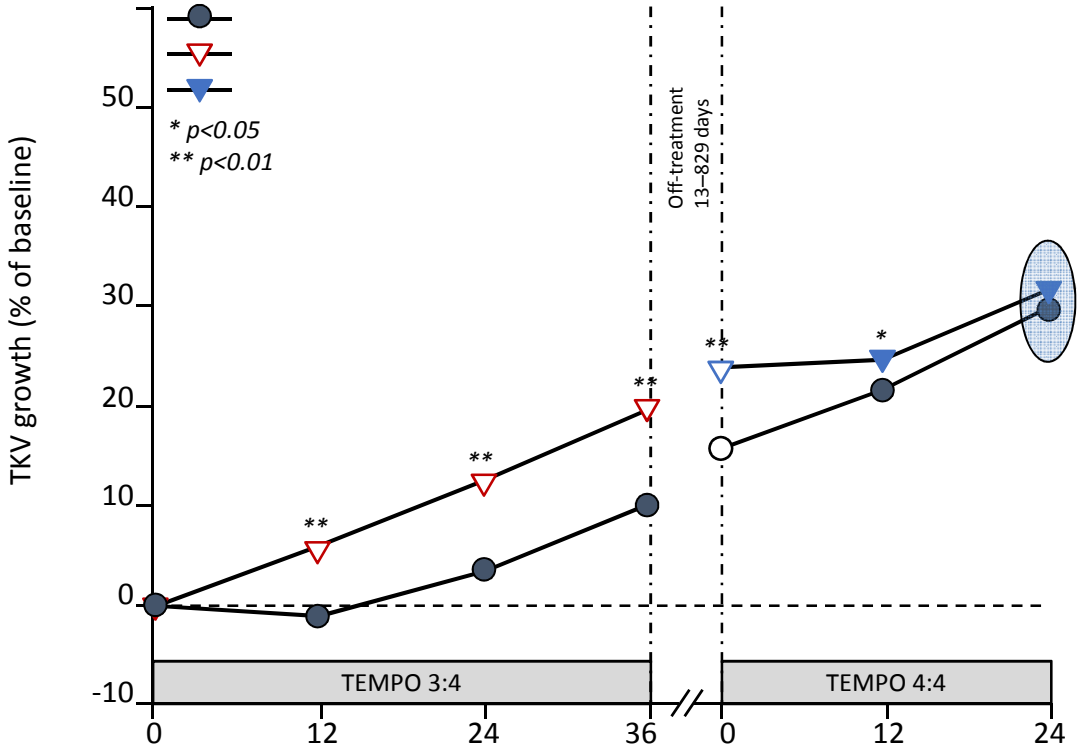
92% of eligible patients were enrolled.
Time from completing TEMPO 3:4 to enrollment in TEMPO 4:4 varied considerably (13–829 days, mean 81, median 37)

Torres VE *et al*. *Nephrol Dial Transplant* 2017 (epub ahead of print Mar 31)

TEMPO 4:4 results, 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



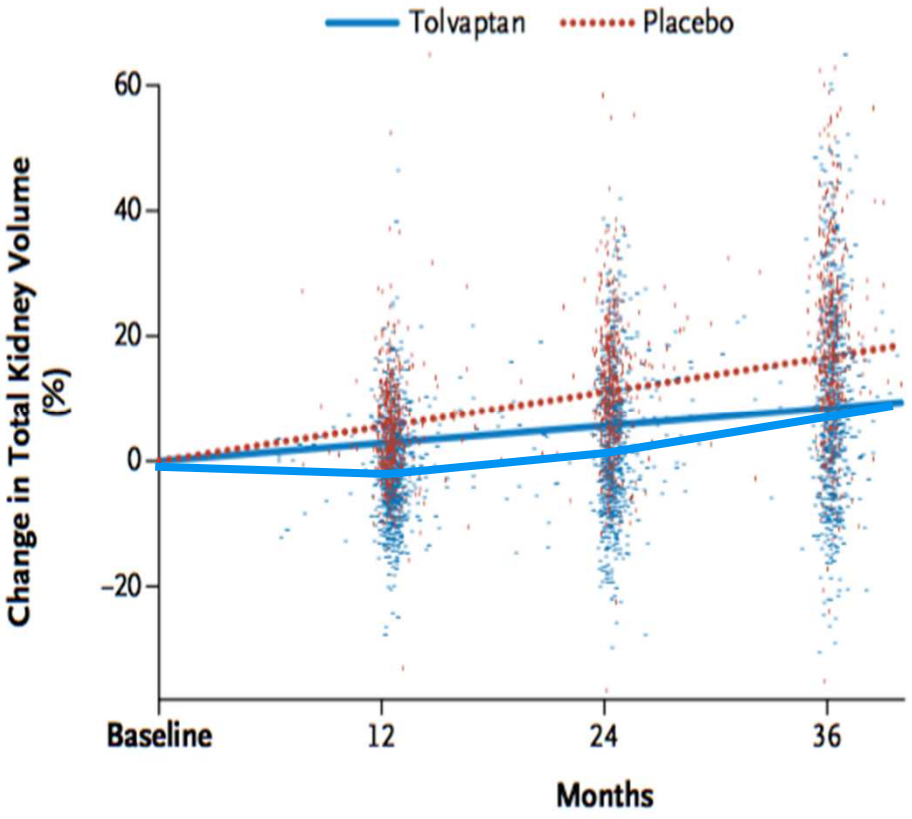
Early-treated N	555	554	555	552	499	535	505
Delayed-treated N	331	312	313	312	289	287	267

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

Open circles and triangles represent off-treatment time points

Torres VE *et al*. *Nephrol Dial Transplant* 2017 (epub ahead of print Mar 31)

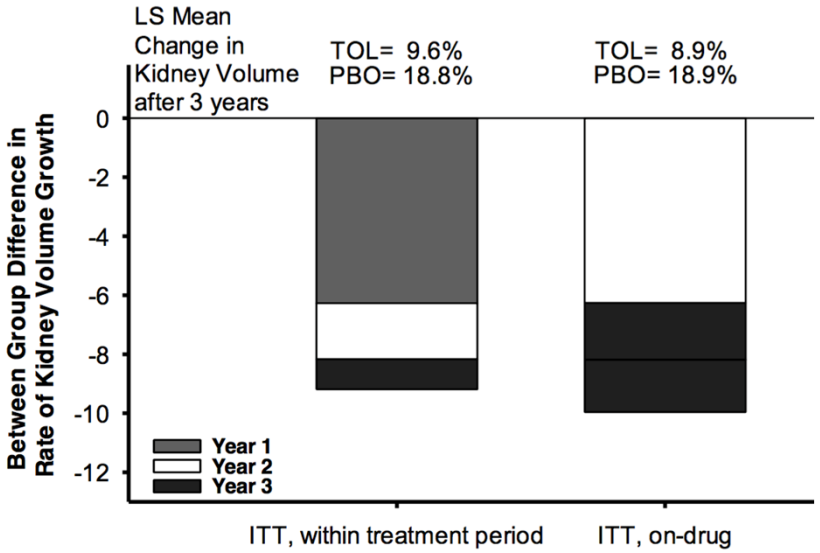
Tempo 3:4 revisted



2.8% vs. **5.5%**

TKV increase per year

Torres VE et al. NEJM 2012;367:2407



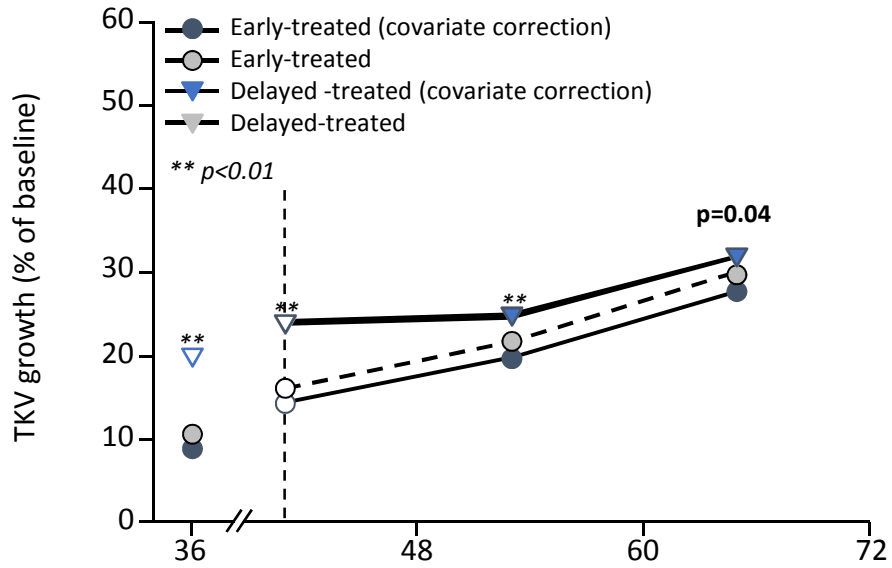
Of the difference in TKV growth between Tolvaptan and placebo over 3 years in Tempo 3:4 (9-10%)

- ***6% ocured in the first year***
- ***1.5 - 2% per year thereafter***
- ***these 1.5 - 2% per year are likely due to an anti-proliferative effect***
- ***4 - 4.5% are likely due to an acute anti-secretory effect***

TEMPO 4:4 results

Impact of adjusting for important covariates on primary TKV endpoint*

Percentage change from baseline in TKV when adjusted for covariates



Early-treated N	552	499	535	505
Delayed-treated N	312	289	287	267

Duration from TEMPO 3:4 baseline (months)

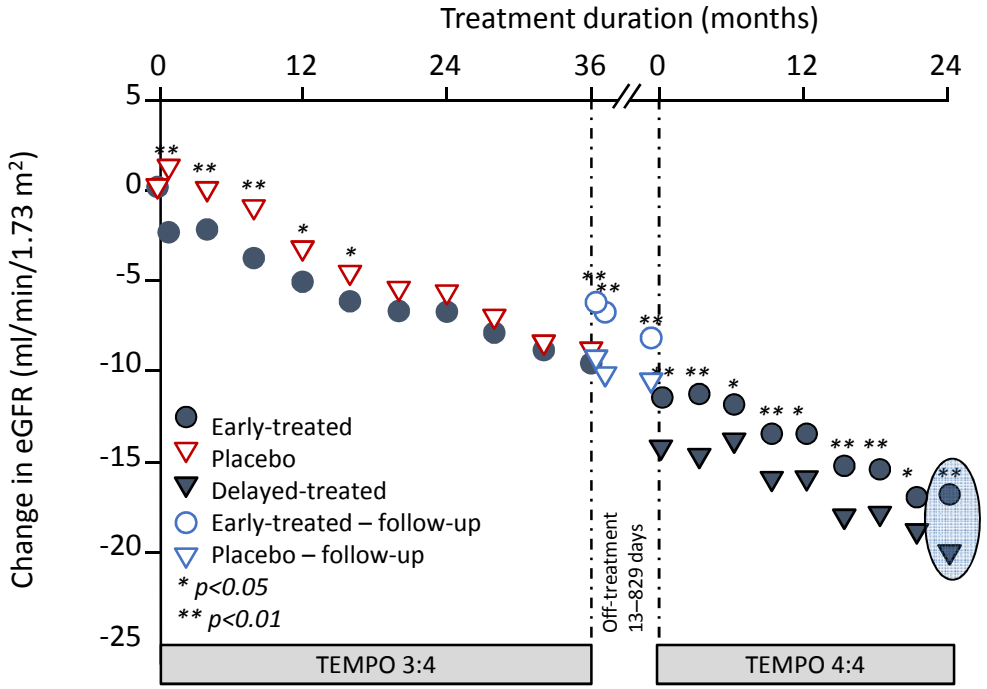
Adjusting for covariate imbalances improved the TKV treatment difference between the early- *vs* delayed-treated groups at month 24 of TEMPO 4:4 from -1.70% to -4.15% (p=0.04)

**The following variables were included in an unstructured variance covariance matrix with fixed factors as in the primary analysis, with the addition of copeptin and baseline (TEMPO 4:4) covariates of age, gender, gender visit interaction, eGFR, eGFR visit interaction, and urine ACR.*

Torres VE *et al*. *Nephrol Dial Transplant* 2017 (epub ahead of print Mar 31)

TEMPO 4:4: results, secondary endpoint

Change in eGFR from TEMPO 3:4 baseline to Tempo 4:4 month 24 in early- vs delayed-treated subjects



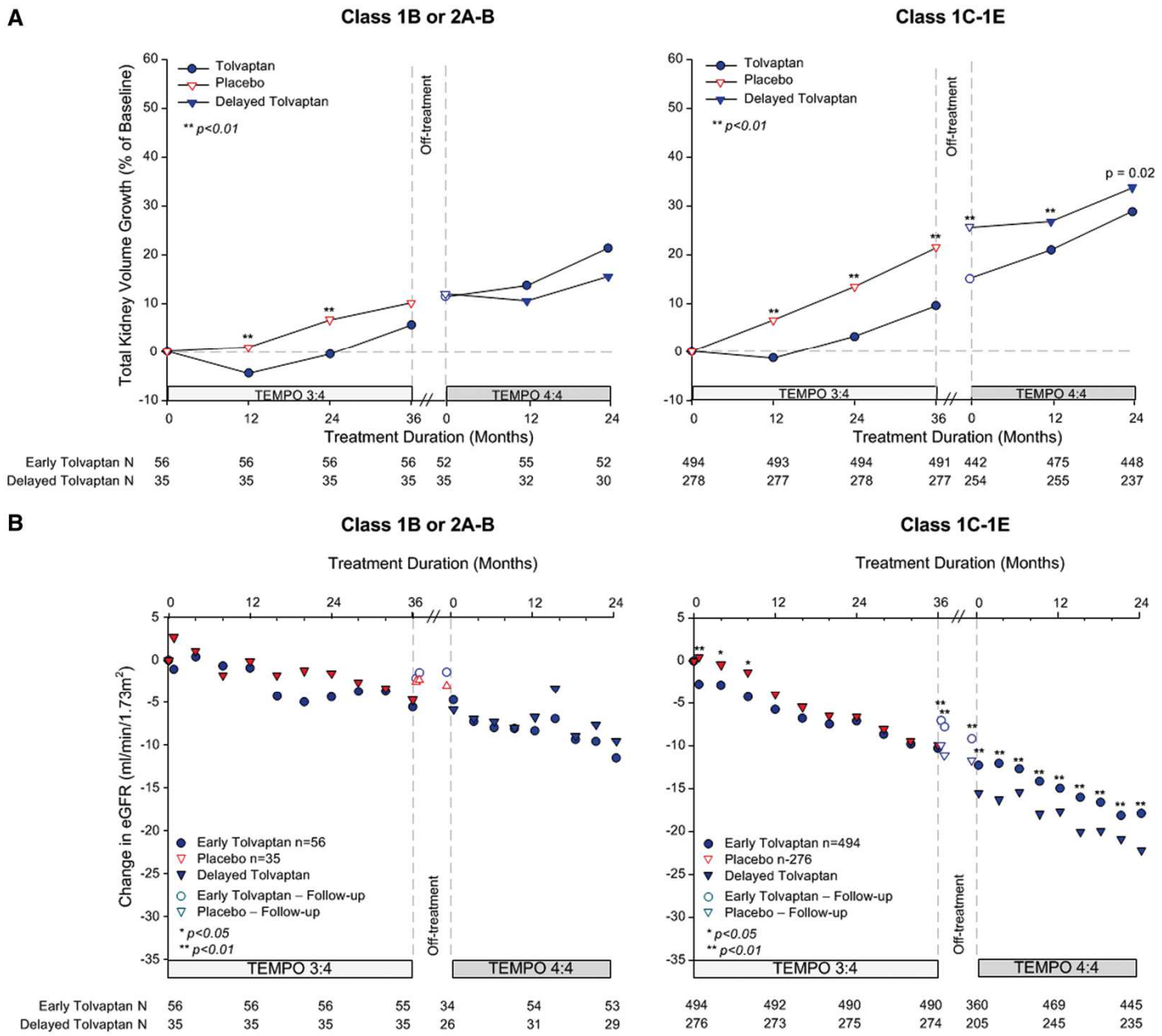
Early-treated N	555	553	551	550	398	528	503
Delayed-treated N	331	308	310	309	231	276	264

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

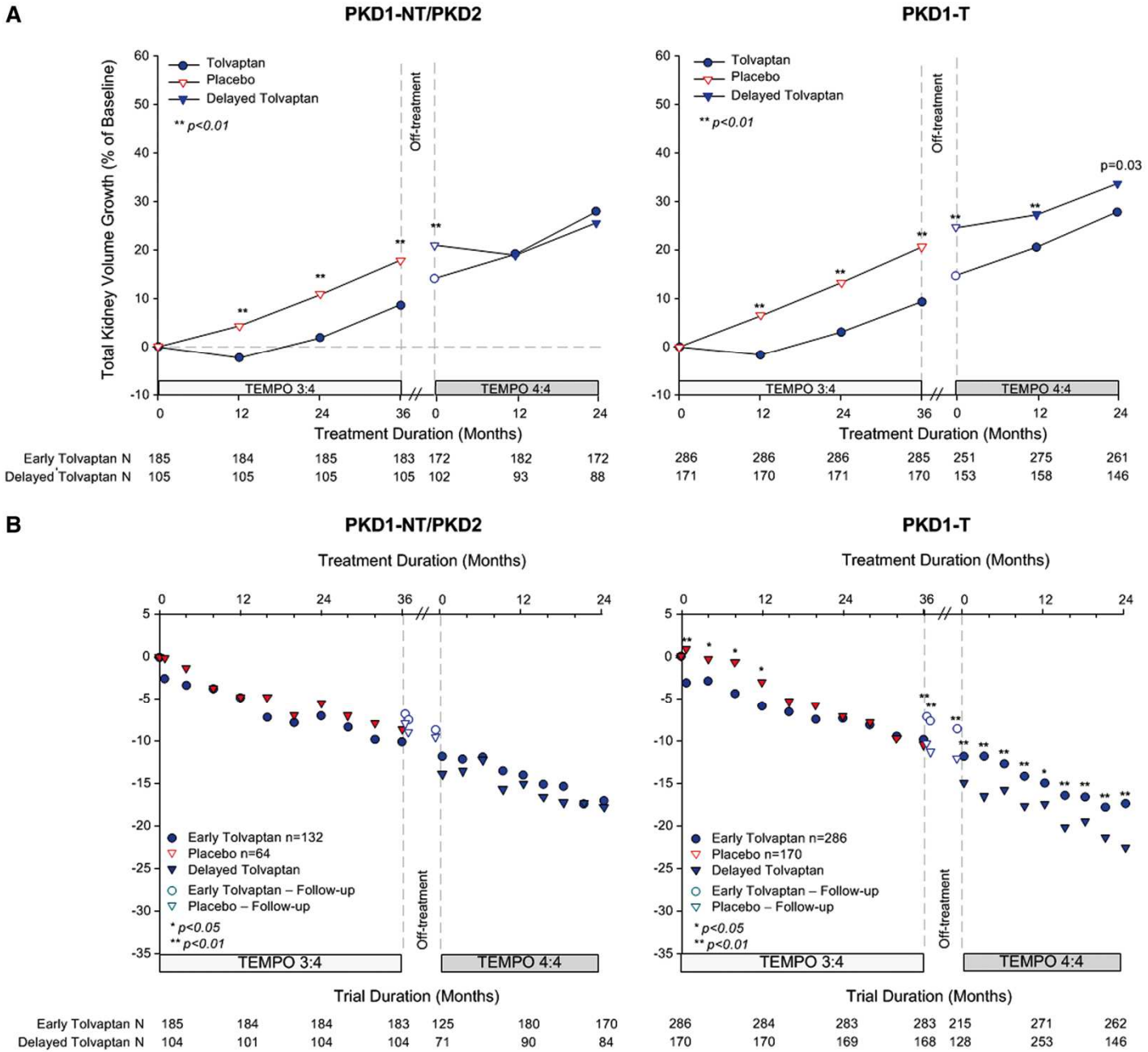
Torres VE *et al*. *Nephrol Dial Transplant* 2017 (epub ahead of print Mar 31)

Subgroup analysis: Mayo Class



Torres VE *et al*. *Nephrol Dial Transplant* 2017 (epub ahead of print Mar 31)

Subgroup analysis: Mutation type



Torres VE *et al*. *Nephrol Dial Transplant* 2017 (epub ahead of print Mar 31)

TEMPO 4:4: conclusions

- Tolvaptan exerts both an acute (anti-secretory) as well as a chronic (anti-proliferative) effect on TKV and a relevant part of the effect in Tempo 3:4 was due to the former
- The effect of Tolvaptan on eGFR seems to be sustained
- Significant benefits of Tolvaptan were seen only in patients with more severe disease
  - Justifies the limitation for the prescription of Tolvaptan only to patients at high risk for progression

REPRISE: study design

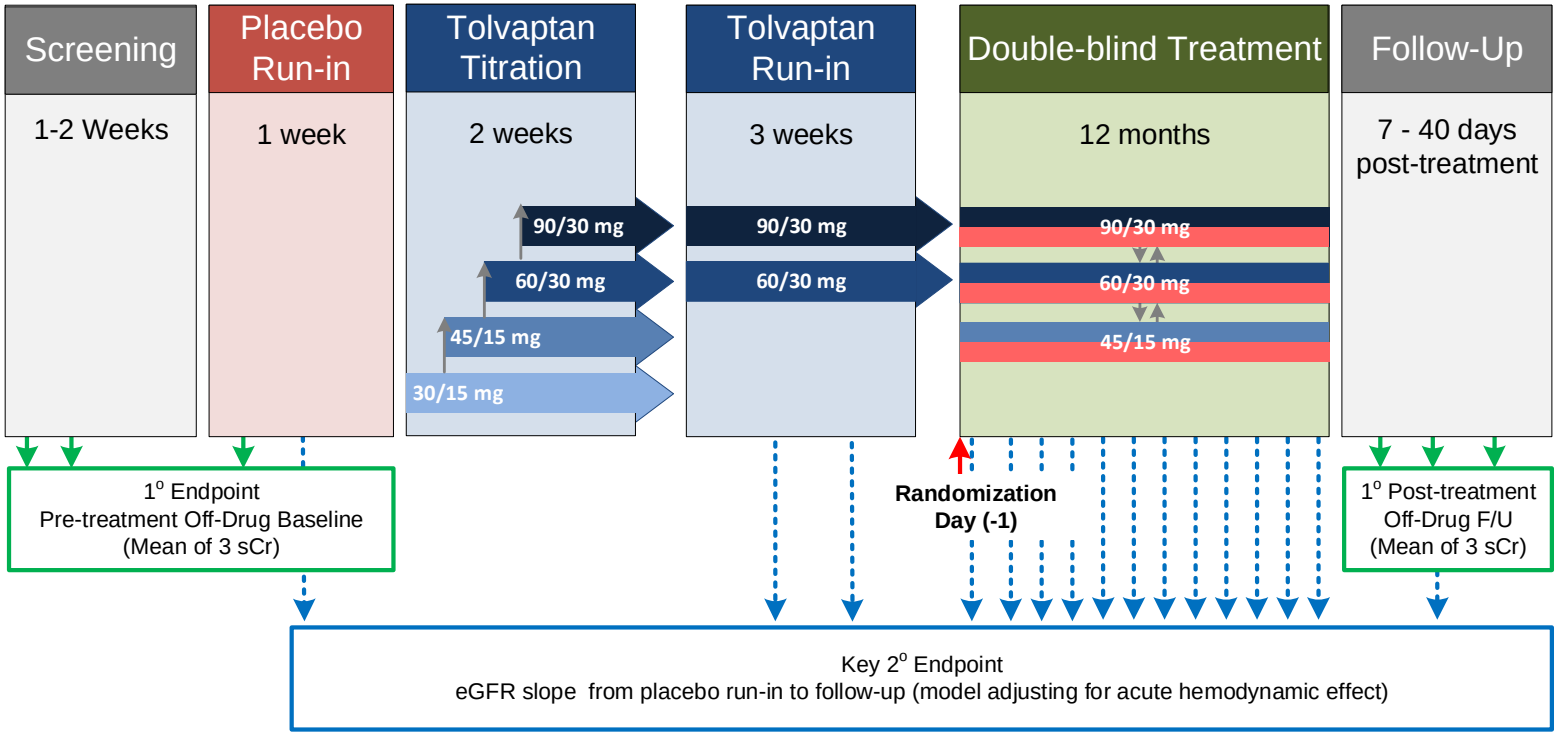
Patient population:

18-55 years old with eGFR 25-65 ml/min/1.73m^2

or

56-65 years old with eGFR 25-44 ml/min/1.73m^2

and historical eGFR-decine > 2 ml/min/1.73m^2 per year

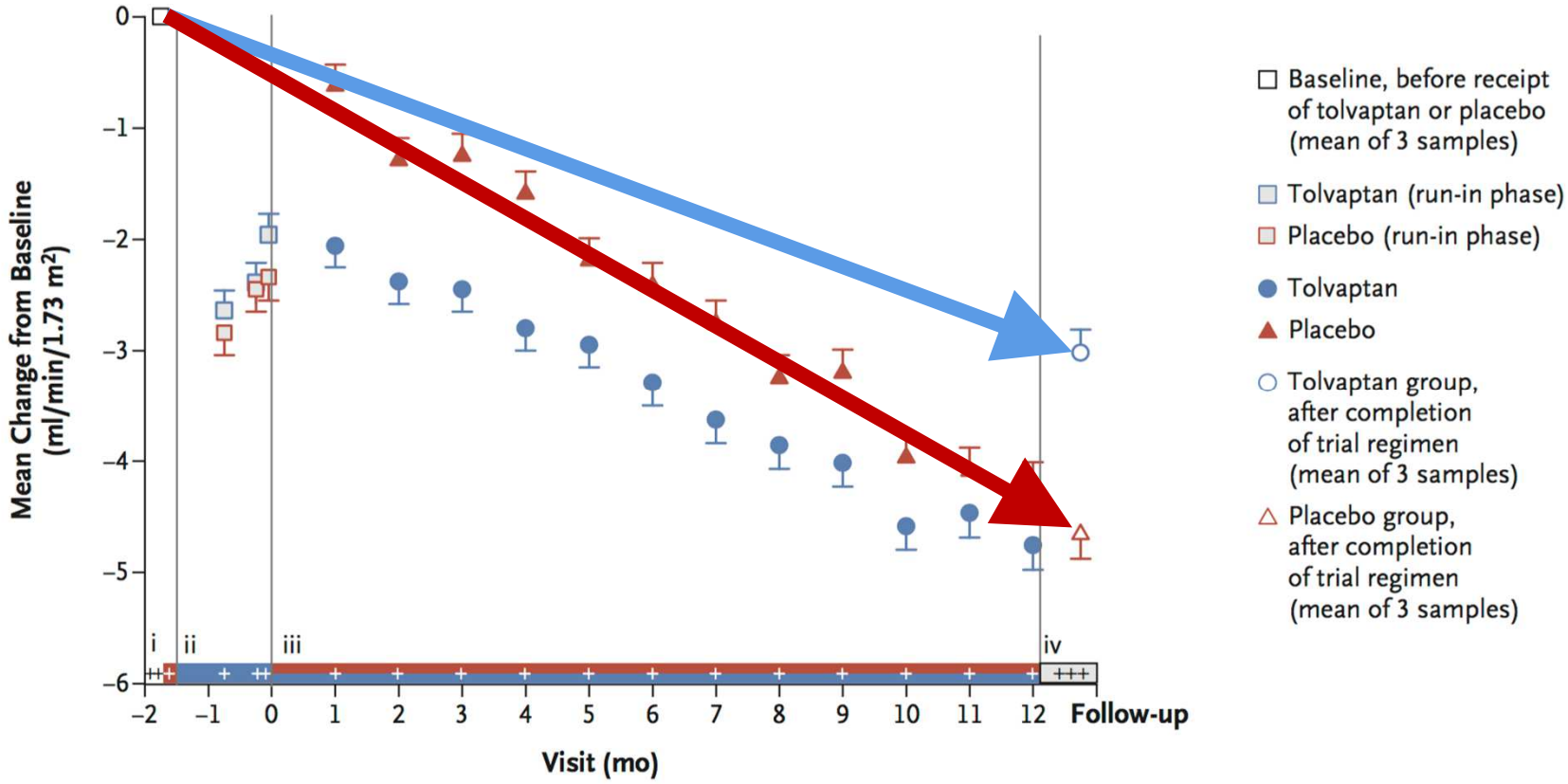


Torres VE *et al*. *NEJM* 2017;377(20):1930

Use of Tovaptan for ADPKD in CKD 4 is outside of Swissmedic approved indication

REPRISE results: primary endpoint

change in eGFR pre- vs. post-treatment



-2.34 vs. **-3.61** ml/min/1.73m²

change in eGFR

Torres VE *et al*. *NEJM* 2017;377(20):1930

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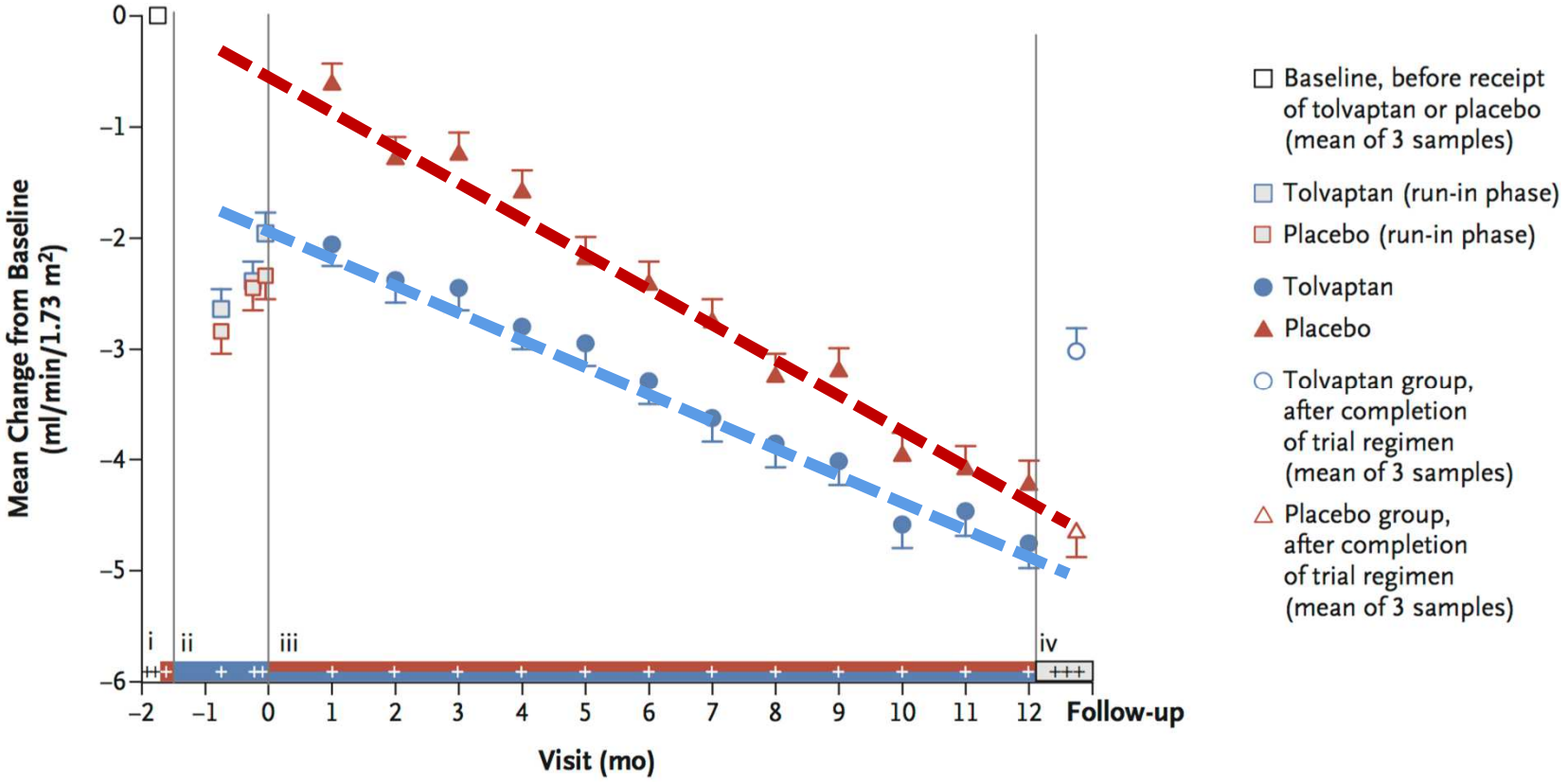
REPRISE results: secondary endpoint

eGFR slope (adjusted for acute effect)



-3.16 vs. **-4.17** ml/min/1.73m^2 per year

slope of eGFR

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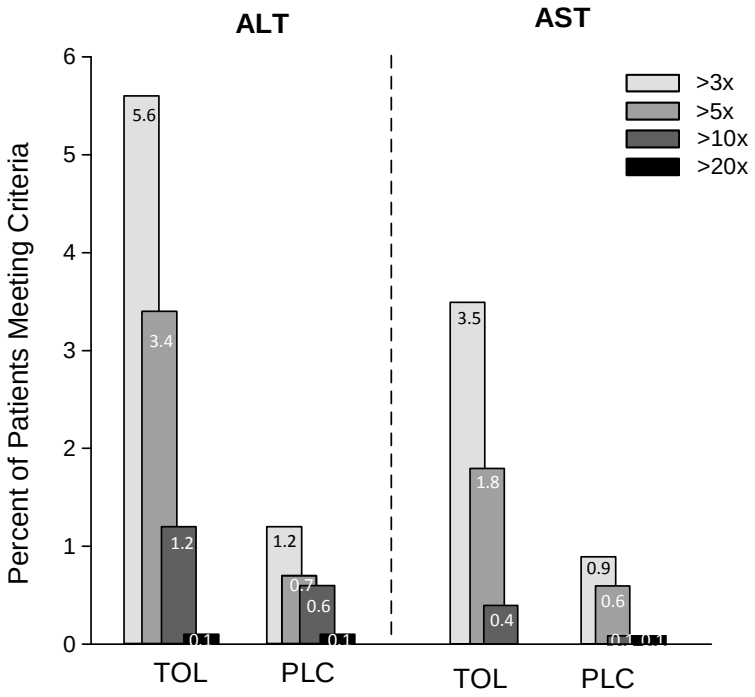
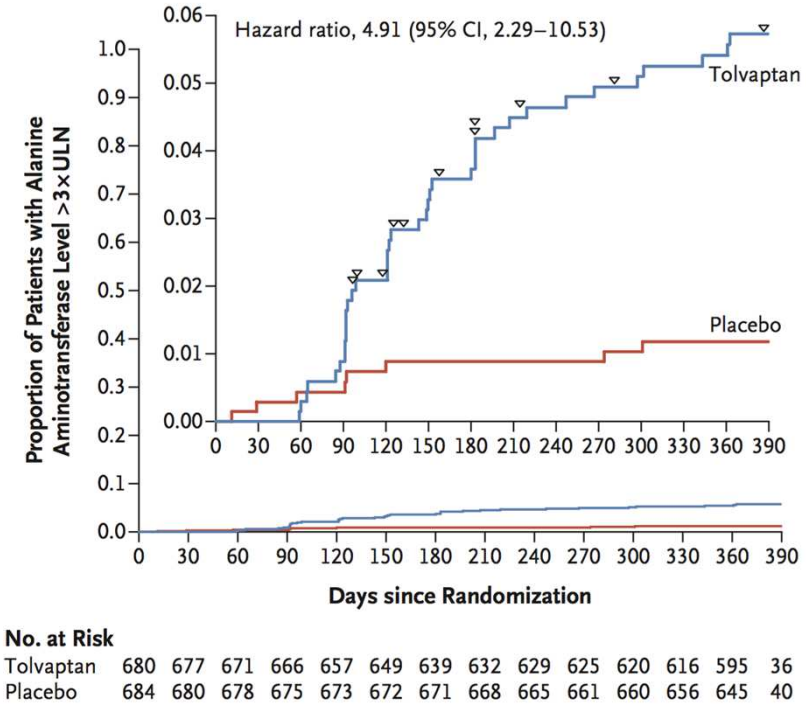
Use of Tovaptan for ADPKD in CKD 4 is outside of Swissmedic approved indication

REPRISE results: safety

liver enzyme elevations





- ***More cumulative AST / ALT elevations than in TEMPO (due to more frequent monitoring)***
- ***All AST / ALT elevations returned to baseline after interruption of treatment***
- ***No increases in billirubin; no Hy's law cases***

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  - taking into consideration the new clinical data
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Recommendations for Diagnostic and Prognostic Evaluation of Autosomal Dominant Polycystic Kidney Disease (ADPKD) with a Focus on Imaging

Empfehlungen zur diagnostischen und prognostischen Evaluation der autosomal-dominanten polyzystischen Nierenerkrankung (ADPKD) mit Fokus auf die Bildgebung

Andreas Kistler[1,3] und Gustav Andreisek[2,3]

The Swiss Society of Radiology (SGR-SSR) and the Swiss Society of Nephrology Working Group of Inherited Kidney Disorders endorse the scientific content of this manuscript. The SGR-SSR agrees in particular with the suggested technique for image acquisition and measuring kidney volume. The society also agrees on the suggestion that treatment and imaging should be performed by the same institution and imaging follow-up should, whenever possible, be performed by the same radiological institution who has performed the baseline study.

Praxis, in press

Criteria for the prescription of Tolvaptan (List of Pharmaceutical Specialties)

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- eGFR ≥ 30 ml/min/1.73m^2
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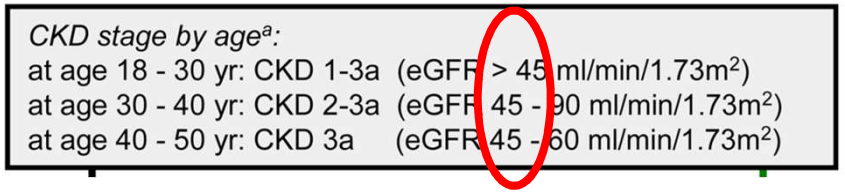
  - Mayo class 1 C, 1D or 1E based on age and (ht)TKV
  - Truncating PKD1 mutation and PRO-PKD-score >6



GFR range for treatment initiation

Given that experience with Tolvaptan is very limited in CKD-stage 3b (GFR 30-45 ml/min/1.73m²), we recommend a very restrictive initiation of Tolvaptan in this GFR range pending further trial data.

Clinical data now support the initiation of Tolvaptan in CKD stage 3b

(clinical data support the initiation of Tolvaptan at an eGFR down to >25 ml/min/1.73m², but initiation of Tolvaptan at an eGFR <30 ml/min/1.73m² is currently off-label)

Kistler and Andreisek, *in press*

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Criterion: confirmed eGFR-loss of ≥ 5 ml/min/1.73m² within 1 year

we suggest that this criterion should not be commonly used as the sole criterion for rapid progression

- measurement errors of serum creatinine
- limited accuracy of the CKD-EPI-Formula
- physiological short-term variability of true GFR based on hydration status, blood pressure and in particular dose adjustments of ACEI/ARB
- An ADPKD patient with a true GFR loss of ≥ 5 ml/min/1.73m² per year will usually fulfill other criteria for rapid progression unless the GFR loss is due to non-ADPKD-related factors

Kistler and Andreisek, *in press*

Criterion: confirmed eGFR-loss of ≥ 5 ml/min/1.73m² within 1 year

If treatment initiation is based on this criterion

- non-ADPKD-related causes for rapid GFR loss need to be excluded
- GFR loss must be based on several eGFR-determinations over time that show a continuous decline
  - We strongly suggest to extend the observation period beyond one year if feasible and to use at least 4 eGFR determinations based on the same method and the same laboratory

Kistler and Andreisek, *in press*

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Ultrasound

CT / MRI

Ellipsoid formula

95%-CI: ± 25-70%

O'Neill et al., AJKD 2005
Turco et al., AJN 2017

We recommend reporting the maximum diameter of the kidneys in all three dimensions (perpendicular to each other) and kidney volume estimation based on the ellipsoid formula whenever an ultrasound imaging is performed in patients with ADPKD. If the maximum longitudinal diameter does not fit a single ultrasound image, panoramic view mode is recommended where available.

Ultrasound

Ellipsoid formula

Kidney length

More precise than TKV compared to MRI-based measurements

Bhutani et al., Kidney Int 2015

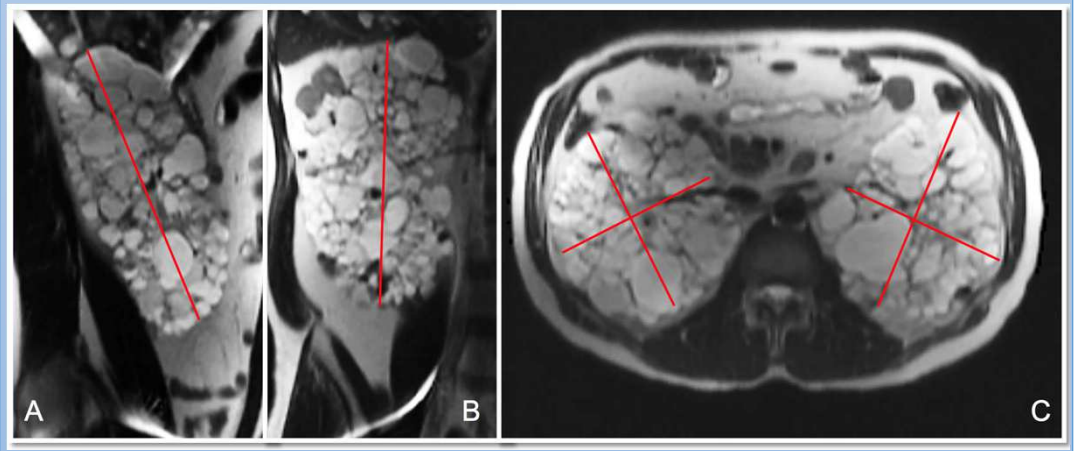
CT / MRI

Stereology

Contour-tracing *(manual / semi-automated)*

Mid-slice method

Ellipsoid formula



95%-CI: ± 12-20%

Irazabal et al., JASN 2015; Spithoven et al., AJKD 2015; Turco et al., AJN 2017

Criterion: Annual TKV increase by ≥ 5% assessed by at least 2 MRI or CT measurements ≥ 6 months apart

http://www.kidney-international.org original article

see commentary on page 139

Increases in kidney volume in autosomal dominant polycystic kidney disease can be detected within 6 months

Andreas D. Kistler[1], Diane Poster[1], Fabienne Krauer[1], Dominik Weishaupt[2], Shagun Raina[1], Oliver Senn[1], Isabelle Binet[3], Katharina Spanaus[4], Rudolf P. Wüthrich[1] and Andreas L. Serra[1]

[1]Clinic for Nephrology, University Hospital, Zürich, Switzerland; [2]Institute of Diagnostic Radiology, University Hospital, Zürich, Switzerland; [3]Clinic for Nephrology, Kantonsspital, St Gallen, Switzerland and [4]Institute for Clinical Chemistry, University Hospital, Zürich, Switzerland

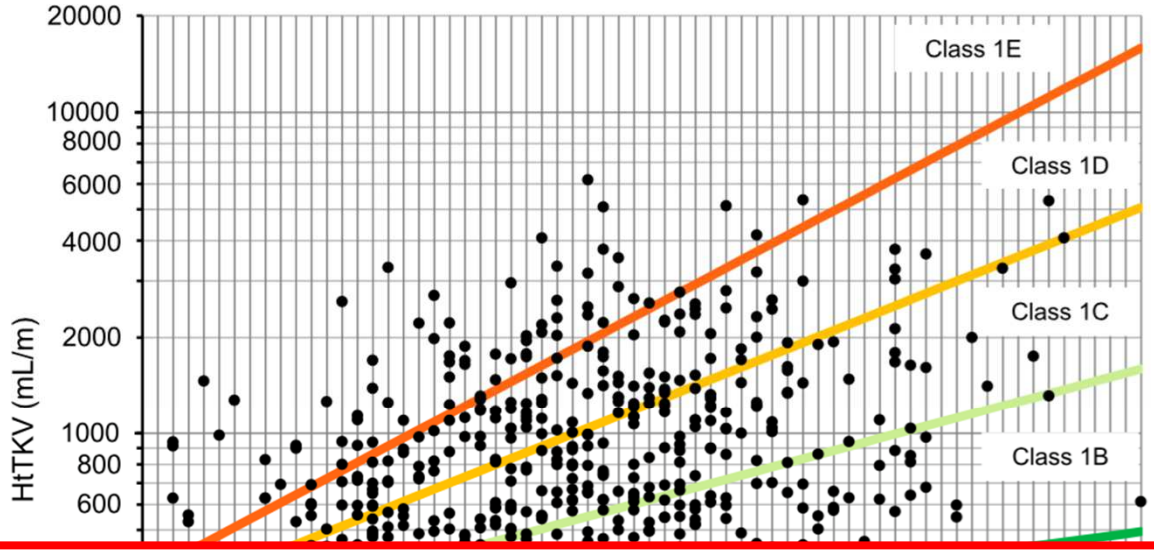
Kidney International (2009) **75**, 235–241; doi:10.1038/ki.2008.558; published online 29 October 2008

Criterion: Annual TKV increase by ≥ 5% assessed by at least 2 MRI or CT measurements ≥ 6 months apart

- ***if possible, use more than two MRI measurements (i.e. at least 3) and determine TKV change by regressing log-transformed TKV against time.***
- ***use the same volume measurement method based on the same MRI-sequences on the same MRI scanner performed at the same institute for all time points.***
- ***be aware of the measurement error of the volumetry methods. Therefore, TKV change from baseline to the last observation should be considerably more than the 95%-CI for the measurement method.***
- Most patient with >5% TKV change per year will belong to Mayo class 1C, 1D or 1E. If a patient with Mayo class 1A or 1B exhibits a TKV progression of >5% per year, the precision of the volumetry and the comparability of the serial measurements should be critically questioned.

Kistler and Andreisek, *in press*

Criterion: Mayo class 1 C, 1D or 1E based on age and htTKV



- ***The classification has been based on MRI or CT images, using the ellipsoid formula***
- ***We prefer MRI over CT due to lower dose of ionizing radiation***
- ***We consider ultrasound-based kidney volume estimates sufficient for patients classified as 1A based on these estimates***
- ***In borderline cases (e.g. upper range of class 1B or lower range of class 1C), precise TKV determination based on contour-tracing should be considered where available***.

Kistler and Andreisek, *in press*

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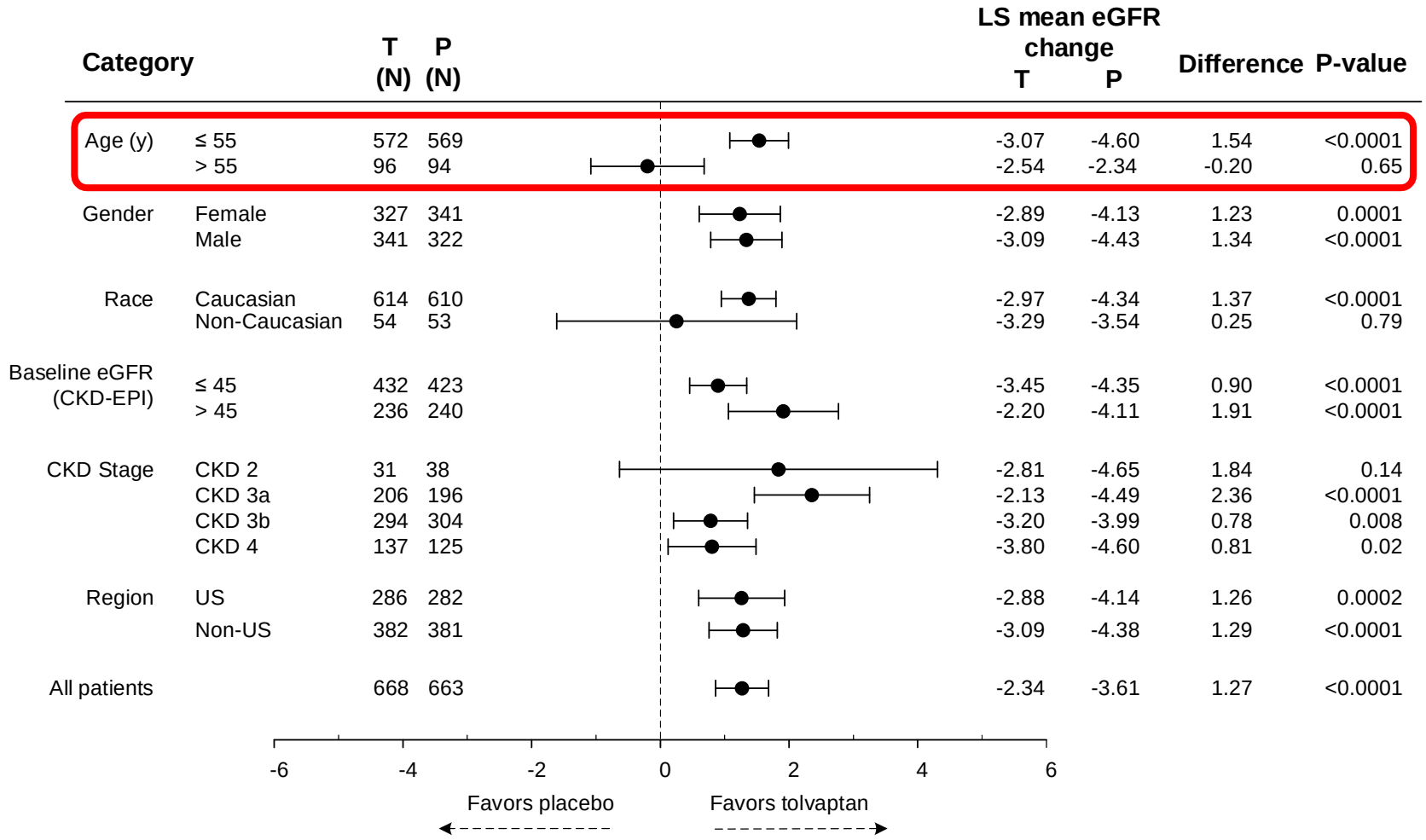
- ***What about age?***

CKD stage by age[a]:
at age 18 - 30 yr: CKD 1-3a (eGFR > 45 ml/min/1.73m^2)
at age 30 - 40 yr: CKD 2-3a (eGFR 45 - 90 ml/min/1.73m^2)
at age 40 - 50 yr: CKD 3a (eGFR 45 - 60 ml/min/1.73m^2)

REPRISE results: primary endpoint

Subgroup analyses



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Thank you for your attention

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www.nephrologie-thurgau.ch