

Schweizer ADPKD-Symposium
Klinik Hirslanden Zürich, 12. Mai 2022



SwissPKD
Schweizer Gesellschaft
polyzystischer Nierenerkrankung

Unsere Erfahrungen und systematische Beurteilung der Tolvaptan (Jinarc®) Therapie bei ADPKD

Stefan Russmann



SUISSE ADPKD
www.adpkd.ch



DRUGSAFETY.CH

HIRSLANDEN 



Doctor: "Don't confuse your Google search with my 6 years of medical school".

Patient: "Don't confuse the one-hour lecture you had on my condition with my 20 years of living with it".

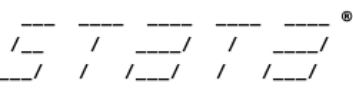


...next: impressions from observing >400 times on average >40 patient-years (total >3600 years) of life with ADPKD





| GFR0 | GFR0_fut_w | GFRdate0 | stage_GFR1 | GFR1 | GFR1_fut | GFRdate1 | stage_GFR2 | GFR2 | GFR2_fut | GFRdate2 | stage_GFR3 | GFR3 | GFR3_fut | GFRdate3 | stage_GFR4 | GFR4 | GFR4_fut | GFRdate4 | stage_GFR5 |
|------|------------|------------|------------|------|----------|-----------|------------|------|----------|------------|------------|------|----------|------------|------------|------|----------|-----------|------------|
| 34.6 | -13.57143 | 12/10/2016 | 4 | 27.4 | 11.85714 | 6/6/2017 | 4 | 25.7 | 27.28572 | 9/22/2017 | 4 | 27.9 | 51.28571 | 3/9/2018 | 4 | 23.4 | 77.28571 | 9/7/2018 | 4 |
| 67.4 | -16.71428 | 1/12/2017 | 3 | 56.1 | 4.428571 | 6/9/2017 | 3.5 | 39.8 | 18.42857 | 9/15/2017 | 3 | 58.7 | 31.42857 | 12/15/2017 | 3 | 54.2 | 58.42857 | 6/22/2018 | 3 |
| 69.7 | 0 | 5/5/2020 | 2 | 69.7 | 0 | 5/5/2020 | 2 | 71.2 | 4 | 6/2/2020 | 2 | 67 | 14 | 8/11/2020 | 2 | 67 | 26.28572 | 11/5/2020 | . |
| 54.2 | -8.571428 | 12/3/2016 | 3 | 57.1 | 4.142857 | 3/2/2017 | 3 | 54.5 | 20 | 6/21/2017 | 3 | 46.1 | 33 | 9/20/2017 | 3 | 56.7 | 59.28571 | 3/23/2018 | 3 |
| 57.5 | -6.571429 | 12/10/2016 | 3 | 48.8 | 4.285714 | 2/24/2017 | 3 | 48.7 | 15.85714 | 5/16/2017 | 3 | 46.4 | 27.28572 | 8/4/2017 | 3.5 | 42.3 | 56.85714 | 2/27/2018 | 3 |
| 82.9 | -13 | 12/10/2016 | 2 | 80.4 | 24.57143 | 8/30/2017 | 2 | 80.3 | 36.57143 | 11/22/2017 | . | . | . | . | . | . | . | . | . |



17.0
MP-Parallel Edition

Copyright 1985-2021 StataCorp LLC
StataCorp
4905 Lakeway Drive
College Station, Texas 77845 USA
800-STATA-PC <https://www.stata.com>
979-696-4600 stata@stata.com

Stata license: Single-user 4-core perpetual
Serial number: 501706304278
Licensed to: Stefan Russmann
ETHZ

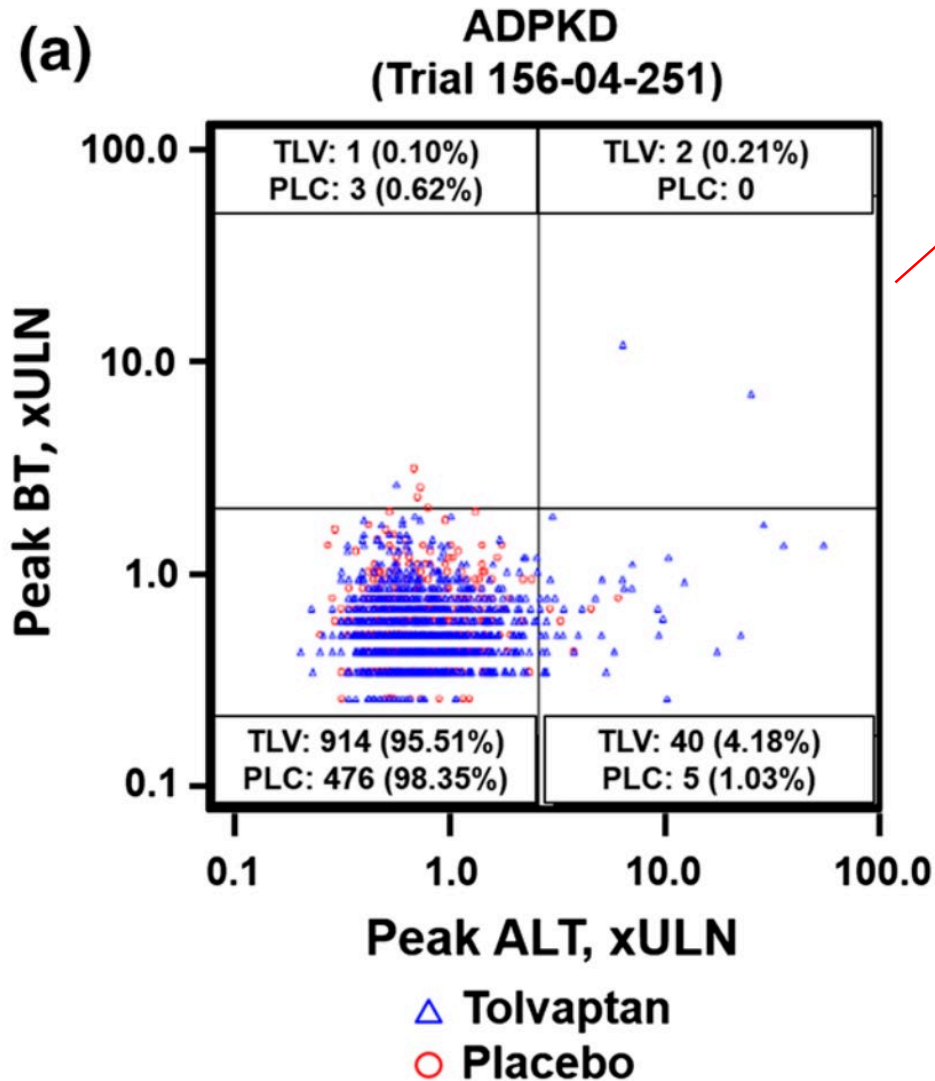
| | | | | | | | | | | | | | | | | | | | | |
|------|-----------|------------|------------|------|----------|------------|------------|------|----------|------------|-----------|------|----------|------------|-----------|------|----------|-----------|-----------|---|
| 52.4 | -13 | 12/10/2016 | 3.5 | 44.2 | 11.85714 | 6/2/2017 | 3 | 45.4 | 25.85714 | 9/8/2017 | 3 | 45.6 | 50.85714 | 3/2/2018 | 3.5 | 3 | 3 | 3 | 3 | |
| 81.5 | 0 | 2/14/2017 | 2 | 84.5 | 3.428571 | 3/10/2017 | 2 | 72.2 | 14.42857 | 5/26/2017 | 3 | 52.7 | 26.28572 | 8/17/2017 | . | . | . | . | . | |
| 40.8 | -5.571429 | 12/3/2016 | 3.5 | 30.5 | 15.85714 | 5/2/2017 | 3.5 | 30.1 | 29 | 8/2/2017 | 3.5 | 32.1 | 52 | 1/10/2018 | 3.5 | 3 | 3 | 3 | 3 | |
| 56.2 | -14 | 12/3/2016 | 3 | 45.6 | 3.857143 | 4/7/2017 | 3.5 | 40.6 | 18.42857 | 7/18/2017 | 3.5 | 37.1 | 31.71428 | 10/19/2017 | 3 | 4 | 4 | 4 | 4 | |
| 35.6 | -10.14286 | 12/16/2016 | 3.5 | 30.5 | 25.42857 | 8/22/2017 | 3.5 | 33.1 | 37.57143 | 11/15/2017 | 4 | 29.9 | 63.85714 | 5/18/2018 | 4 | 2 | 2 | 2 | 2 | |
| 90 | -7 | 12/10/2016 | 1 | 90 | 3.571429 | 2/22/2017 | 1 | 90 | 16.42857 | 5/23/2017 | 1 | 90 | 28.57143 | 8/16/2017 | 1 | 1 | 1 | 1 | 1 | |
| 58 | -6 | 12/10/2016 | 2 | 65.1 | 3.428571 | 2/14/2017 | 2 | 63.3 | 14.42857 | 5/2/2017 | 2 | 63.1 | 30.71428 | 8/24/2017 | 2 | 6 | 6 | 6 | 6 | |
| 70.6 | -15 | 12/3/2016 | 2 | 60 | 3.571429 | 4/12/2017 | 2 | 58.8 | 15.57143 | 7/5/2017 | 2 | 68 | 30.71428 | 10/19/2017 | 2 | 6 | 6 | 6 | 6 | |
| 69.7 | -13 | 12/3/2016 | 2 | 68.5 | 24.85714 | 8/25/2017 | 2 | 66.3 | 28.85714 | 9/22/2017 | 2 | 65.2 | 64.85714 | 6/1/2018 | 2 | 6 | 6 | 6 | 6 | |
| 90 | -12.28571 | 12/10/2016 | 1 | 90 | 3.142857 | 3/28/2017 | 1 | 90 | 15 | 6/19/2017 | 1 | 90 | 80.42857 | 9/20/2018 | 1 | 1 | 1 | 1 | 1 | |
| 70.3 | -16.85714 | 12/10/2016 | 3 | 58.2 | 4.428571 | 5/8/2017 | 3 | 53.9 | 17.71428 | 8/9/2017 | 3 | 50.6 | 33 | 11/24/2017 | 3 | 5 | 5 | 5 | 5 | |
| 61.9 | -16.85714 | 12/10/2016 | 3 | 49.7 | 4.428571 | 5/8/2017 | 3 | 55.1 | 22 | 9/8/2017 | 3 | 47.5 | 33 | 11/24/2017 | 3 | 5 | 5 | 5 | 5 | |
| 62.9 | -6.571429 | 12/3/2016 | 3 | 56.4 | 11.71429 | 4/10/2017 | 3 | 51.5 | 31.28572 | 8/25/2017 | 3 | 55.4 | 56.28571 | 2/16/2018 | 3 | 5 | 5 | 5 | 5 | |
| 89.6 | -25.42857 | 3/14/2017 | 1 | 90 | 11.85714 | 11/30/2017 | 2 | 79.3 | 23 | 2/16/2018 | 2 | 73.3 | 48.71429 | 8/15/2018 | 2 | 6 | 6 | 6 | 6 | |
| 90 | -13.14286 | 12/10/2016 | 1 | 90 | 3.714286 | 4/7/2017 | 2 | 85.5 | 15.71429 | 6/30/2017 | 1 | 90 | 28.14286 | 9/25/2017 | 1 | 1 | 1 | 1 | 1 | |
| 74.6 | -9.857142 | 12/10/2016 | 2 | 81.8 | 2.428571 | 3/6/2017 | 2 | 72.8 | 16 | 6/9/2017 | 2 | 75.8 | 46.57143 | 1/9/2018 | 2 | 7 | 7 | 7 | 7 | |
| 90 | -8.142858 | 1/18/2017 | 1 | 90 | 3.714286 | 4/11/2017 | 1 | 90 | 19.14286 | 7/28/2017 | 1 | 90 | 47.85714 | 2/14/2018 | 1 | 1 | 1 | 1 | 1 | |
| 90 | 0 | 3/8/2018 | 1 | 90 | 3.857143 | 4/4/2018 | 1 | 90 | 15.71429 | 6/26/2018 | 1 | 90 | 23.71428 | 8/21/2018 | 1 | 1 | 1 | 1 | 1 | |
| 47.6 | 0 | 4/25/2018 | 3 | 51.5 | 4 | 5/23/2018 | 2 | 60.5 | 59.42857 | 6/15/2019 | . | . | . | . | . | . | . | . | . | |
| 90 | -8.285714 | 12/3/2016 | 1 | 90 | 3.142857 | 2/21/2017 | 1 | 90 | 15.14286 | 5/16/2017 | 1 | 90 | 26.57143 | 8/4/2017 | 2 | 6 | 6 | 6 | 6 | |
| 40.9 | -11.71429 | 12/10/2016 | 3.5 | 41.4 | 2.857143 | 3/22/2017 | 3.5 | 32.6 | 15.85714 | 6/21/2017 | 3.5 | 32.1 | 41.85714 | 12/20/2017 | 4 | 4 | 4 | 4 | 4 | |
| 60.7 | 0 | 3/30/2017 | 3 | 60.7 | 0 | 3/30/2017 | 3 | 58 | 12.14286 | 6/23/2017 | 3 | 52.3 | 36.14286 | 12/8/2017 | 2 | 6 | 6 | 6 | 6 | |
| 89.6 | -21.28572 | 10/2/2017 | 1 | 90 | 4 | 3/28/2018 | 1 | 90 | 12.28571 | 5/25/2018 | 1 | 90 | 28.71428 | 9/17/2018 | 1 | 1 | 1 | 1 | 1 | |
| 79.4 | -13.85714 | 12/10/2016 | 2 | 76.4 | 3.714286 | 4/12/2017 | 2 | 72.9 | 15.42857 | 7/3/2017 | 2 | 74.2 | 43 | 1/12/2018 | 2 | 7 | 7 | 7 | 7 | |
| 54.6 | -15 | 12/3/2016 | 3.5 | 36.1 | 3.571429 | 4/12/2017 | 3.5 | 41.5 | 15.57143 | 7/5/2017 | 3.5 | 44.3 | 27.71428 | 9/28/2017 | 3.5 | 4 | 4 | 4 | 4 | |
| 90 | -7 | 12/10/2016 | 1 | 90 | 10.71429 | 4/13/2017 | 1 | 90 | 22.85714 | 7/7/2017 | 1 | 90 | 46.85714 | 12/22/2017 | 1 | 1 | 1 | 1 | 1 | |
| 87.1 | -16.71428 | 12/6/2017 | 2 | 79.1 | 2.571429 | 4/20/2018 | 2 | 86.8 | 14.57143 | 7/13/2018 | 2 | 83.8 | 34.57143 | 11/30/2018 | 2 | 7 | 7 | 7 | 7 | |
| 46.8 | -14.71429 | 3/6/2017 | 3 | 45.1 | 3.857143 | 7/14/2017 | 3 | 46.4 | 20.42857 | 11/7/2017 | 3 | 48.3 | 31.28572 | 1/22/2018 | 3 | 4 | 4 | 4 | 4 | |
| 90 | -8.857142 | 3/2/2017 | 1 | 90 | 3.285714 | 5/26/2017 | 1 | 90 | 16 | 8/23/2017 | 1 | 90 | 39 | 1/31/2018 | 2 | 89.4 | 62.28571 | 7/13/2018 | 1 | |
| 32.3 | -. | 4/285714 | 11/22/2017 | 4 | 29.7 | 3.428571 | 12/19/2017 | 3.5 | 30.5 | 12.57143 | 2/21/2018 | 4 | 26.9 | 19.42857 | 4/10/2018 | 4 | 26.8 | 48.85714 | 11/2/2018 | 4 |
| 45.2 | -12.85714 | 12/10/2016 | 3.5 | 39.5 | 4 | 4/7/2017 | 3.5 | 38.1 | 21 | 8/4/2017 | 3.5 | 38.1 | 34 | 11/3/2017 | 3.5 | 40.6 | 65 | 6/8/2018 | 3.5 | |
| 51.3 | -8 | 9/7/2018 | 3 | 54.6 | 4 | 11/30/2018 | 3 | 50.2 | 17.71428 | 3/6/2019 | 3.5 | 44.5 | 35.71429 | 7/10/2019 | 3 | 52.9 | 61.57143 | 1/7/2020 | 3.5 | |
| 40.8 | -6.714286 | 2/16/2017 | 3.5 | 32.8 | 11.28571 | 6/22/2017 | 3.5 | 35 | 35.14286 | 12/6/2017 | 3.5 | 37.1 | 72.14286 | 8/22/2018 | 3.5 | 33.8 | 109.1429 | 5/8/2019 | 4 | |
| 90 | -13 | 12/10/2016 | 2 | 80.3 | 3.857143 | 4/7/2017 | 2 | 68.7 | 15.85714 | 6/30/2017 | 2 | 69.5 | 27.85714 | 9/22/2017 | 1 | 90 | 51.85714 | 3/9/2018 | 2 | |

| Variables | |
|---------------|---|
| Name | Label |
| ID | ADPKD patient ID |
| IDanony | |
| IDanony_n | |
| DOB | DOB |
| age0 | age at baseline visit (y... 3=20-29, 4=30-39, 5... |
| agecat_dec | 1=male, 2=female |
| height | height (cm) |
| tolvst_date | start date tolvaptan |
| tolv_dose | starting dose tolvaptan |
| mayo | 1=A, 2=B, 3=C, 4=D, 5... |
| reas_dose_red | reason for tolvaptan d... |
| reas_stop | reason for tolvaptan o... |
| stop_date | date stop tolvaptan |
| tolv_ther | 1=stop, 2=continued,... |
| last_visit | most recent ADPKD c... |
| fut_tolv_y | follow-up time on tolv... |
| fut_tolv_m | follow-up time under t... |
| fut_tol_w | follow-up time under t... |
| max_tolv_dose | 1=45/15, 2=60/30, 3=... |
| stage_GFR0 | 1=90+, 2=60-89, 3=4... |
| GFR0 | GFR 0 |
| GFR0_fut_w | |
| GFRdate0 | GFRdate baseline bef... |
| stage_GFR1 | 1=90+, 2=60-89, 3=4... |
| GFR1 | GFR 1 |
| GFR1_fut | time visit0 to GFR1 (w... |
| GFRdate1 | GFRdate 1 |
| stage_GFR2 | |
| GFR2 | GFR 2 |
| GFR2_fut | |
| GFRdate2 | GFRdate 2 |
| stage_GFR3 | |

Tolvaptan bei ADPKD



Hepatotoxicity surveillance of tolvaptan in phase III clinical trial (ADPKD patients)



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

Data from SUISSSE ADPKD cohort

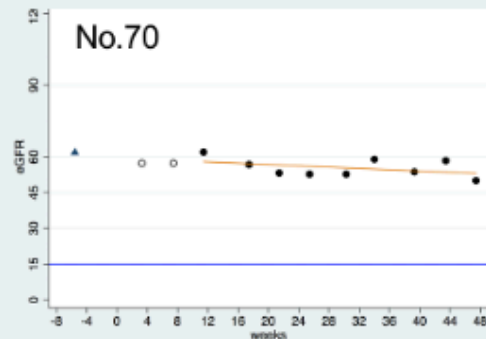
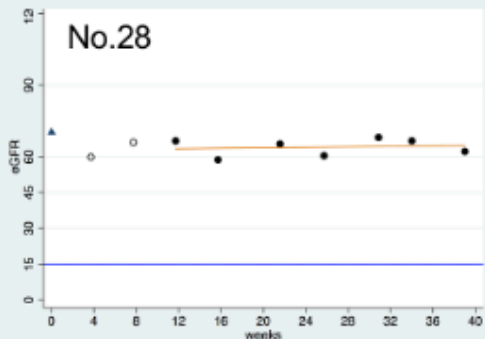
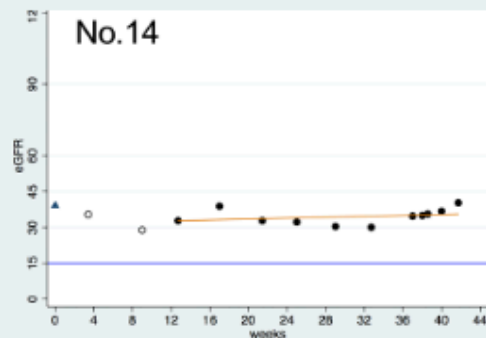
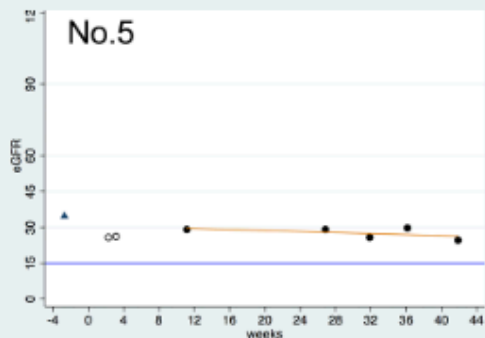
2018 analysis, 76 patients



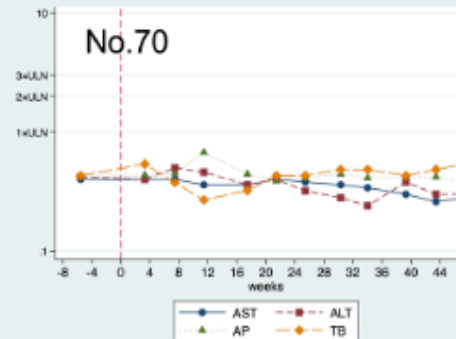
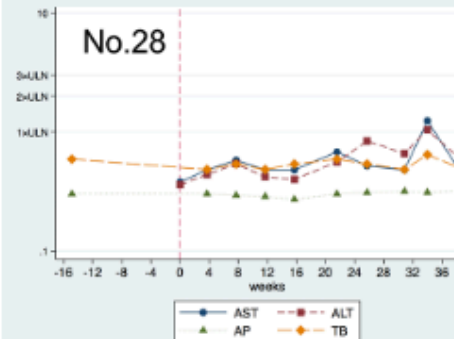
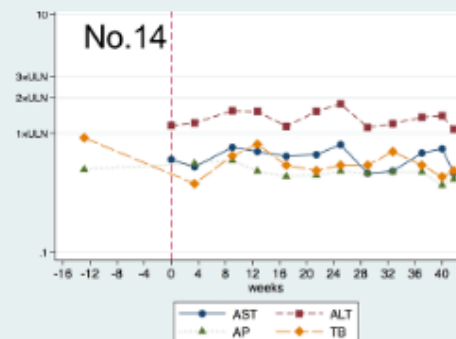
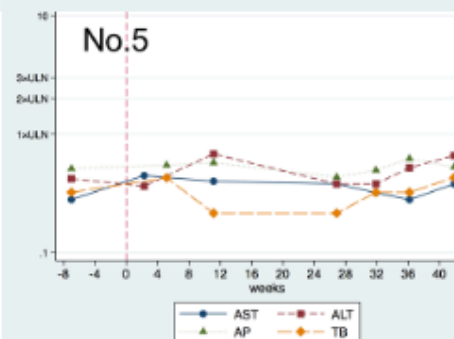
DRUGSAFETY.CH

Representative Samples of 4 Patients

Course of eGFR



Course of liver values



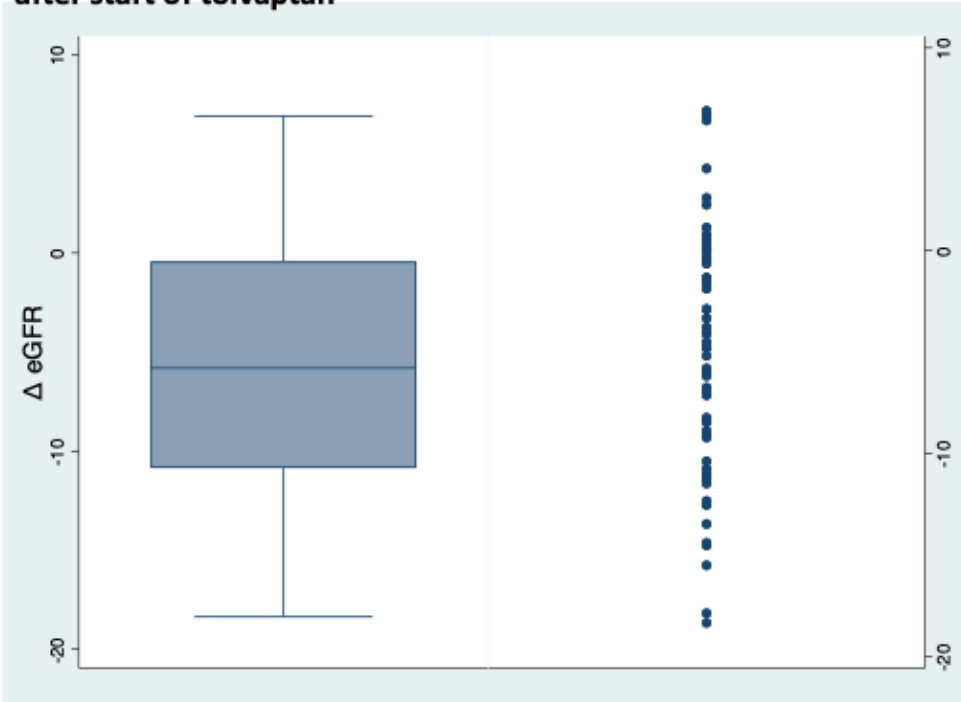
The x-axis represents time in weeks from start of tolvaptan. The y-axis represents eGFR (mL/min/1.73 m²). These samples were selected because there were more than 2 visits within 11 weeks and 5 visits from 11 weeks after start of tolvaptan.

Triangle: baseline value; Hollow circle: values until 11weeks | after: start of tolvaptan; Circle: values from 11 weeks after start of tolvaptan; Line: simple linear regression from 11weeks after start of tolvaptan. eGFR: estimated glomerular filtration rate

ULN: upper limits of normal, ALT: alanine aminotransferase, AST: aspartate aminotransferase, AP: alkaline phosphatase, TB: total bilirubin.

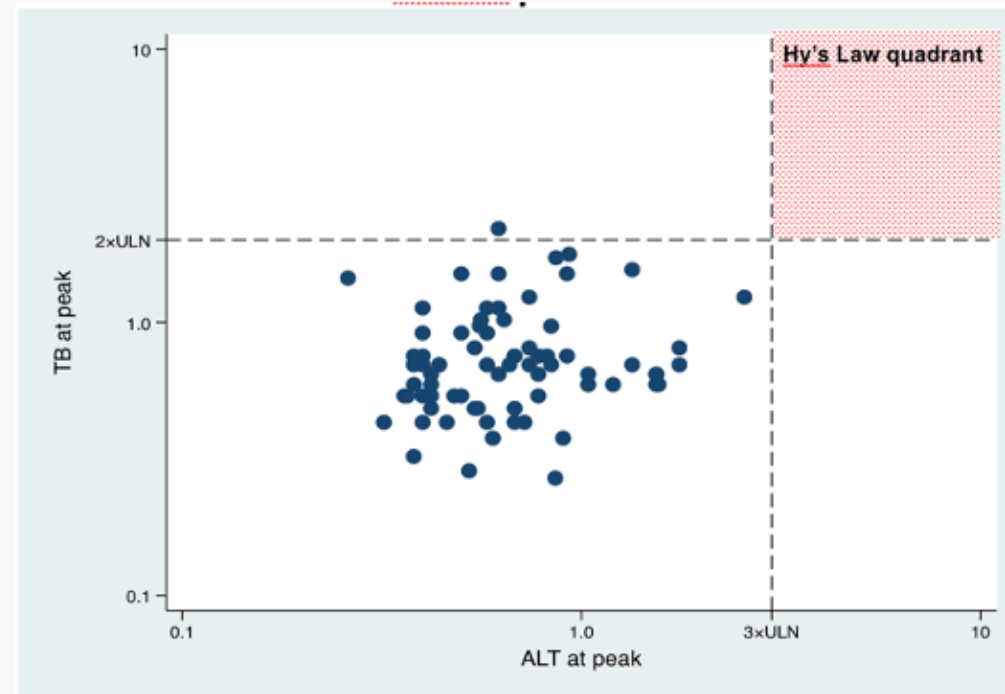
Initial delta eGFR and analysis of Drug-Induced Serious Hepatotoxicity

Box and scatter plot of delta eGFR from baseline to 4 week visit after start of tolvaptan



The y-axis represents the delta of eGFR between baseline and the first visit after start of tolvaptan (mL/min/1.73 m²). Number of observations was 67, since 9 patients did not have a documented value of eGFR within 11 weeks after start of tolvaptan. The box indicates 50% of the observed data points between the 1st and 3rd quartiles. The line within the box represents the median. The whiskers show the data between the upper adjacent value and the lower adjacent value.

eDISH - Evaluation of Drug-Induced Serious Hepatotoxicity



Each point in the figure represents the unique subject's peak serum ALT and peak serum TB values during the available follow-up time. Peak serum ALT is shown along the x-axis and peak serum TB is shown along the y-axis as x-fold ULN on log scale. ULN; upper limits of normal, ALT; alanine aminotransferase, TB; total bilirubin



Hepatotoxicity monitoring after 2018

- ALT increases in **two patients** in March and April 2019 during tolvaptan treatment
- 5 and 10 times upper limit of normal, respectively
- No likely explanations other than tolvaptan found

-> STOP TOLVAPTAN

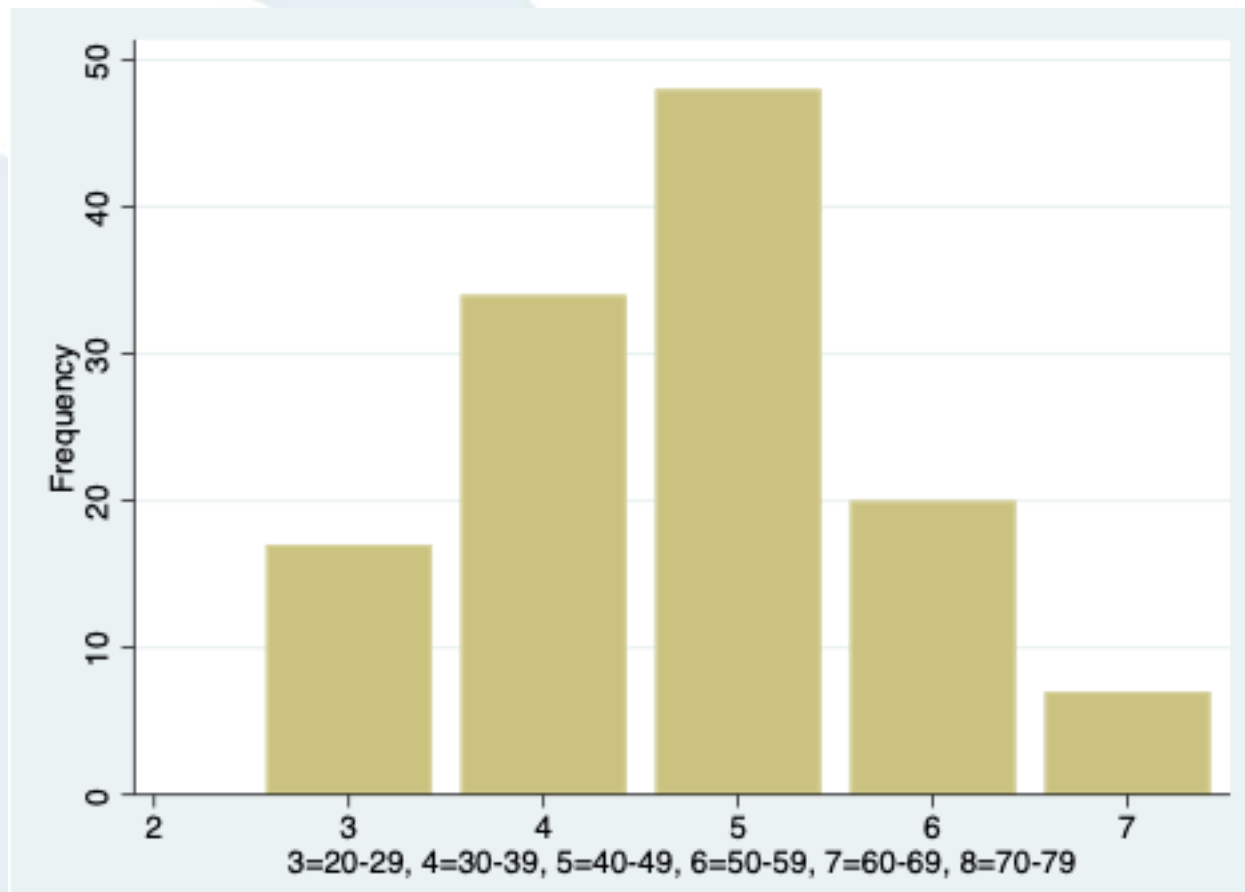
-> Full recovery without complications soon after stop



Characteristics of our tolvaptan patients - age

2021 analysis, 126 patients

Age at start of tolvaptan



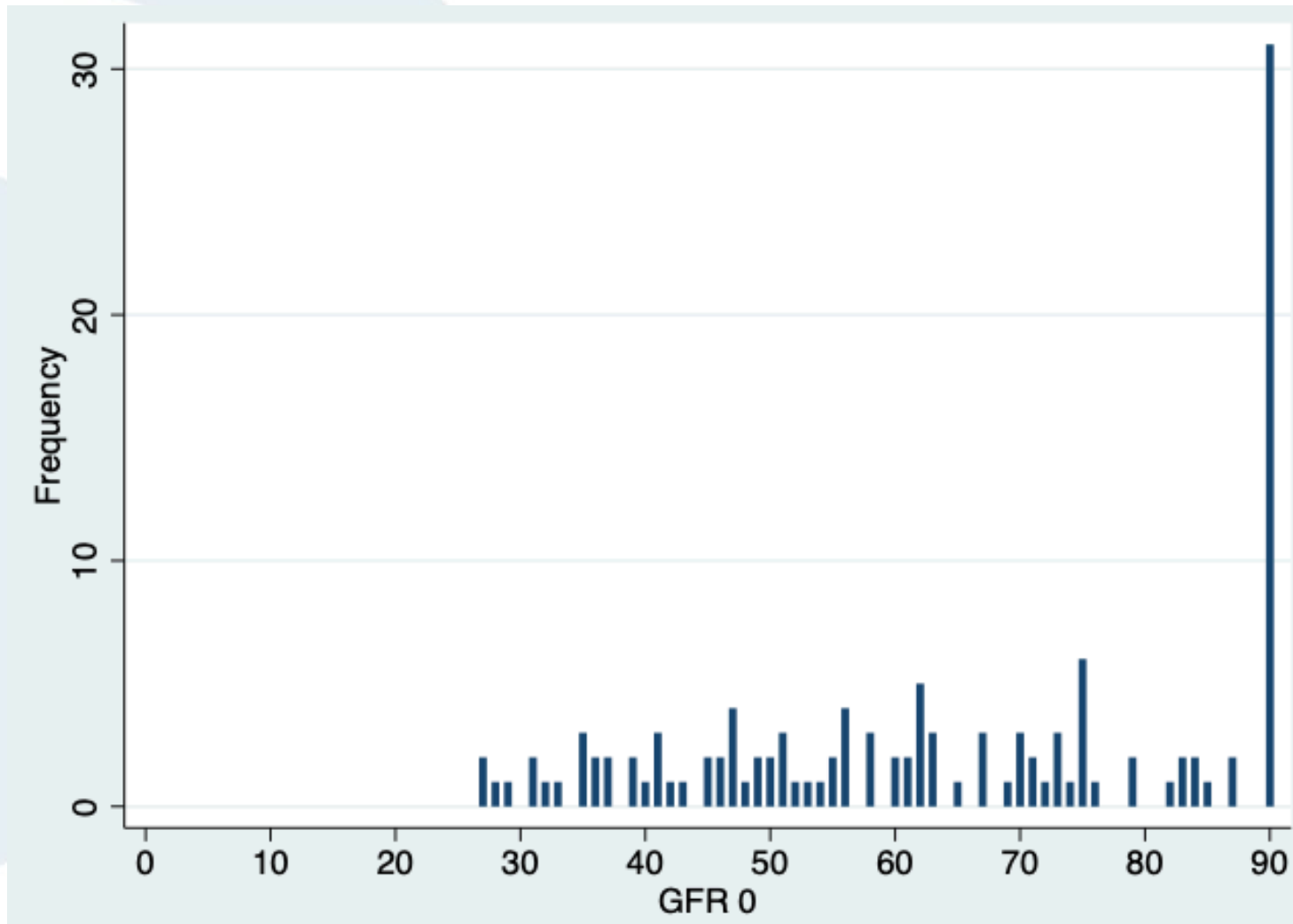
Characteristics of our tolvaptan patients - renal function

2021 analysis, 126 patients



DRUGSAFETY.CH

eGFR at start of tolvaptan



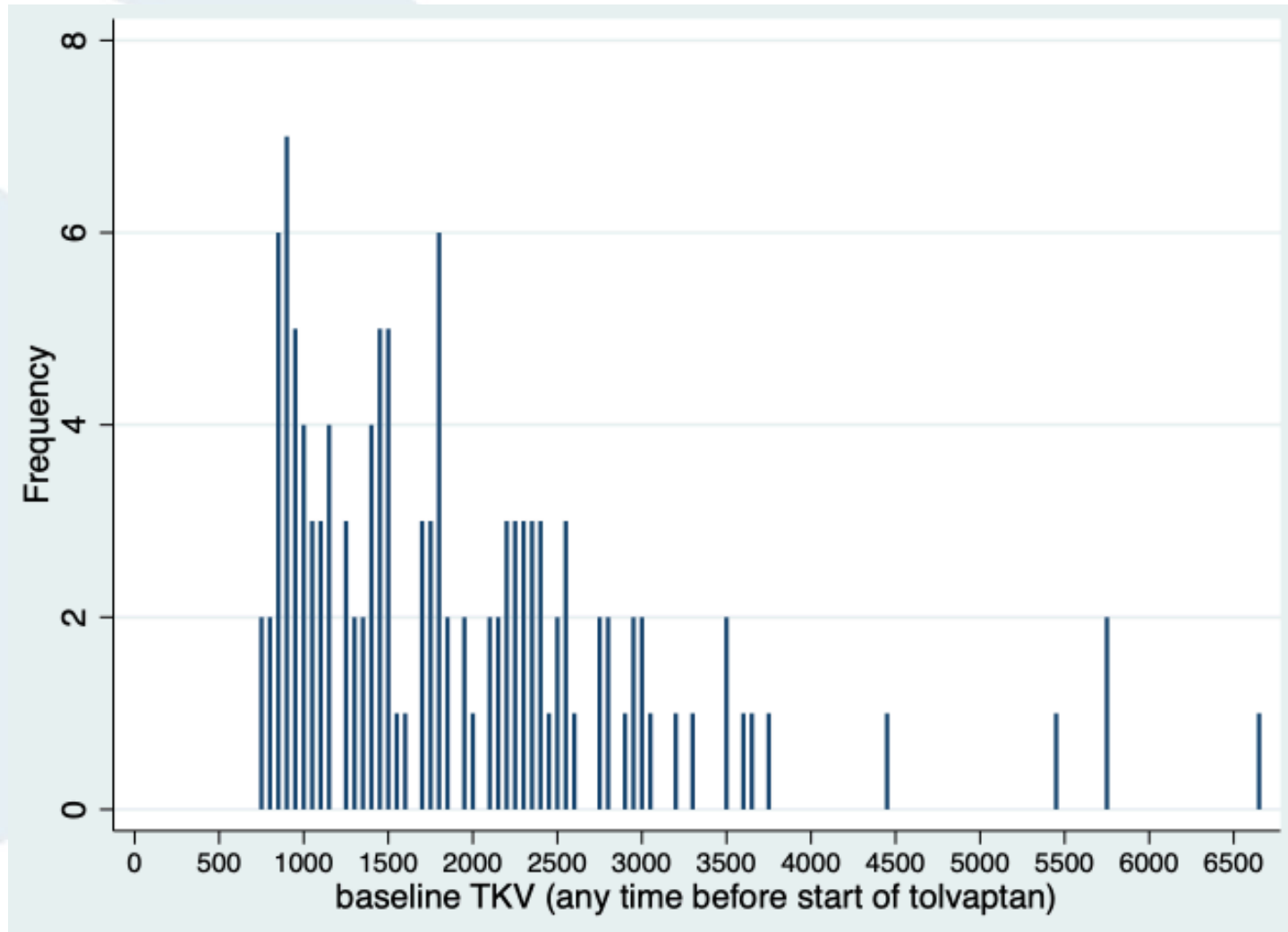
Characteristics of our tolvaptan patients - kidney volume

2021 analysis, 126 patients



DRUGSAFETY.CH

Total kidney volume (ml) at start of tolvaptan



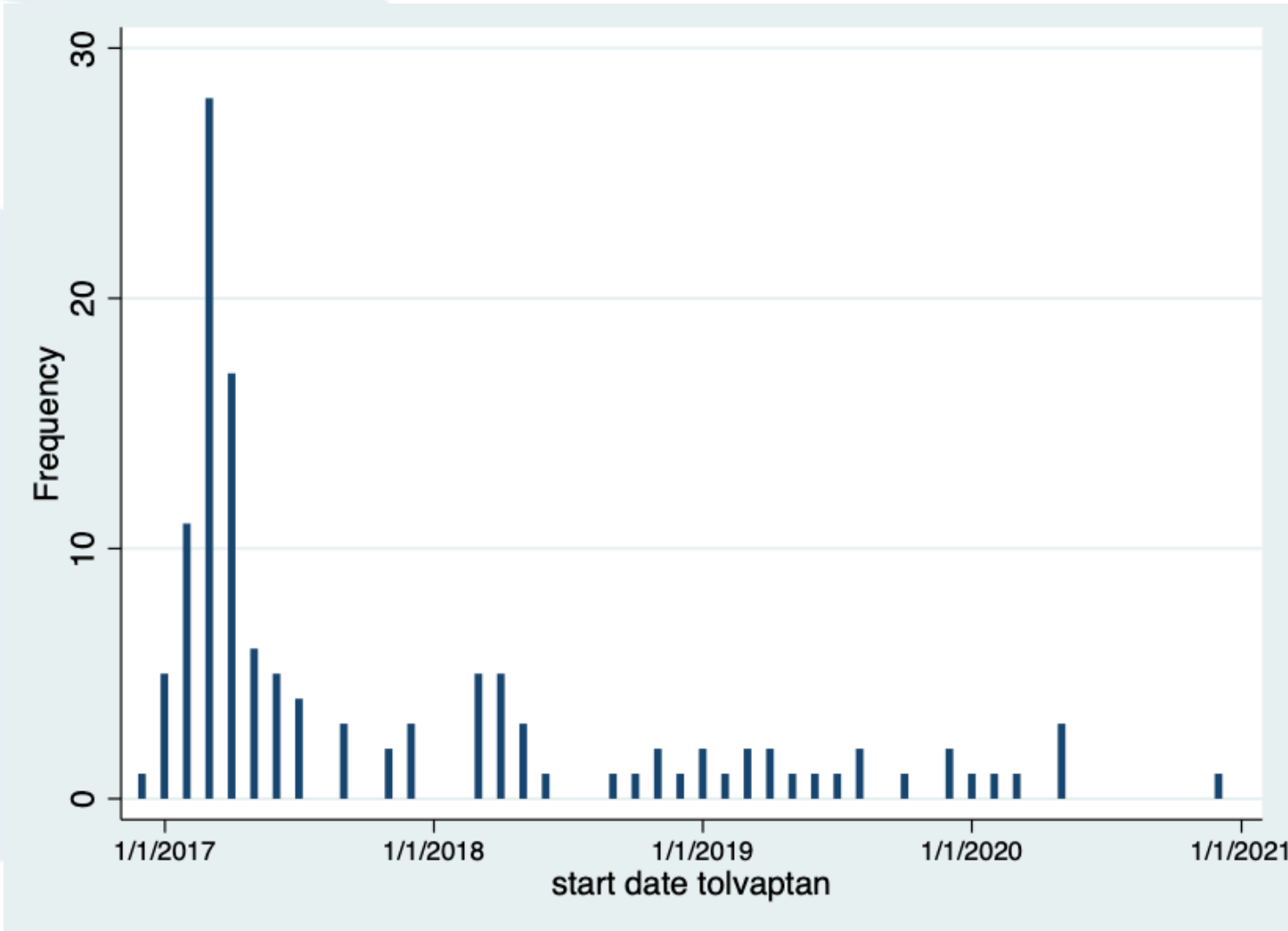
Tolvaptan start calendar date

2021 analysis, 126 patients



DRUGSAFETY.CH

Start date tolvaptan



Compliance with tolvaptan treatment

2021 analysis, 126 patients



DRUGSAFETY.CH

Therapy course

| Therapy course | Freq. | Percent | Cum. |
|-------------------|-------|---------|--------|
| discontinued | 7 | 5.56 | 5.56 |
| continued | 110 | 87.30 | 92.86 |
| loss of follow-up | 3 | 2.38 | 95.24 |
| paused | 2 | 1.59 | 96.83 |
| renal failure | 4 | 3.17 | 100.00 |
| Total | 126 | 100.00 | |

Tolvaptan maximum maintenance dose

| Tolvaptan dose | Freq. | Percent | Cum. |
|----------------|-------|---------|--------|
| 45/15 | 8 | 6.35 | 6.35 |
| 60/30 | 8 | 6.35 | 12.70 |
| 90/30 | 109 | 86.51 | 99.21 |
| 90/0 | 1 | 0.79 | 100.00 |
| Total | 126 | 100.00 | |

Note: Among the 8 patients with a dose of 45/15 and the 8 patients with a dose of 60/30, this may not be the final maintenance dose yet if patients started tolvaptan therapy only recently.



Progression of eGFR under treatment with tolvaptan

2021 analysis, 126 patients

Delta eGFR vs. baseline after 1, 2 and 3 years

| Follow-up time | Obs | Mean | Std. dev. | Min | Max |
|----------------|-----|-----------|-----------|-------|----------|
| 1 year | 61 | -6.085246 | 6.646524 | -20.1 | 9.900001 |
| 2 years | 54 | -5.87963 | 6.762504 | -22.2 | 10.9 |
| 3 years | 30 | -8.456667 | 7.293866 | -23.1 | 5.500001 |

Note: for calculation delta eGFR max = 90 ml/min/1.73m²

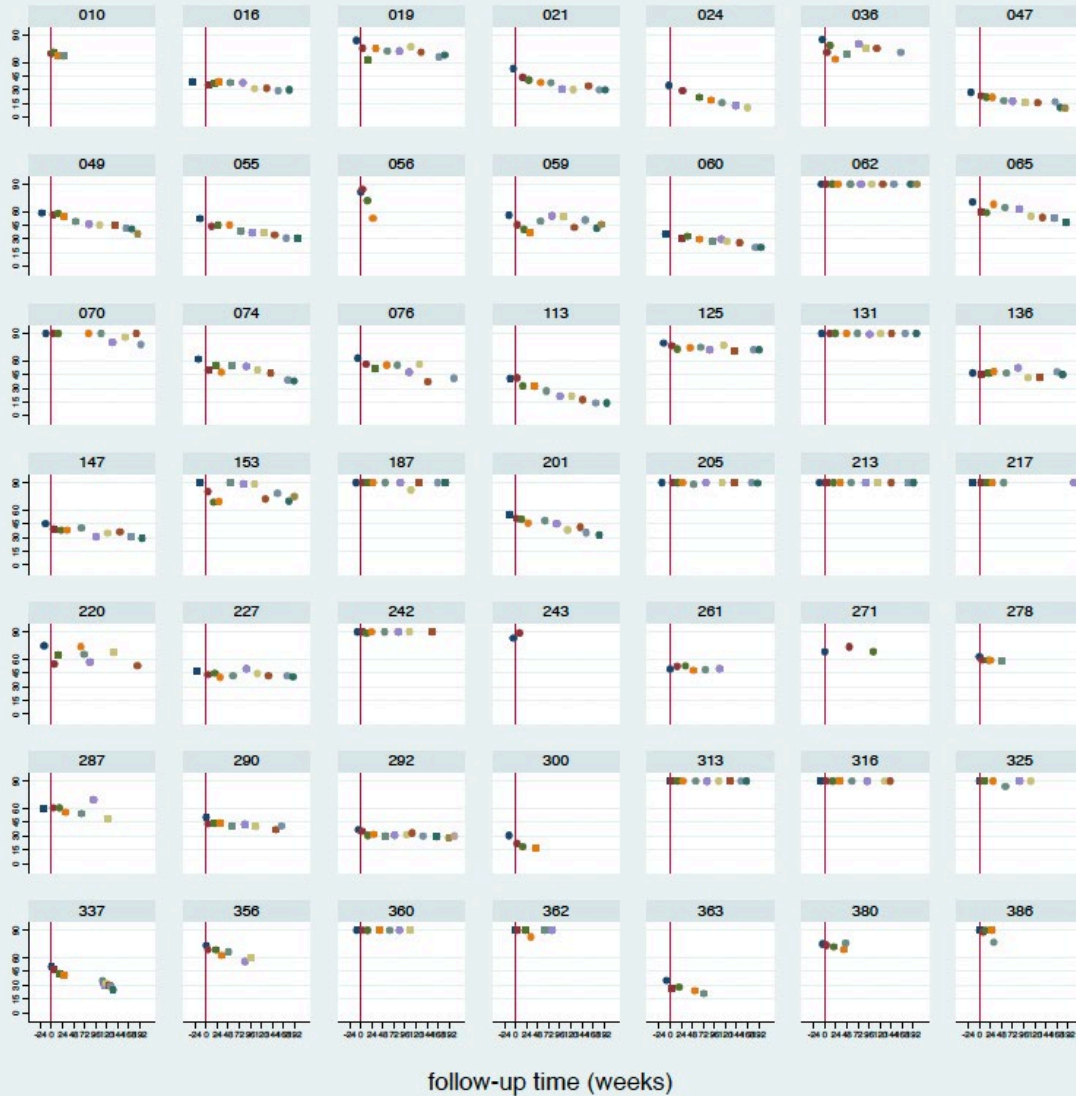
Progression of eGFR under treatment with tolvaptan

2021 analysis, 126 patients



DRUGSAFETY.CH

Mayo class D, course of eGFR



Delta eGFR vs. baseline after 1, 2 and 3 years

| Follow-up time | Obs | Mean | Std. dev. | Min | Max |
|----------------|-----|-----------|-----------|-------|----------|
| 1 year | 61 | -6.085246 | 6.646524 | -20.1 | 9.900001 |
| 2 years | 54 | -5.87963 | 6.762504 | -22.2 | 10.9 |
| 3 years | 30 | -8.456667 | 7.293866 | -23.1 | 5.500001 |

Note: for calculation delta eGFR max = 90 ml/min/1.73m²

Tolvaptan bei Hyponatriämie durch SIADH





ORIGINAL ARTICLE

Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease

Rajiv Agarwal, M.D., Arjun D. Sinha, M.D., Andrew E. Cramer, B.S.,
Mary Balmes-Fenwick, M.S., Jazmyn H. Dickinson, B.S.,
Fangqian Ouyang, M.S., and Wanzhu Tu, Ph.D.

CONCLUSIONS

Among patients with advanced chronic kidney disease and poorly controlled hypertension, chlorthalidone therapy improved blood-pressure control at 12 weeks as compared with placebo. (Funded by the National Heart, Lung, and Blood Institute and the Indiana Institute of Medical Research; CLICK ClinicalTrials.gov number, NCT02841280.)

Prof. Dr. med. Stefan Russmann

- *FMH Klinische Pharmakologie und Toxikologie*
- *Senior Consulting Physician, Hirslanden Hospitals Zurich and Aarau*
- *Associate Professor of Clinical Pharmacology and Toxicology, University of Zurich*
- *Alumni Adj. Associate Professor of Epidemiology, Boston University*
- *Lecturer of Pharmacoepidemiology and Drug Safety, ETH Zurich*

russmann@drugsafety.ch

www.drugsafety.ch



Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

