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SUISSE ADPKD Cohort
Treatment and Outcomes with Tolvaptan, first in class Vasopressin V2 Antagonist

Hirslanden, 22 March 2018

Stefan Russmann

INSTITUT FÜR ALLGEMEINE INNERE MEDIZIN UND NEPHROLOGIE

Database development with outcomes and safety analyses for a patient cohort with autosomal dominant polycystic kidney disease (ADPKD)

Conducted by Emiri Grimes

External supervisors: Prof. Dr. Stefan Russmann, Prof. Dr. Andreas L. Serra, Dr. David Niedrig

Internal supervisor: Prof. Dr. Ursula Quitterer

Emiri Grimes

- Master Student ETH Pharmacoepidemiology
- Data Analysis

Emiri Grimes is a pharmacist from Japan with several years of working experience in the pharmaceutical industry. She is currently conducting her Master Thesis at ETH Zurich in a collaborative project with drugsafety.ch and Prof. Andreas Serra on a cohort of patients with polycystic kidney disease.

Dr. sc. nat. ETH David Niedrig

- Forschung und Entwicklung
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ADPKD - Course of the illness -

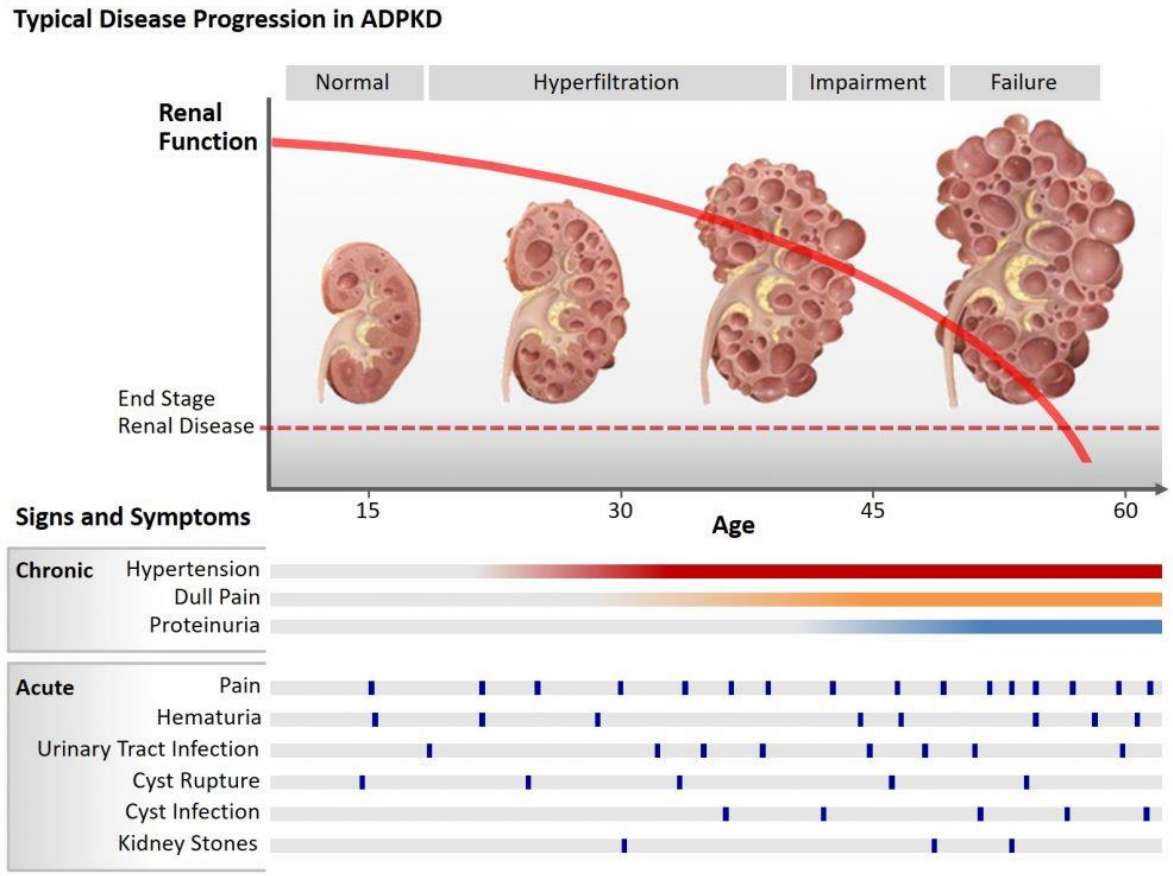
- Cysts grow in number and size
- Disease progression is highly variable

-> Increase of total kidney volume (TKV)

-> Malfunction of the adjacent renal parenchyma

-> decrease of GFR (glomerular filtration)

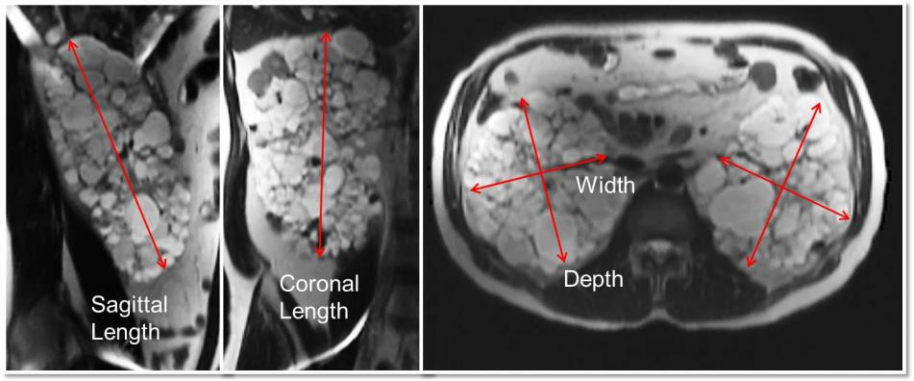
=> Leading to dialysis / kidney transplantation



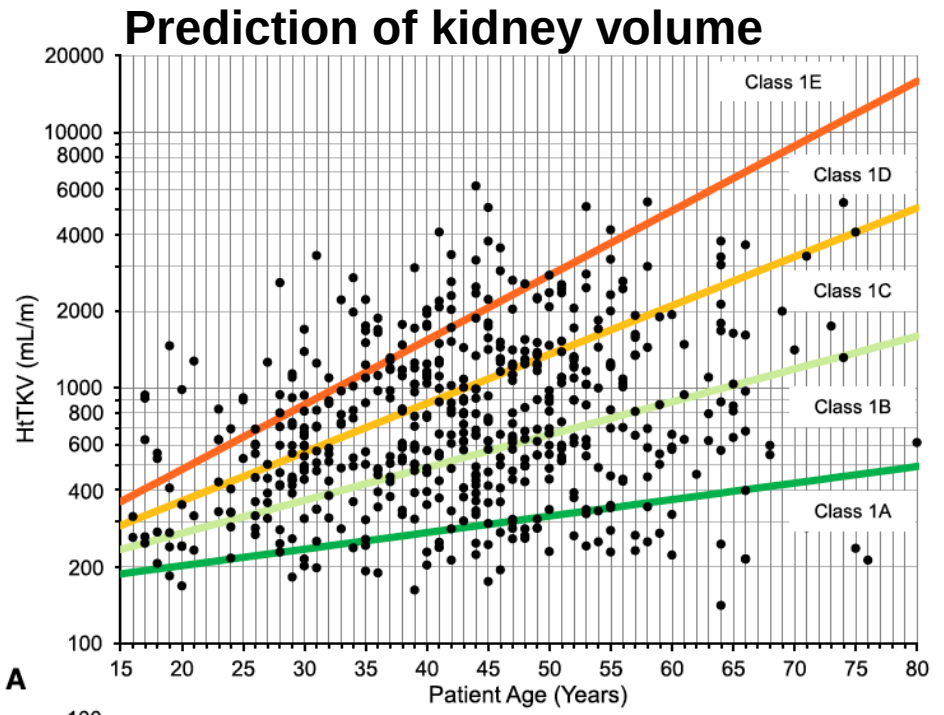
http://palladiobio.com/polycystic-kidney-disease/

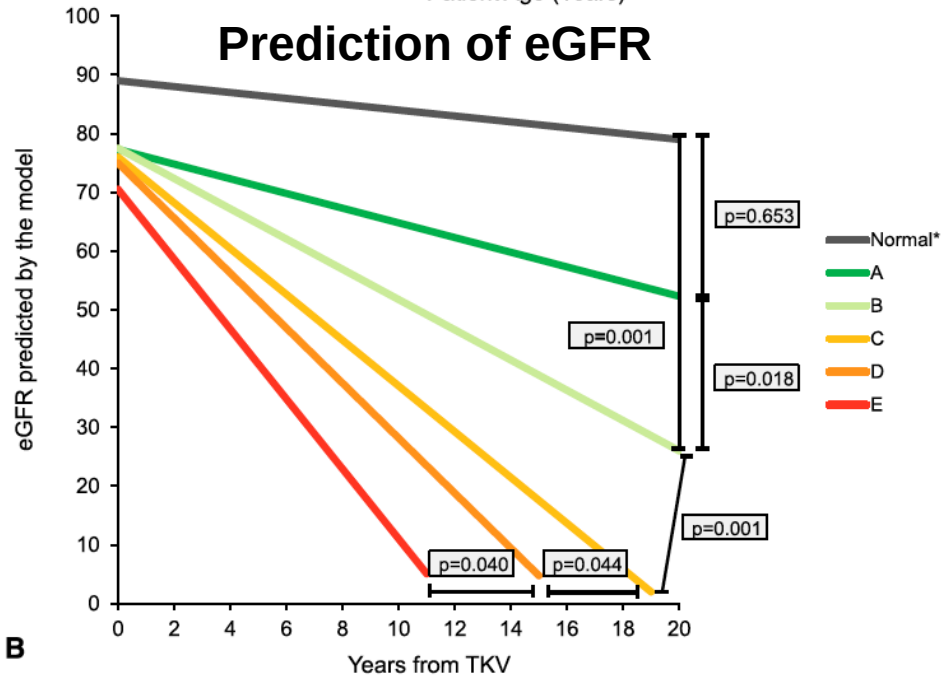
Mayo classification

Imaging with measurement of htTKV (height-adjusted total kidney volume) can predict future TKV and eGFR (class A to E)



http://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754





Irazabal, M.V., et al, ., *J Am Soc Nephrol* 2015. 26(1): 160-72.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease

Vicente E. Torres, M.D., Ph.D., Arlene B. Chapman, M.D., Olivier Devuyst, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D., Jared J. Grantham, M.D., Eiji Higashihara, M.D., Ph.D., Ronald D. Perrone, M.D., Holly B. Krasa, M.S., John Ouyang, Ph.D., and Frank S. Czerwiec, M.D., Ph.D., for the TEMPO 3:4 Trial Investigators*

N Engl J Med 2012;367:2407-18

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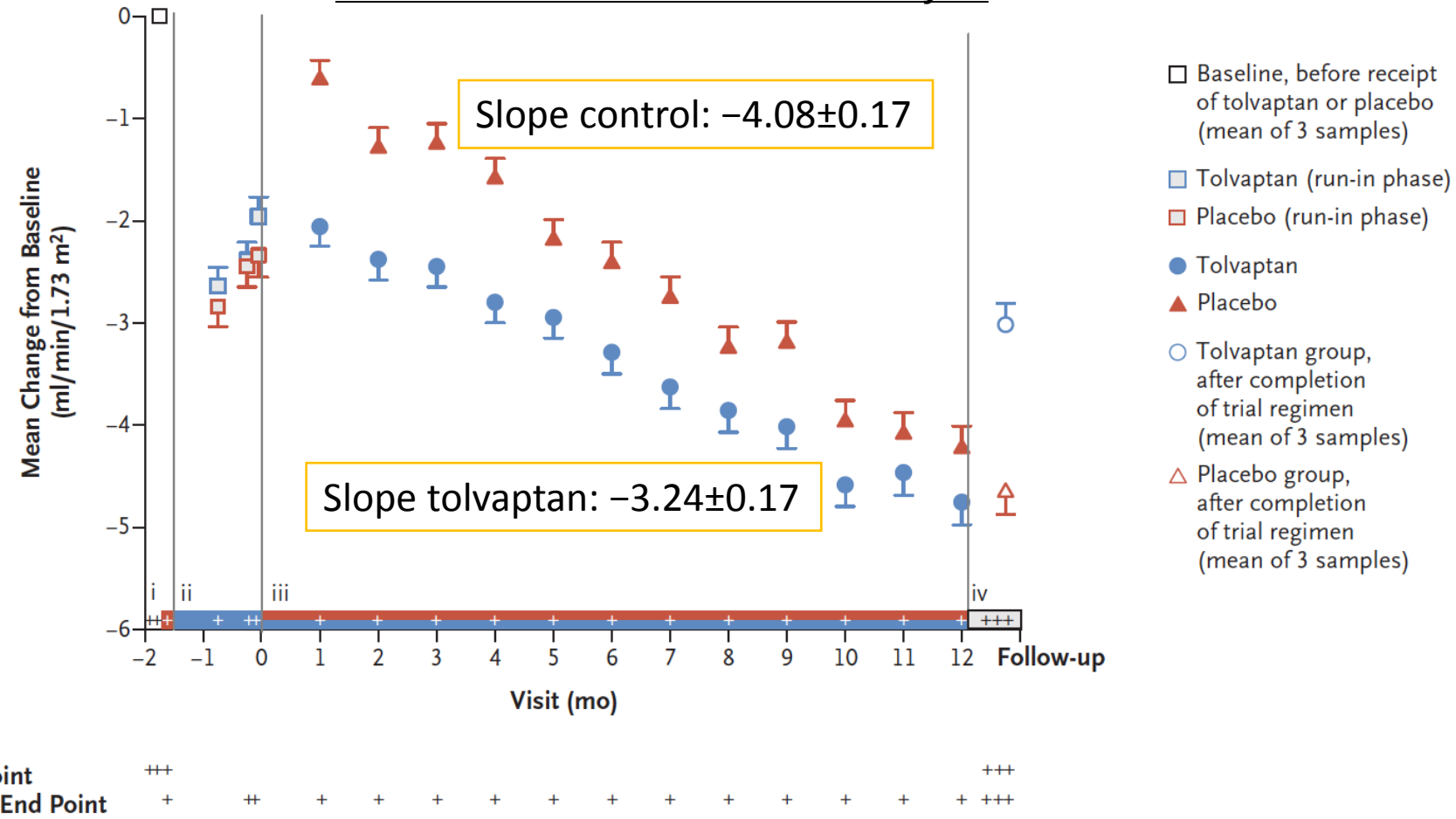
N Engl J Med 2017;377:1930-42

Phase III trial efficacy of tolvaptan, outcome eGFR

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

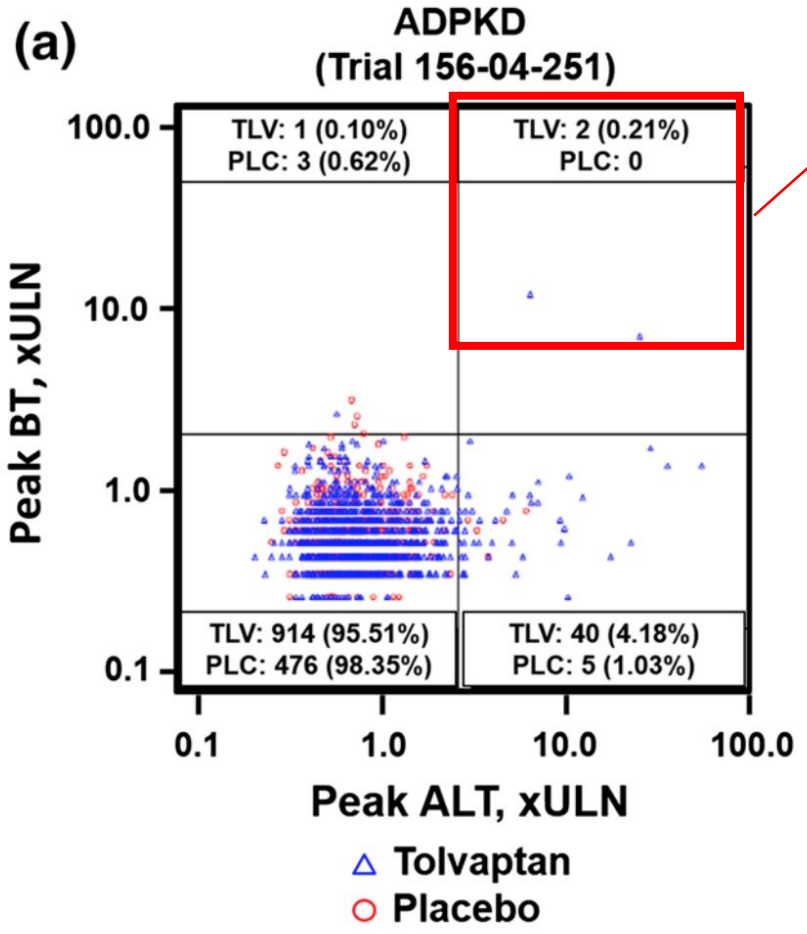
Course of eGFR in clinical trial over 1 year



Extrapolation suggests that time to CKD stage 5 for tolvaptan vs. control would be extended <u>from 6.2 to 9.0 years.</u>

Evaluation of drug-induced hepatotoxicity using an eDISH plot

Safety data from tolvaptan phase III clinical study



2 of 957 subjects taking tolvaptan (0.2 %) met the **Hy's Law criteria** (ALT >3x ULN, total bilirubin >2x ULN

Watkins, P.B., et al., *Drug Saf*, 2015. 38(11): 1103-13.

Clinical trial vs. clinical practice

The 5 too's of clinical trials

- too few
- too simple
- too median-aged
- too narrow
- **too short follow-up**

Clinical trial vs. clinical practice

In clinical practice…

- Larger population
- Population of users expands after drug approval
  - age
  - sex
  - ethnicity
  - use in pregnancy
- Complex concomitant diseases/medicines

- Identification of rare adverse reactions
- Window to actual impact of medicinal product (“real world”)

SUISSE ADPKD
www.adpkd.ch

Angemeldet als: Stefan Russmann
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Start Visiten Datenexport Reports Administration

Visiten

Patientendaten «162-MZ-1953»

Geschlecht:	w	Eintragsdatum:	22.06.2010
Gruppe:	Tolvaptan	Benutzer:	fkrauer
Hausarzt:	Dr. med. Brigitte Winzeler, Moosbrunnenstrasse 14, 8426 Lufingen	Updatedatum:	03.01.2018
Nephrologe:	kein(e)	Benutzer:	lfrei

Visitenübersicht

Visite	Untersuchung	Status	Ausgefüllt	Erfasser	
Screening	12.03.2010	Eingegeben	22.06.2010 14:47	fkrauer	Formular
V1	21.06.2010	Eingegeben	22.06.2010 14:55	fkrauer	Formular
V2	16.12.2010	Eingegeben	05.03.2011 14:49	fkrauer	Formular
V3	-	Eingegeben	08.07.2011 11:21	fkrauer	Formular
V4					Formular

Visite V3

Patient «162-MZ-1953»

Status: Eingegeben
Gruppe: Tolvaptan
Erfasser: fkrauer - 08.07.2011 11:21
Editiert: flavia - 26.11.2015 09:52

Allgemein | Labor | Medikamente

16

Untersuchungsdatum

Datum der Untersuchung dd.mm.yyyy

11

ADPDK Symptome

ADPKD-Symptome Angaben über Zeitpunkt / Dauer / Häufigkeit und Therapie

☐ Nein, bzw. keine

Methods - Efficacy -

- Course of eGFR of all SUISSE ADPKD patients taking tolvaptan.
- Plot eGFR at baseline and monthly during follow-up
- Calculate simple linear regression for eGFR values (begining 11 weeks after start of tolvaptan because of known short-term renal hemodynamic effects

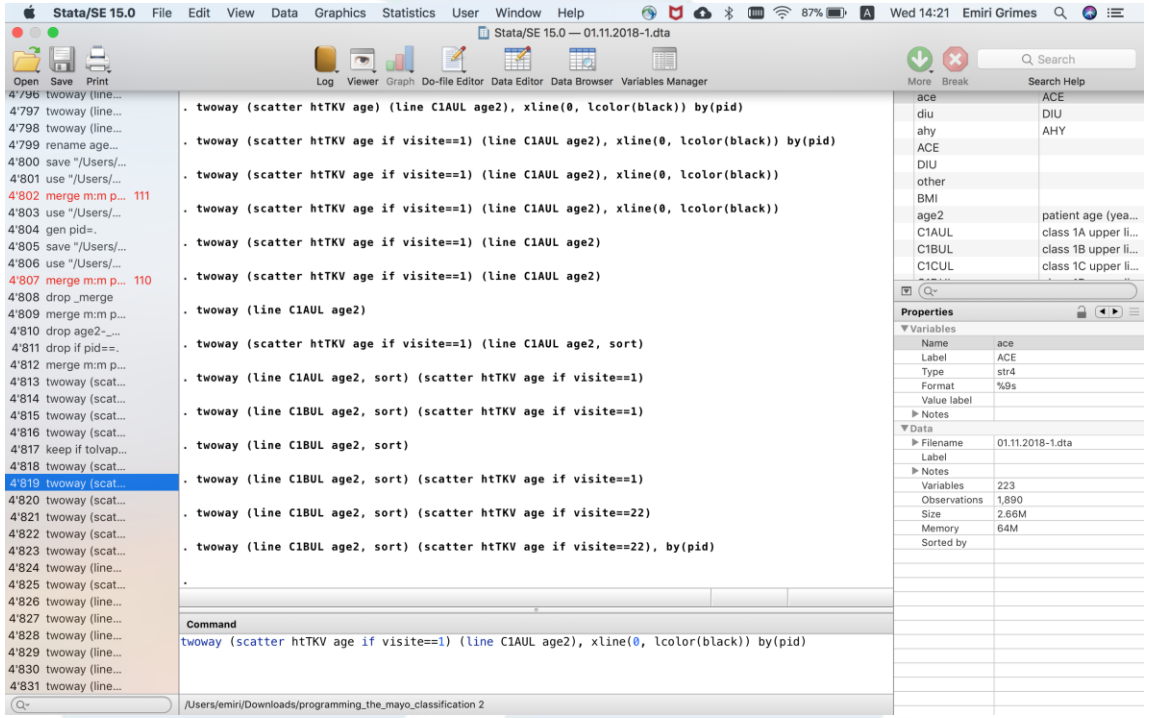
<u>Tolvaptan’s short-term renal hemodynamic effects</u>

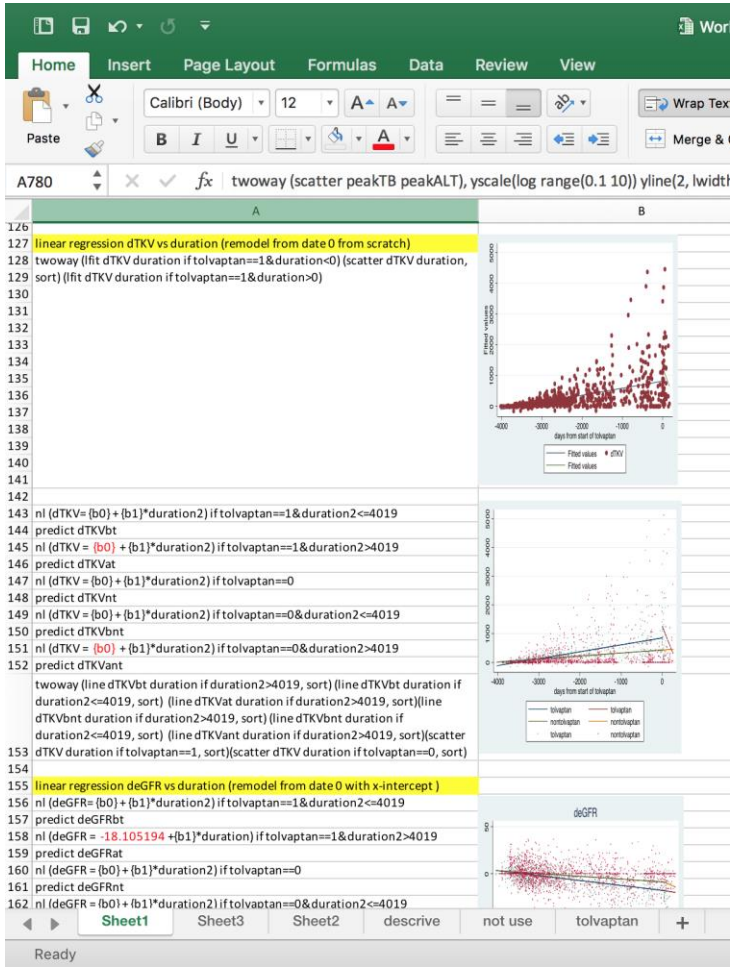
- Short-term and reversible increase in serum creatinine and decrease in eGFR, potentially due to hemodynamic mechanisms (possibly related to the increase in vasopressin release caused by tolvaptan)

Methods - Safety -

- Follow the time course of following liver enzymes under treatment with tolvaptan for each patient
  - ALT; alanine aminotransferase
  - AST; aspartate aminotransferase
  - AP; alkaline phosphatase
  - TB; total bilirubin
- eDISH plot

Data analysis using Stata 15



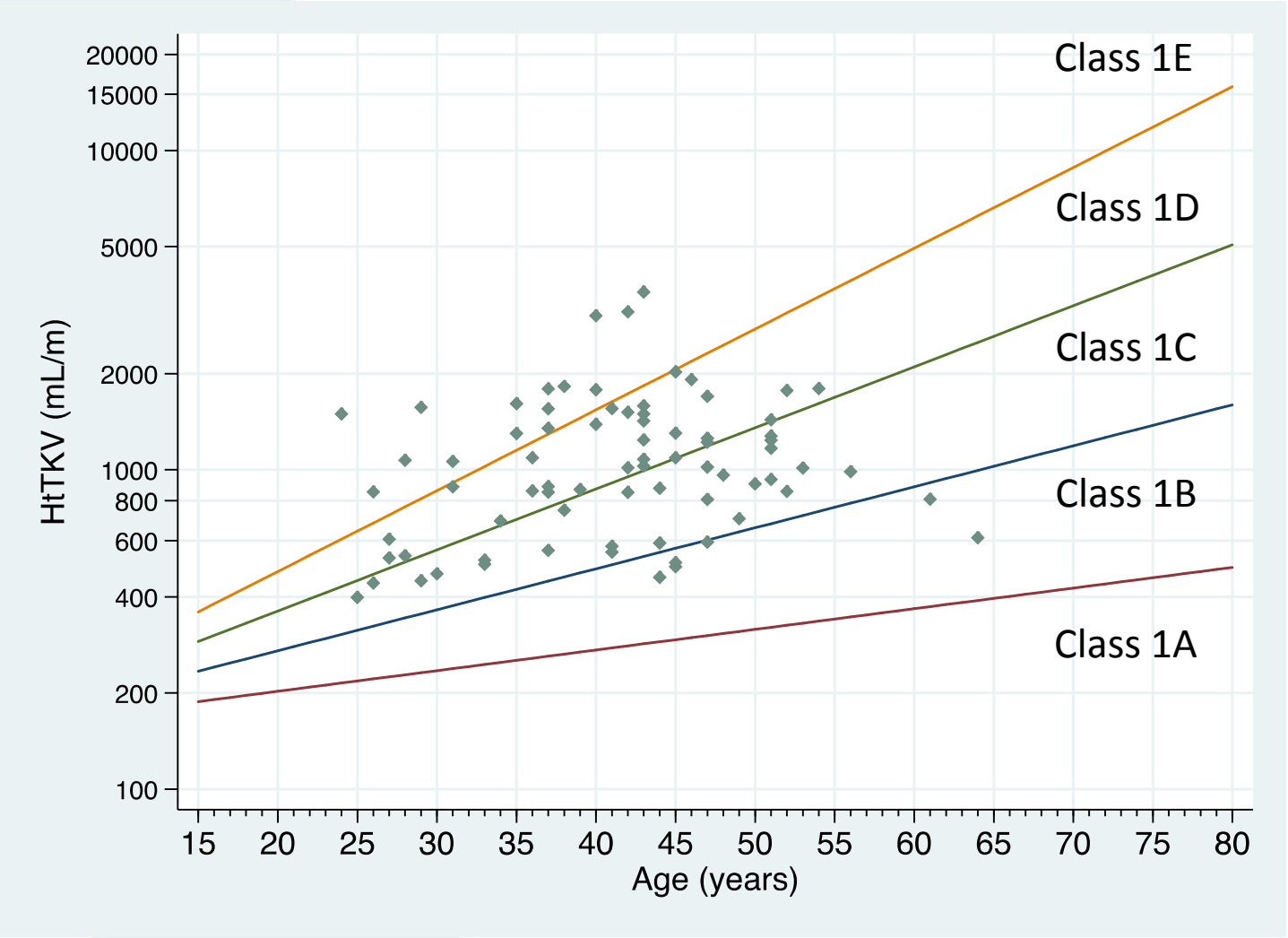


- Original raw data include >520,000 single values

Baseline characteristics

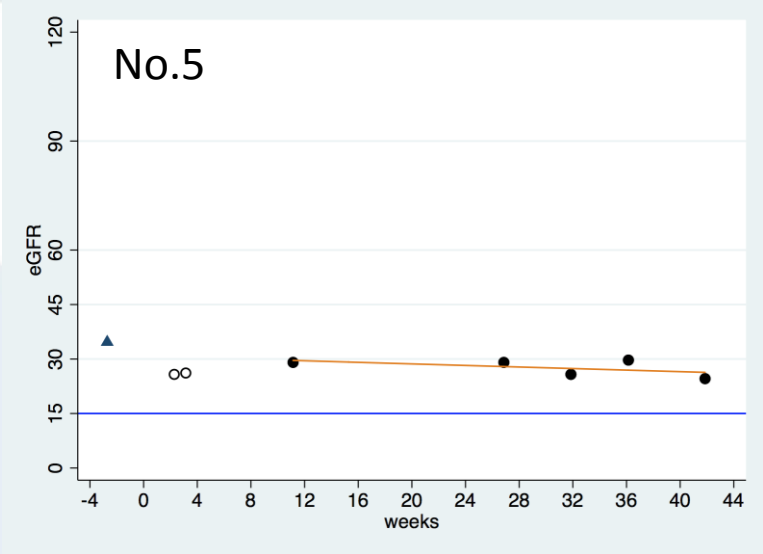
Characteristic at baseline	Tolvaptan (N=76)
Age (year)	41.2±8.6
Sex	
Male	55 (72.4)
Female	21 (27.6)
Height (cm)	178.9±9.4
Weight (kg)	83.5±14.0
Body Mass Index (kg/m^2)	26.0±3.8
eGFR	68.6±25.9
TKV	2046.0±1122.9
htTKV	1139.4±608.7
Blood pressure (mmHg)	
Systolic	135.5±12.2
Diastolic	87.8±8.6
CKD Stage	
1	17 (22.4)
2	24 (31.6)
3	33 (43.4)
4	2 (2.6)
5	
Anti hypertensive treatment	
Any	65 (85.5)
ACE/ARB	40 (52.6)
DIU	6 (7.9)
other	37 (48.7)

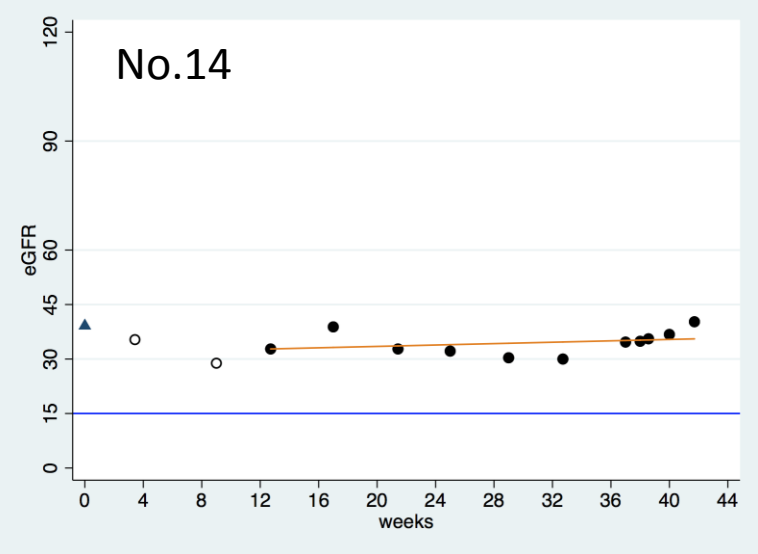
Mayo classification at baseline

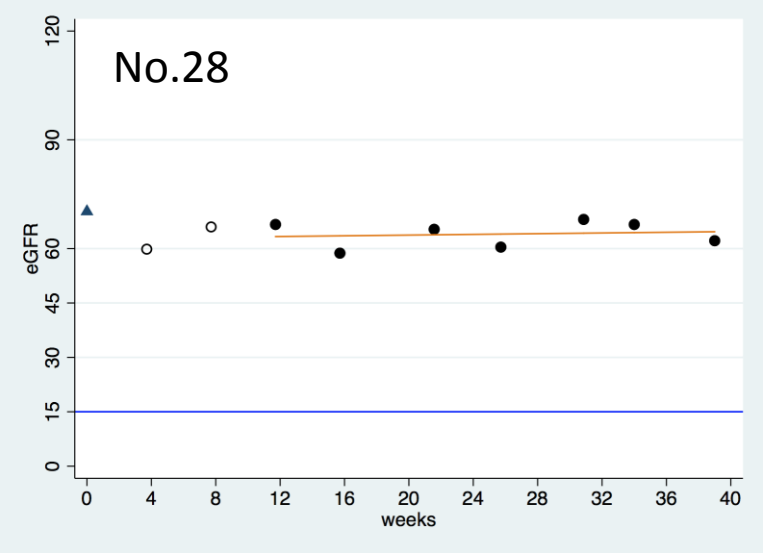


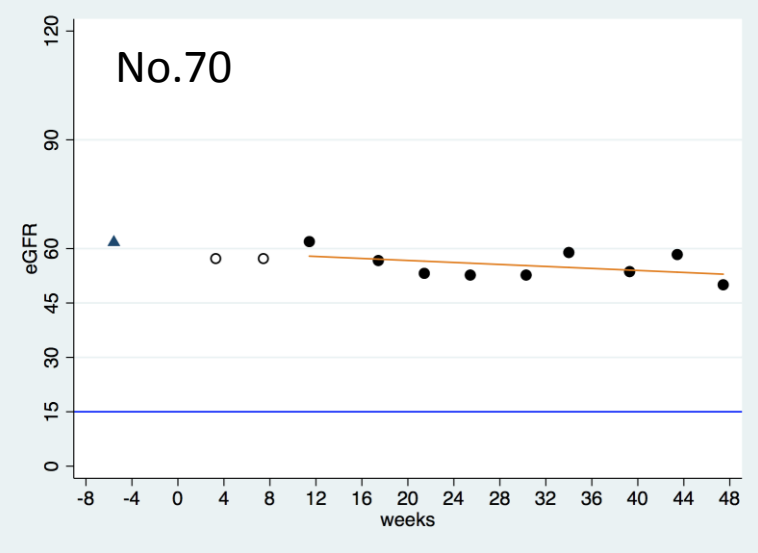
Efficacy

- Representative samples of time course of eGFR (out of 76 patients)



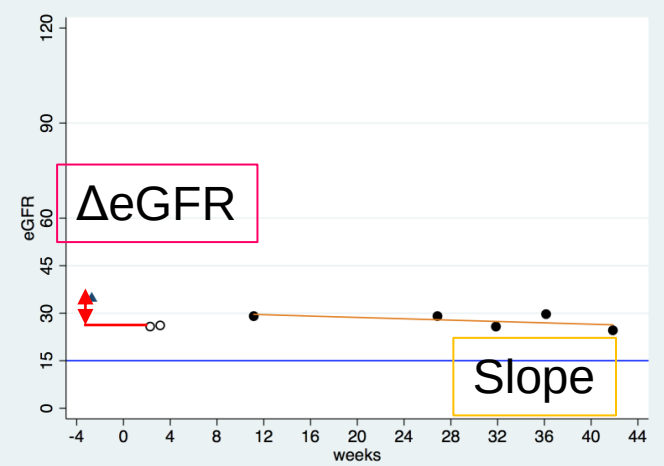


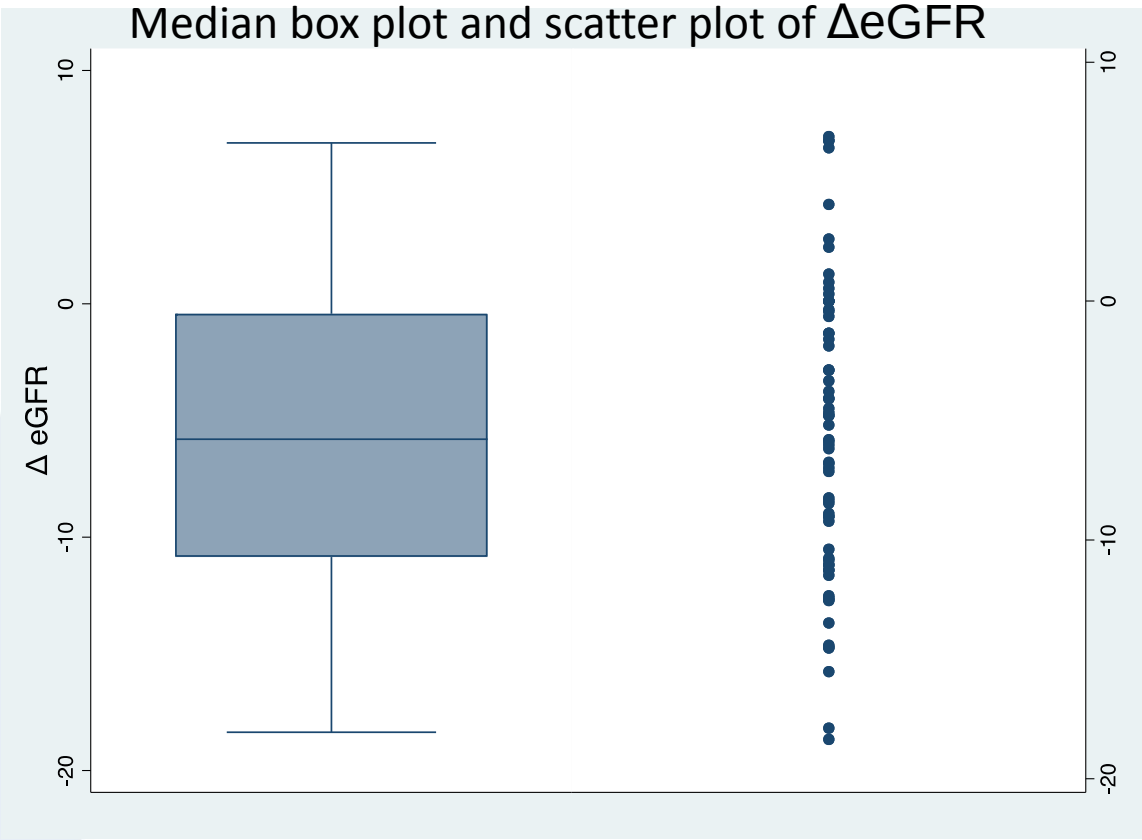




Efficacy

Initial ΔeGFR and slope

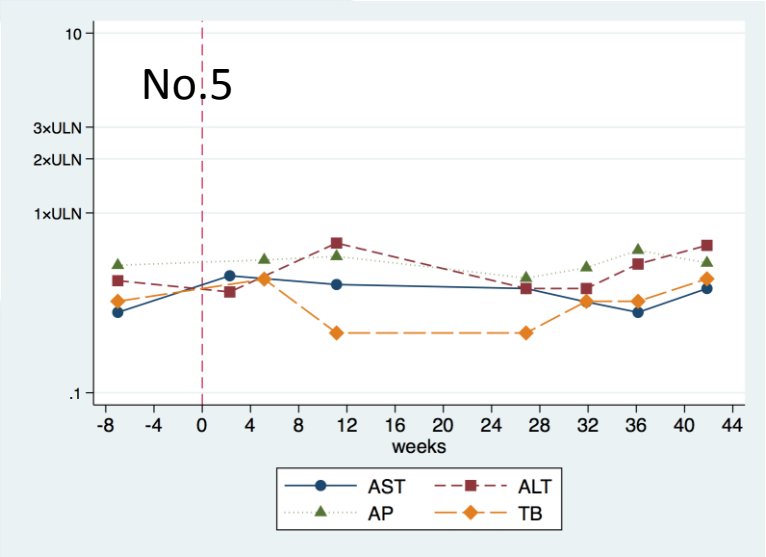


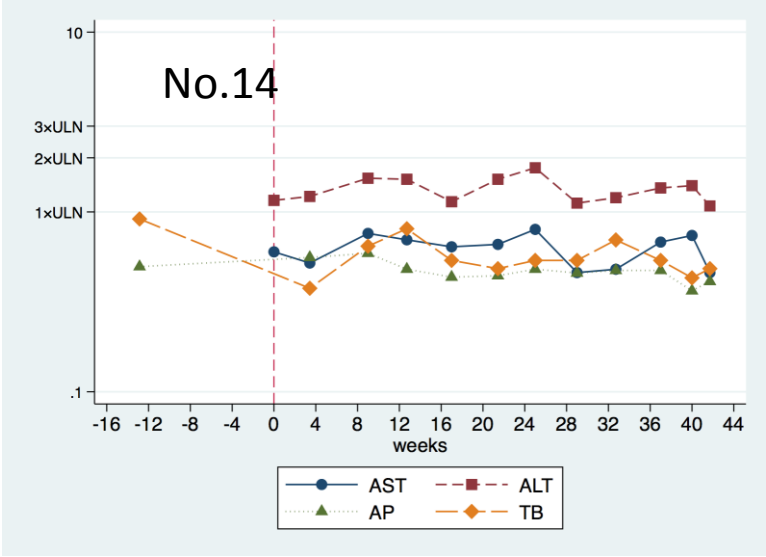


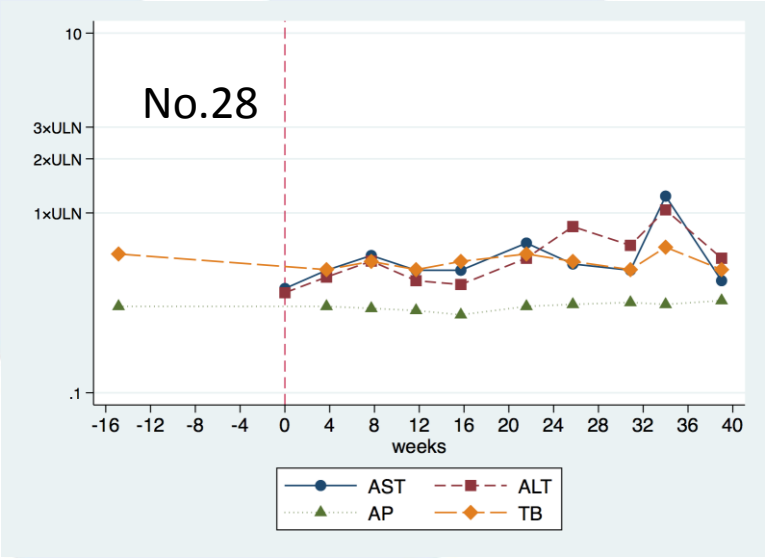
	Number of obs	Median	Mean	Std. Err.	[95% Conf. Interval]	
ΔeGFR between baseline and first value after start of tolvaptan (hemodynamic effects)	67	-5.803	-5.574	0.752	-7.075	-4.074
Slope of linear regression after 11 weeks	76	0.010	0.005	0.069	-0.133	0.143

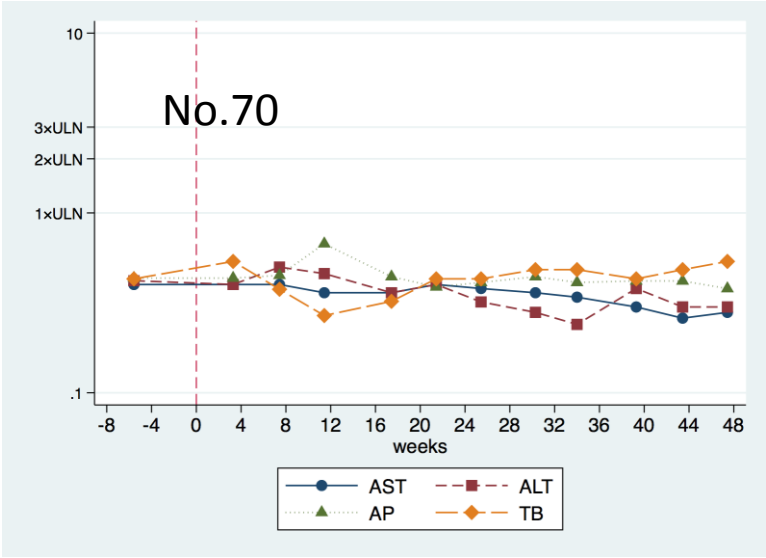
Safety

Representative samples of time course of liver enzymes (out of 76 patients)

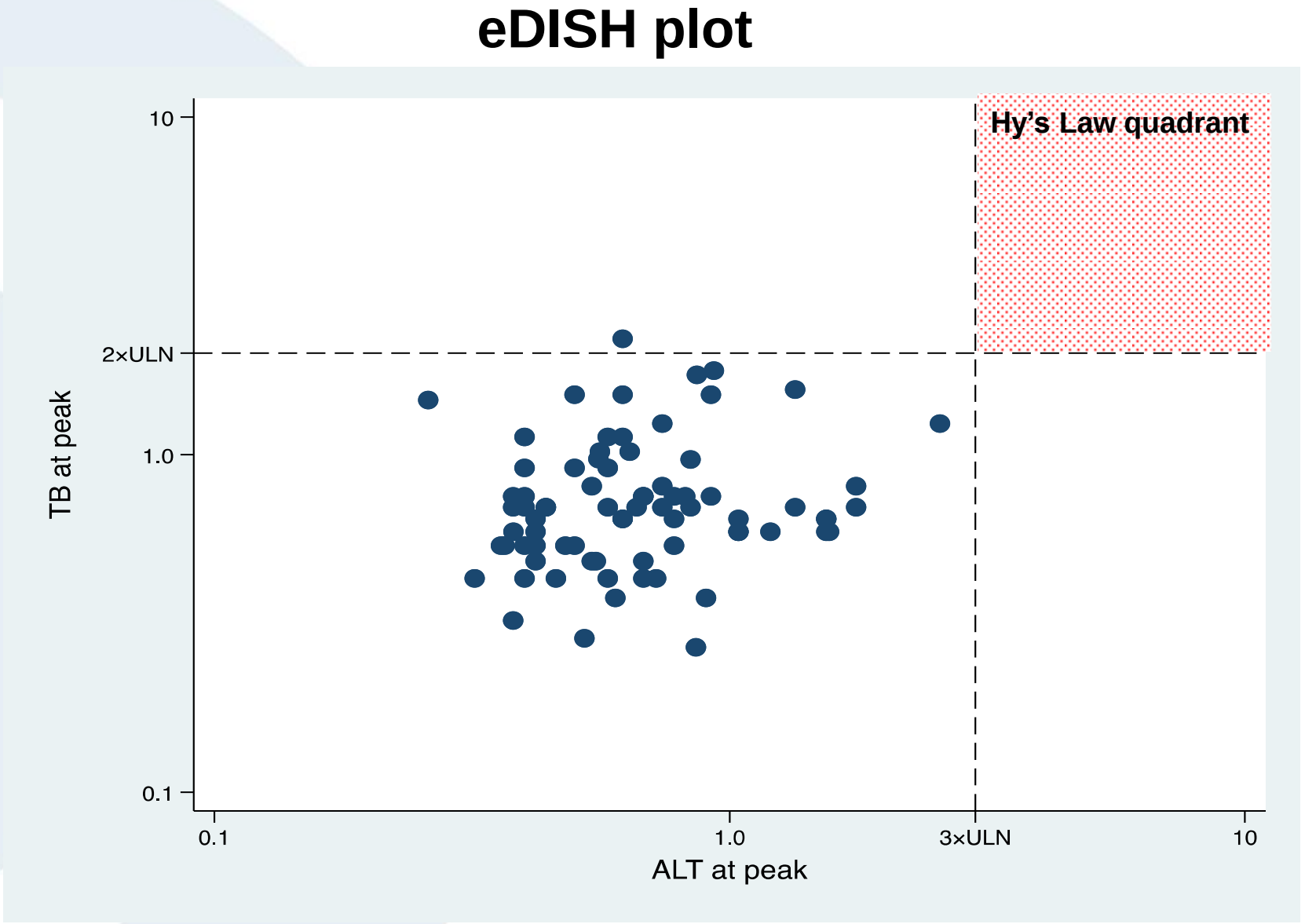








Safety


eDISH plot
Hy's Law quadrant
10
2×ULN
1.0
0.1
TB at peak
0.1
1.0
3×ULN
10
ALT at peak

Comparison of results with phase III clinical study

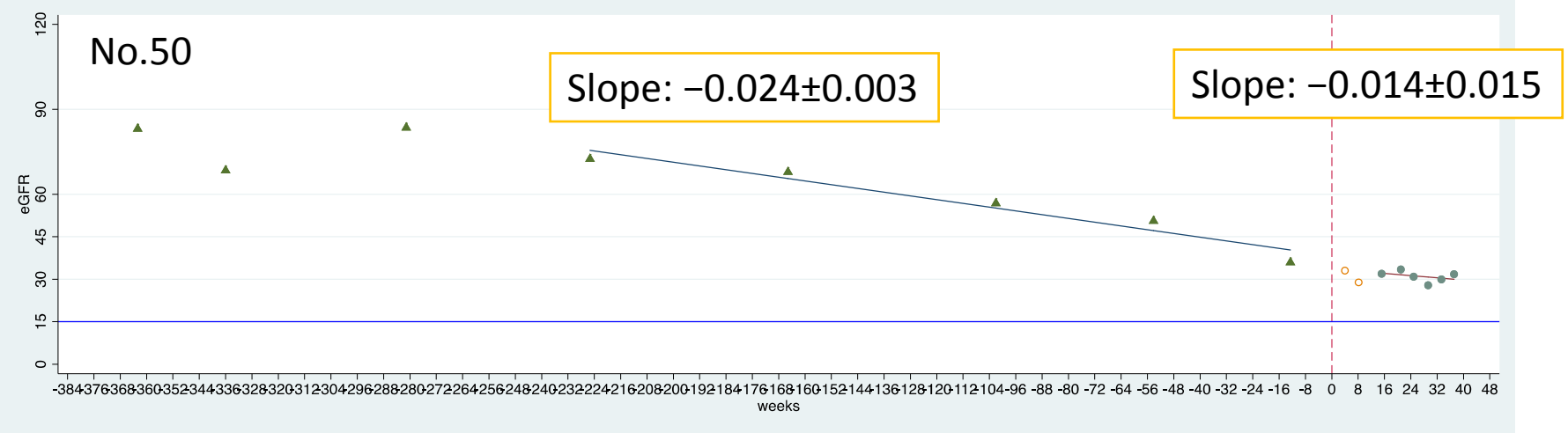
(Torres, V.E., et al. N Engl J Med, 2017. 377(20): 1930-1942.)

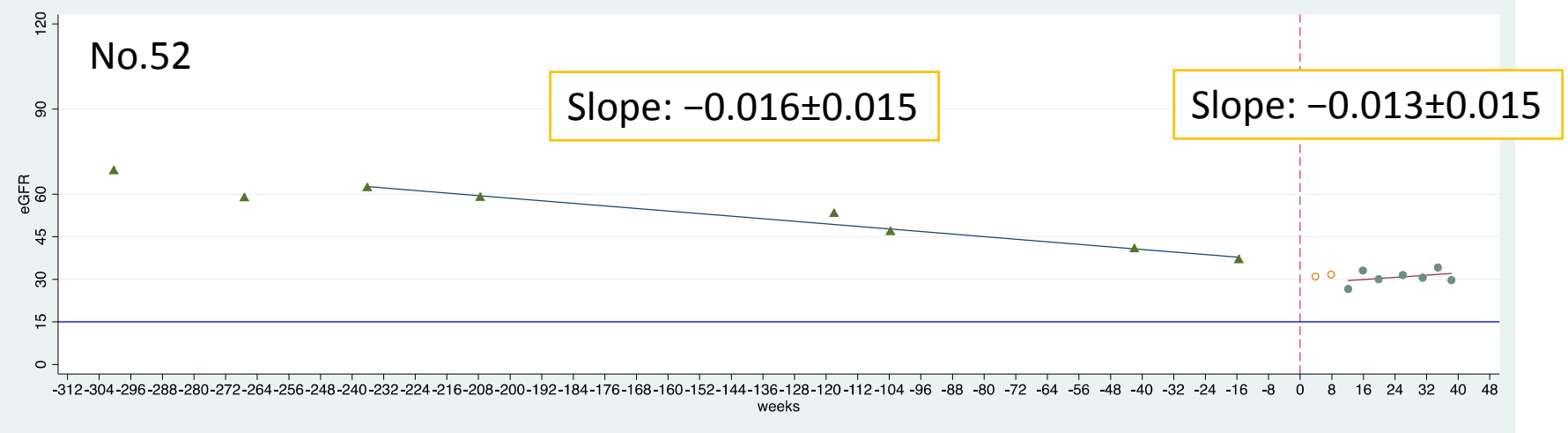
	SUISSE ADPKD		Torres, V.E., et al.	
	Number of obs.	Mean	Number of obs.	Mean
eGFR at baseline	76	68.6±25.9	683	40.7±10.9
ΔeGFR between baseline and first value after start of tolvaptan	67	-5.57±0.75	680	Around -2 ～ -3
Slope of linear regression	76	0.0053±0.0692	680	−3.24±0.17

- Slower dose escalation in SUISSE ADPKD compared to clinical study

Quality control of data

- Good examples





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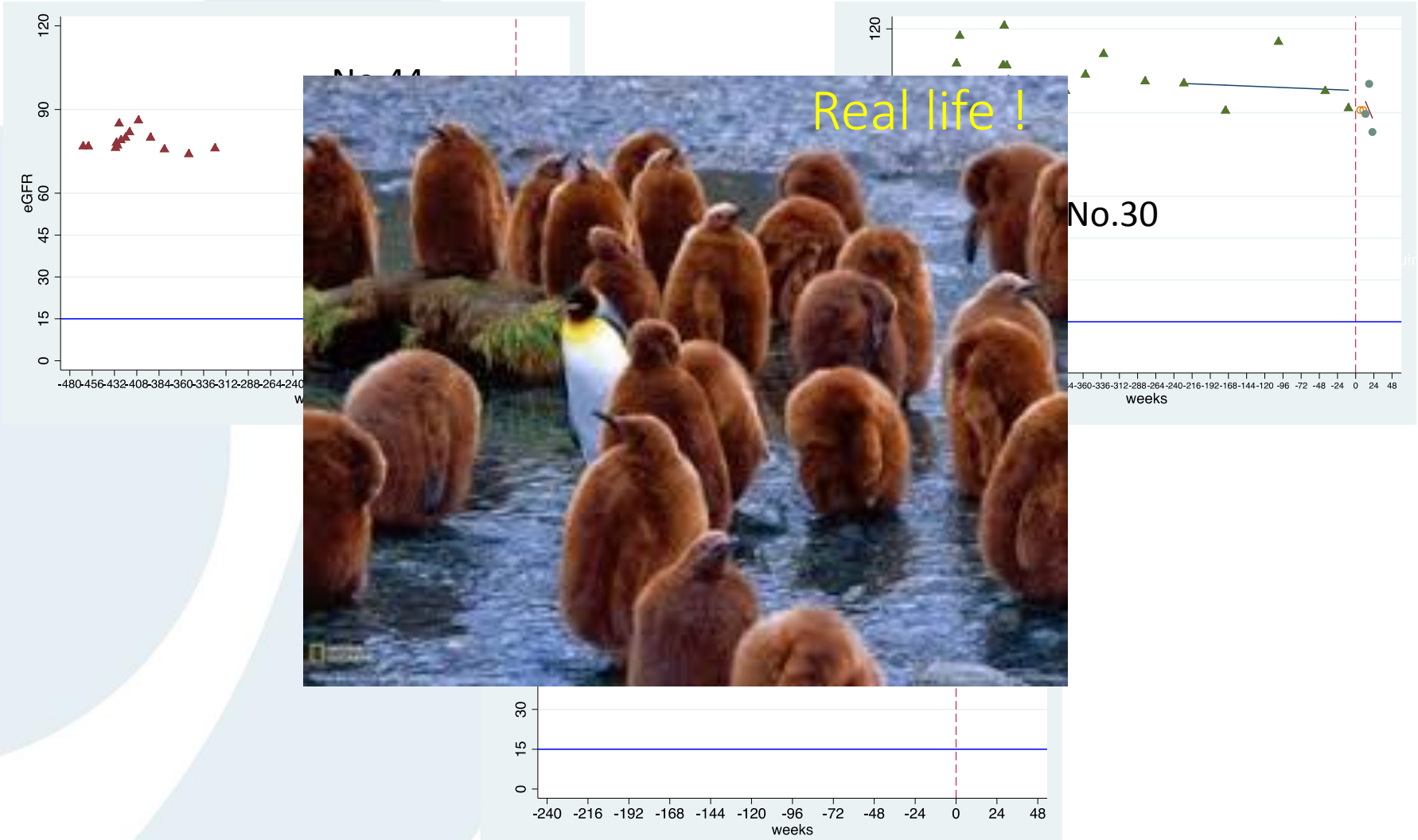
Poor examples



Conclusions

- Efficacy and safety of tolvaptan in clinical practice appears overall comparable to results from pivotal clinical trials

- Additional follow-up analyses over a longer time period are required

Further plans…

- Further follow-up analyses and quality controls
- Genetic analyses
- Further development of clinical research database including automated import of laboratory data

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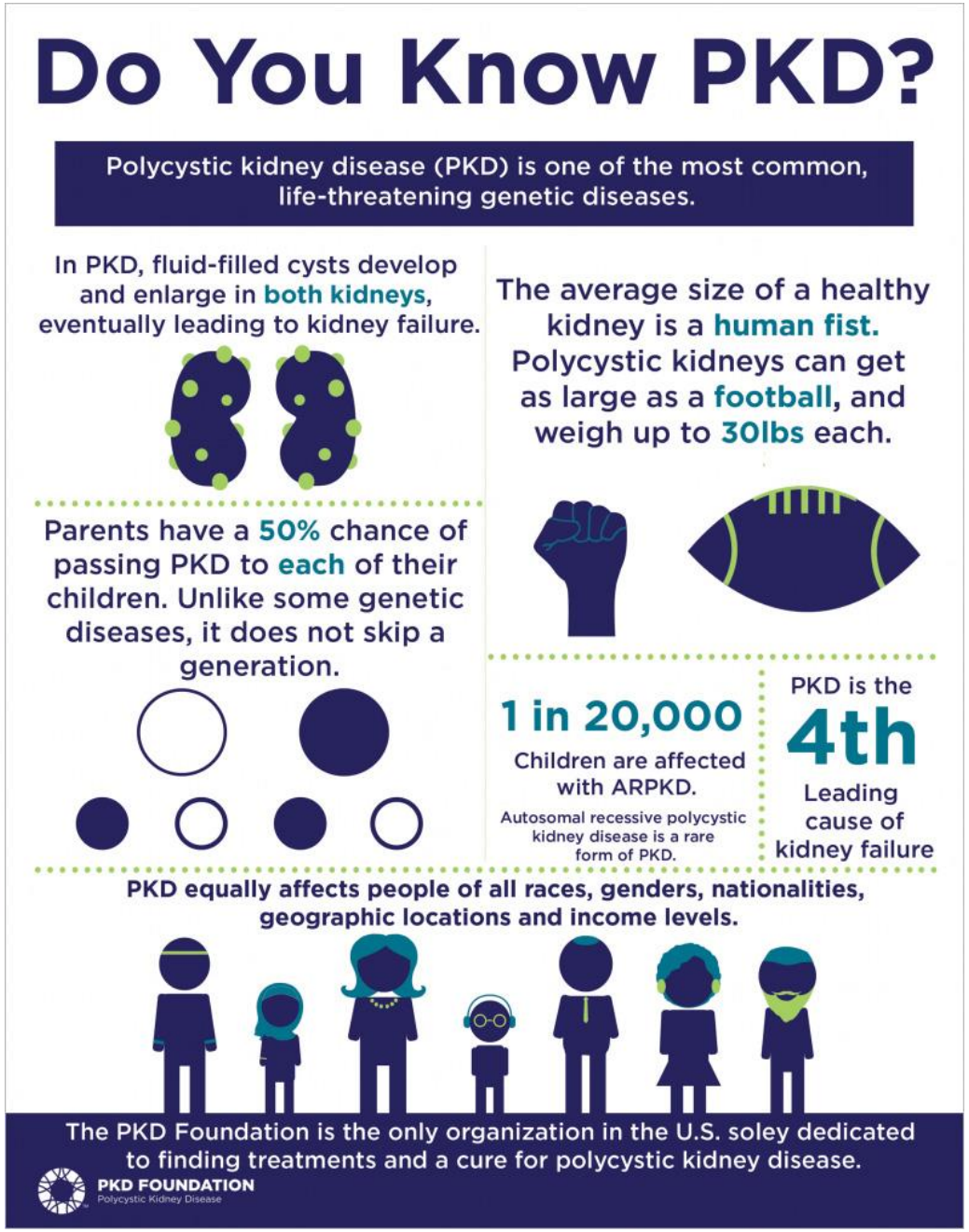
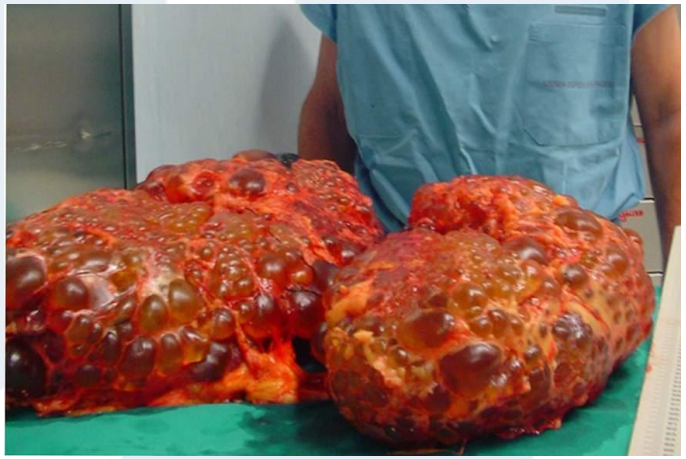
ADPKD



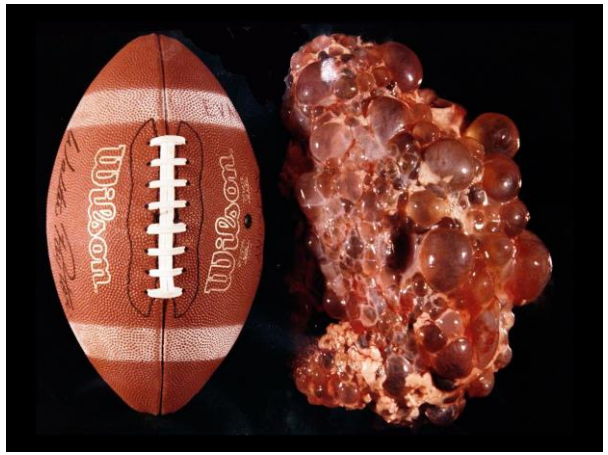
Source: PKD foundation

Autosomal dominant polycystic kidney disease (ADPKD)

- Mutations of PKD 1 / 2 genes on chromosome 16 / 4, encoding for polycystin 1 / 2 on renal tubular epithelia
- The most prevalent, potentially lethal, monogenic disorder (1 in 400 to 1,000 live births)
- The 4th leading cause of kidney failure
- More than 50 percent of people with ADPKD will develop kidney failure by age 50



https://www.nih.gov/news-events/news-releases/two-drugs-are-no-more-effective-one-treat-common-kidney-disease



https://21630.bbnc.bbcust.com/news

Risk of cholestatic liver disease associated with flucloxacillin and flucloxacillin prescribing habits in the UK: Cohort study using data from the UK General Practice Research Database

Stefan Russmann, James A. Kaye, Susan S. Jick & Hershel Jick

Boston Collaborative Drug Surveillance Program, Boston University School of Medicine, Lexington, MA, 02421, USA

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E-mail: russmann@bu.edu

Keywords
cholestasis, flucloxacillin, GPRD, liver disease, oxytetracycline, population-based cohort study

Received
21 September 2004
Accepted
17 November 2004

Aims
To provide additional quantification of the risk of flucloxacillin-related liver disease and to describe time trends in flucloxacillin prescribing in the UK.

Methods
This was a cohort study using data from the UK General Practice Research Database. We identified patients with a first-time prescription for flucloxacillin or, for comparison, oxytetracycline from 1992 to 2002 and cases who developed clinically documented cholestatic liver disease of uncertain origin after first-time use of these drugs. We also determined the annual frequency of first-time use of flucloxacillin from 1991 to 2000.

Results
We identified 283 097 and 131 189 first-time users of flucloxacillin and oxytetracycline, respectively. The risk of cholestatic liver disease per 100 000 first-time users was 8.5 (95% CI 5.4, 12.6) in the 1–45 days and 1.8 (95% CI 0.6, 4.1) in the 46–90 days after starting flucloxacillin, and 0.8 (95% CI 0.02, 4.3) in the 1–45 days after starting oxytetracycline. The frequency of first-time use of flucloxacillin remained stable between 1991 and 2000.

Conclusions
Flucloxacillin is now established as an important cause of cholestatic liver disease. Warnings about the risk have not had an impact on prescribing practices in the UK, where it remains the predominantly prescribed antistaphylococcal oral antibiotic. This situation in the UK is in sharp contrast to regulatory actions and changes in prescribing habits in Australia after identification of the risk of cholestasis associated with flucloxacillin, and to the predominant use of the alternative drug dicloxacillin in the USA.

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Nonsteroidal Antiinflammatory Drugs and Acute Myocardial Infarction in Patients with No Major Risk Factors

Hershel Jick, M.D., James A. Kaye, M.D., Dr.P.H., Stefan Russmann, M.D., and Susan S. Jick, D.Sc.

Study Objective. To assess the risk of long-term use of five nonsteroidal antiinflammatory drugs (NSAIDs)—rofecoxib, celecoxib, ibuprofen, naproxen, and diclofenac—in relation to acute myocardial infarction.

Design. Five separate nested case-control studies, one for each NSAID, designed to minimize important biases present in other observational studies.

Setting. University-affiliated research program.

Data Source. The United Kingdom General Practice Research Database (GPRD).

Measurements and Main Results. We identified all people in the GPRD aged 30–79 years who had a first recorded prescription for rofecoxib, celecoxib, ibuprofen, naproxen, or diclofenac after January 1, 1999. Cases of newly diagnosed, first-time acute myocardial infarction were then identified from the study population, along with matched control subjects. Relative risk estimates for acute myocardial infarction in patients with no recorded major clinical risk factors for acute myocardial infarction were determined for each NSAID according to receipt of 2–4, 5–9, 10–19, or 20 or more prescriptions compared with receipt of only 1 prescription. Results were adjusted for relevant variables possibly related to the risk for acute myocardial infarction. No material elevation of risk according to the number of prescriptions received for ibuprofen or naproxen was noted. However, a substantial increased risk similar to that found in clinical trials was noted in patients who received 10 or more prescriptions for rofecoxib, celecoxib, or diclofenac.

Conclusion. Extensive use of rofecoxib, celecoxib, and diclofenac increases the risk of acute myocardial infarction, but similar use of ibuprofen and naproxen does not.

Key Words: cyclooxygenase 2, COX-2, nonsteroidal antiinflammatory drugs, NSAIDs, acute myocardial infarction, AMI, observational study, rofecoxib, celecoxib, diclofenac.

(Pharmacotherapy 2006;26(10):1379–1387)

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evaluation

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY (2009)
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ORIGINAL REPORT

Effectiveness of rosuvastatin compared to other statins for the prevention of cardiovascular events—a cohort study in 395 039 patients from clinical practice†

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SUMMARY

Purpose This study compared the effectiveness of rosuvastatin (RSV) to other statins prescribed in clinical practice in prevention of cardiovascular (CV) events.

Methods This longitudinal inception cohort study, using Thomson Healthcare's MarketScan databases, included patients aged ≥ 18 starting statin therapy during August 2003–December 2005. Patients were followed until 90 days after index statin monotherapy exposure, start of another lipid-lowering therapy, an event, end of eligibility, or end of study. The primary endpoint was a composite of CV death (in-hospital only), myocardial infarction, unstable angina, coronary revascularization, stroke, and carotid revascularization. Adjusted time-to-event analyses incorporating a propensity score covariate were used, and analyses were stratified by duration of statin exposure.

Results Among 395 039 patients who met inclusion/exclusion criteria, 12% initiated RSV, and 9622 (2.4%) of the total patient population experienced an outcome event. The median duration of statin treatment and follow-up was 100 days and 180 days, respectively. No statistically significant difference in CV event rates between RSV and other statins was observed after adjustment for demographics and medical/prescription history (HR = 0.99, 95%CI = 0.93–1.06). However, with longer exposure time, there was a suggestion of increased benefit with RSV compared to other statins.

Conclusions The primary analysis showed similar incidence rates of CV-related events between the statin cohorts over a median of 180 days of follow-up. Copyright © 2009 John Wiley & Sons, Ltd.

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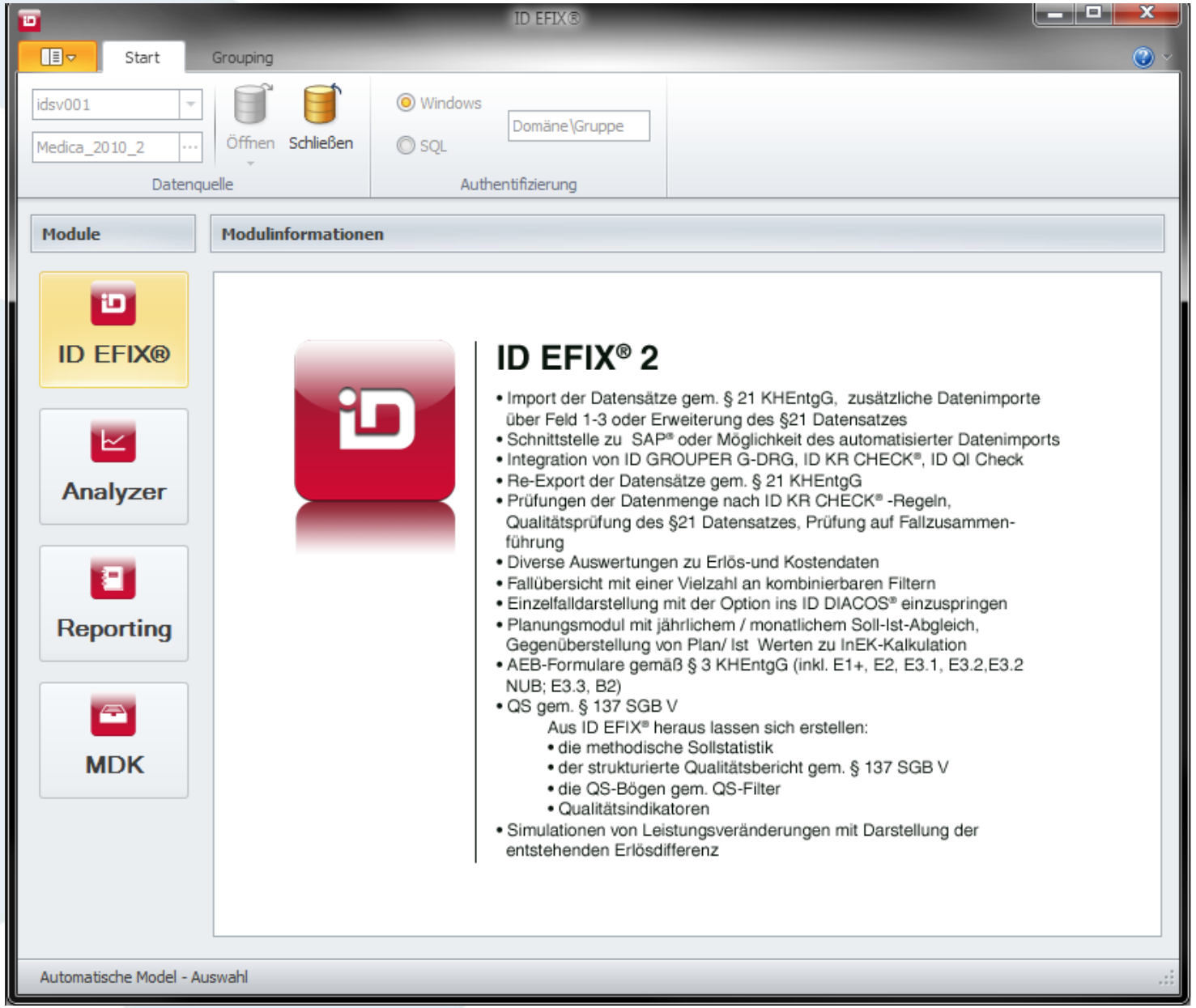
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Automatische Model - Auswahl

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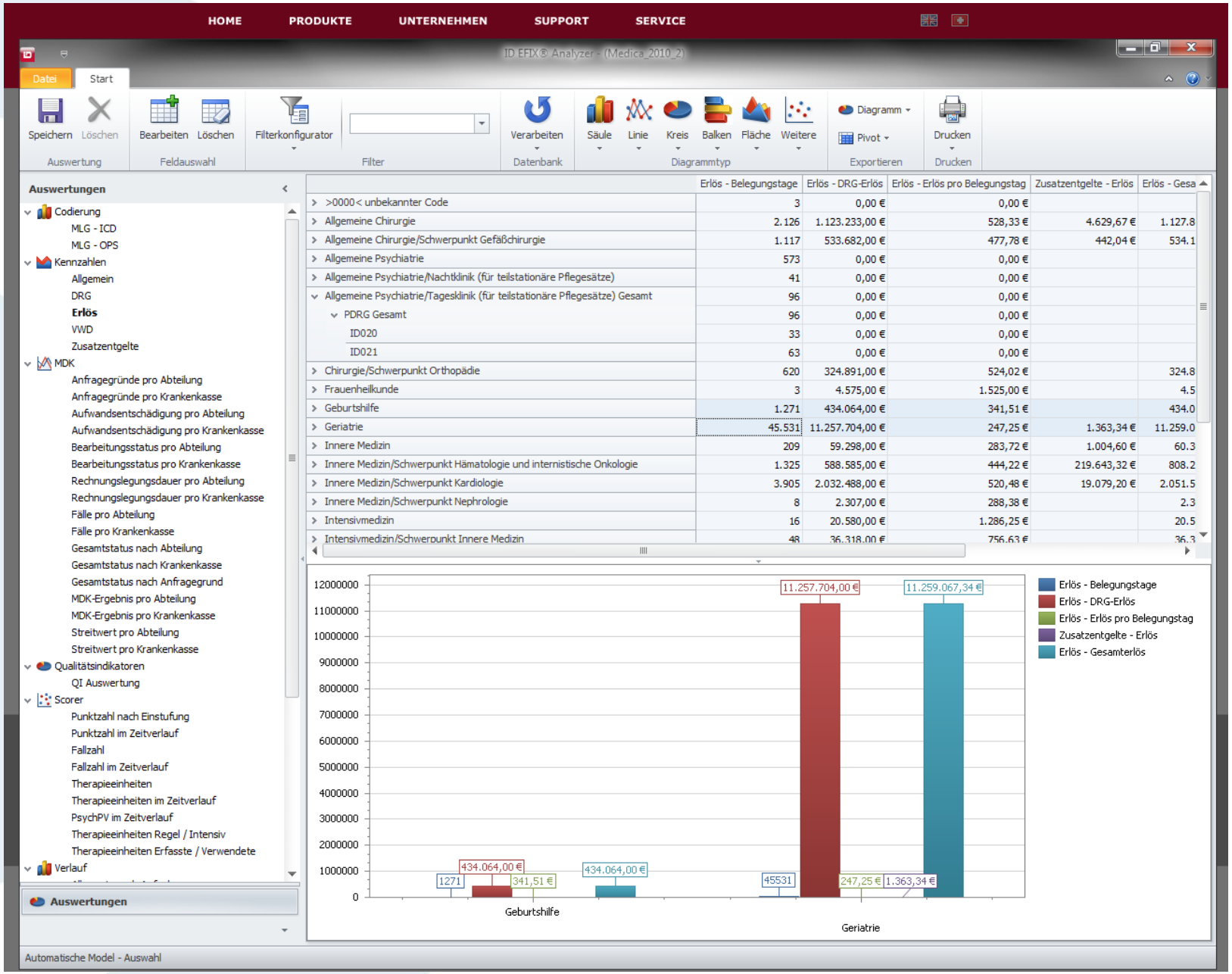

eDISH plot and Hy's Law

- eDISH plot displays peak serum ALT and TB values for every subject at a glance
- Provides quick and sensitive screening for drug-induced liver injury (DILI) in clinical trials
- Even a single drug-related Hy's Law case in a clinical trial is a signal of potential risk of severe DILI in clinical practice
  - Hy's Law: ALT >3x upper limit of normal & total bilirubin >2x ULN
  - Additional assessment of causal relationship to drug
  - Severe DILI can be estimated to occur at a rate of at least one-tenth the rate of Hy's Law cases

ADPKD - Treatment -

- Immunosuppressant sirolimus studied in prospective clinical trials, but no significant effect on disease progression

  Serra et al., N Engl J Med. 2010 Aug 26;363(9):820-9.

- **Tolvaptan first effective treatment for ADPKD, approved in Switzerland in April 2016**
  - Arginine vasopressin V2 receptor (AVPV2) antagonist
  - Indication: ADPKD patients with chronic kidney disease (CKD) stage 1 to 3 at the start of treatment and/or signs of rapidly progressive disease
  - 45 mg + 15 mg , 60 mg + 30 mg or 90 mg + 30 mg twice daily
  - Idiosyncratic hepatotoxicity requires monitoring of liver values

Study Aims

1. Describe characteristics of patients with ADPKD treated with tolvaptan in the Suisse ADPKD cohort

2. Conduct the first available efficacy and safety data analysis of tolvaptan in clinical practice

Primary outcomes

- **Efficacy**
  progression of decline in renal function (eGFR) before vs. after start of tolvaptan

- **Safety**
  incidence and time course of increased liver values under treatment with tolvaptan

Results

Next steps…

- Longer follow-up time / more data desirable
  - eGFR for longer time after start of tolvaptan
  - Secondary outcome
    - Efficacy: TKV
    - Safety: frequency of adverse effects
- Quality control of data