

UNA MALATTIA NON PIU' ORFANA

► 17 DICEMBRE 2019
TORRE DEL GRECO
HOTEL SAKURA

**REAL LIFE EXPERIENCE NEL
MANAGEMENT DEL PAZIENTE CON
ADPKD ALLA LUCE DELLE NUOVE
EVIDENZE CLINICHE**

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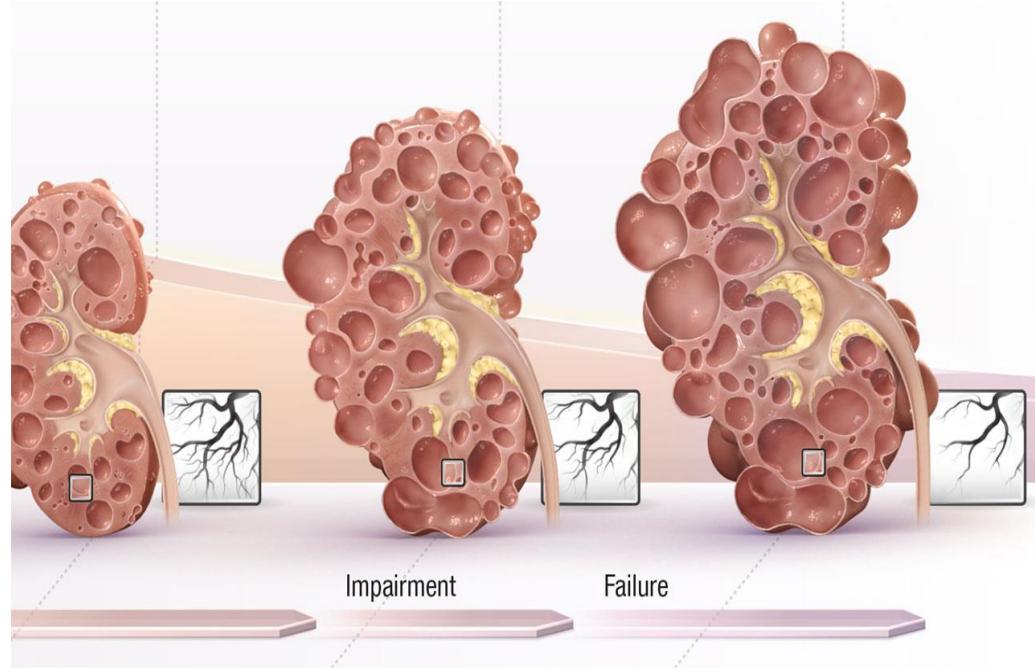


Con il contributo di



AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

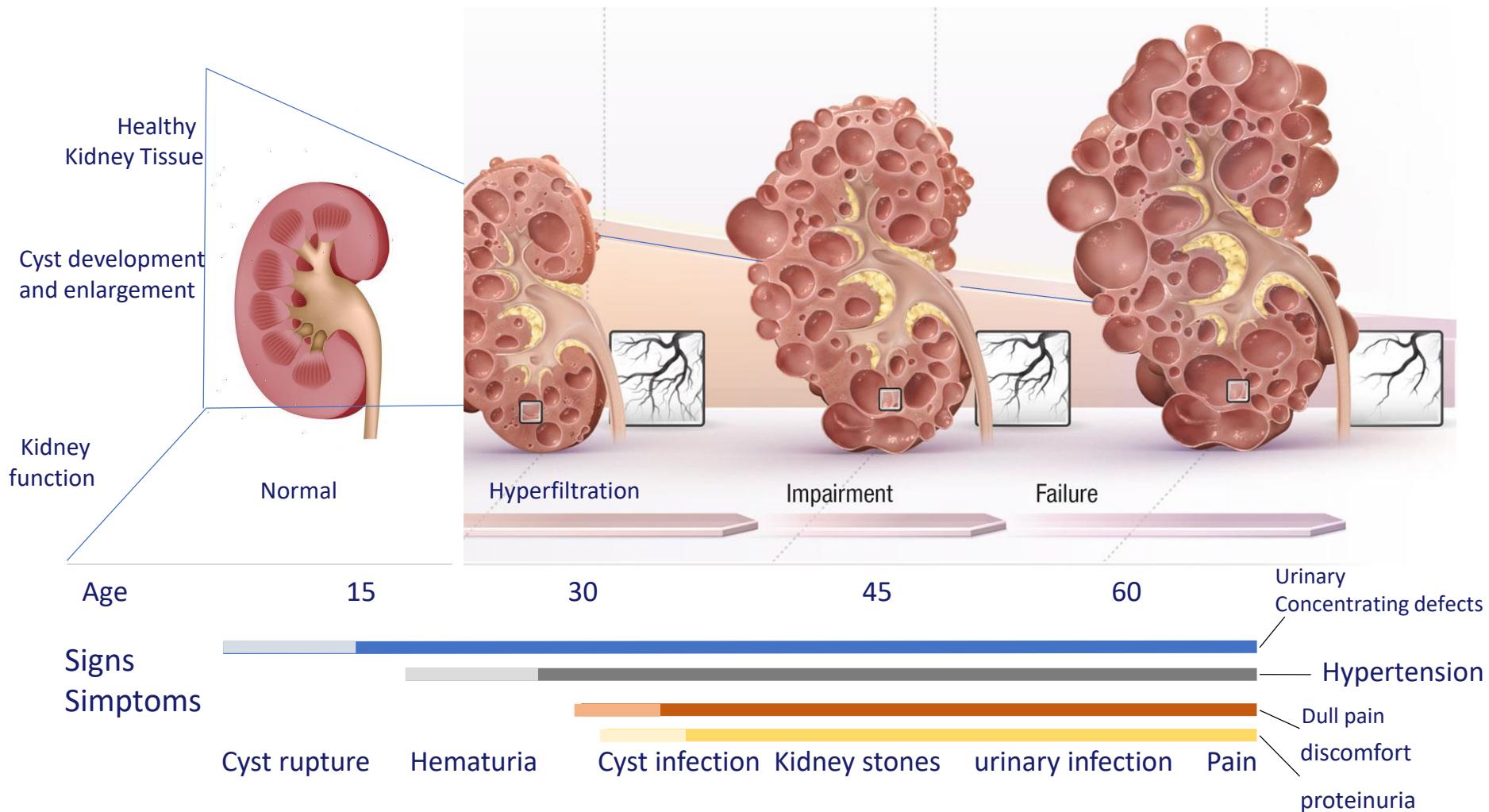
- THE MOST COMMON MONOGENIC HEREDITARY KIDNEY DISEASE
Inherited kidney disease that affects 12.5 million people worldwide in all ethnic groups
- PREVALENCE AT BIRTH 1: 400 - 1:1000 (Caucasians)
- USUALLY, LATE ONSET DISORDER
- BILATERAL RENAL CYST DEVELOPMENT
- EXTRARENAL MANIFESTATIONS
- 6-10% of ESRD (USA-Europe)



a major burden for public health

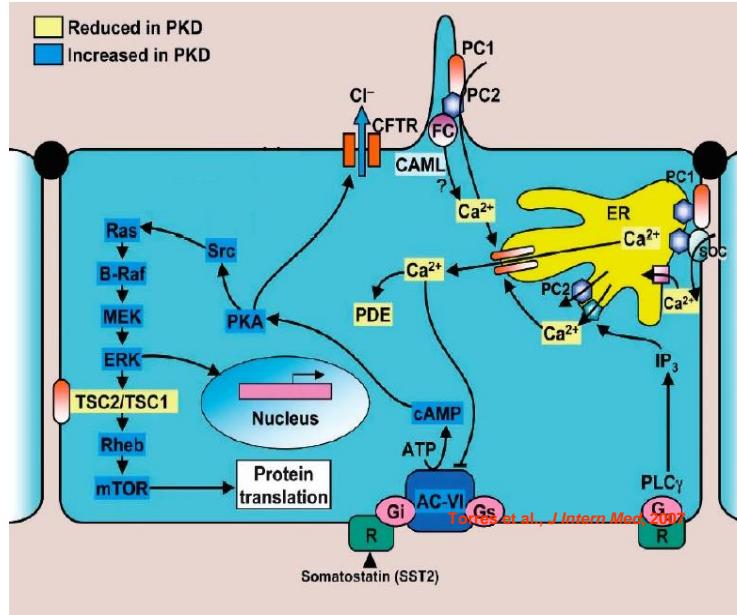
Medical care costs exceed \$ 200 million a year (USA)

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)



ADPKD

the changing face of clinical management

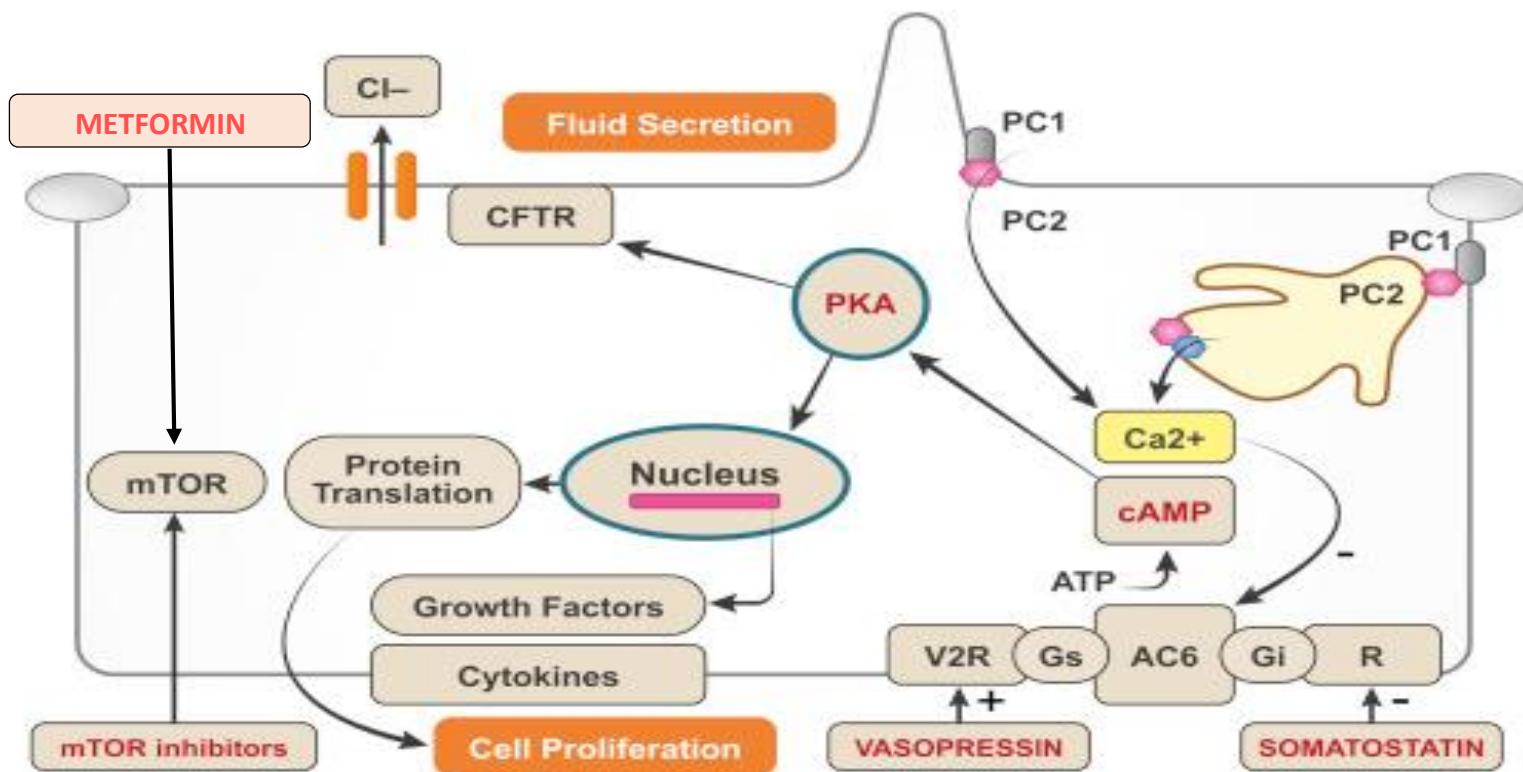


understanding of polycystin function and cystic pathogenesis

ADPKD as untreatable,
progressing relentlessly
towards end-stage renal disease

ADPKD as treatable disease

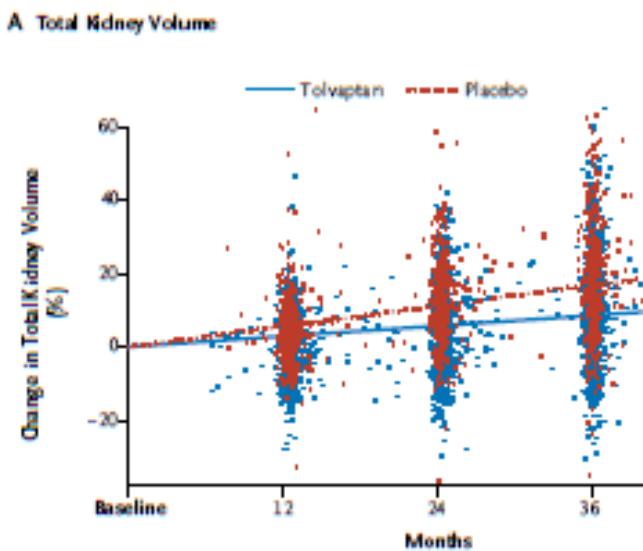
Therapeutic approaches in ADPKD



Drugs that inhibit cyst growth always show the greatest benefit in the rapid ADPKD progression stage but do not show significant improvements in early and later stages

Tempo 3:4 trial

Tolvaptan reduced the annual rate of change of total kidney volume (TKV) by 49%.



B Treatment Effect for Total Kidney Volume

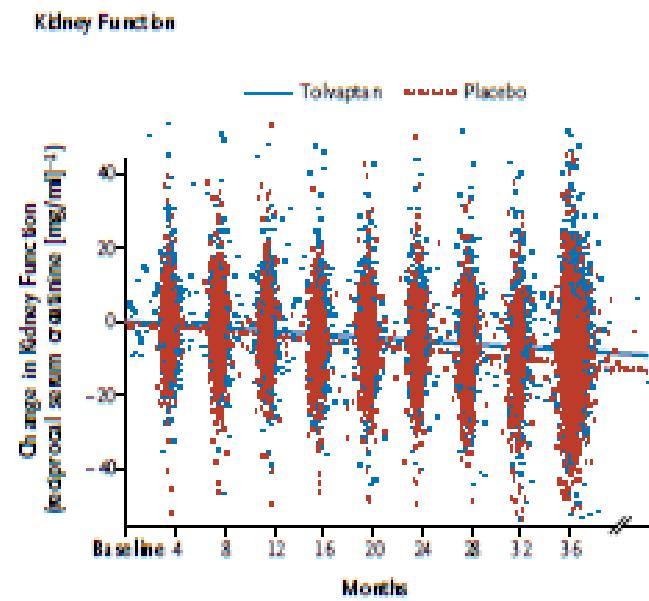
Subgroup	Absolute Treatment Effect		Relative Treatment Effect		Annual Slope Tolvaptan %/yr	Annual Slope Placebo %/yr	PValue
		Difference in annual slope (%/yr)		%			
Sex							
Male	-2.5	-3.0	37.3	4.15	6.62	<0.001	
Female	-2.5	-3.0	71.1	1.24	4.29	<0.001	
Age							
<35 yr	-2.5	-3.0	28.0	4.37	6.06	0.02	
≥ 35 yr	-2.5	-3.0	58.2	2.23	5.34	<0.001	
Hypertension							
Yes	-2.5	-3.0	50.5	3.01	6.09	<0.001	
No	-2.5	-3.0	51.2	1.62	3.32	0.008	
Estimated eGFR							
<80 ml/min	-2.5	-3.0	57.2	2.27	5.32	<0.001	
≥ 80 ml/min	-2.5	-3.0	47.5	2.92	5.56	<0.001	
Total kidney volume							
<1500 ml	-2.5	-3.0	48.8	2.24	4.37	<0.001	
≥ 1500 ml	-2.5	-3.0	51.1	3.29	6.74	<0.001	
All patients	-2.5	-3.0	49.2	2.80	5.51	<0.001	

Over a 3-year period, the increase in total kidney volume in the tolvaptan group was 2.8% per year (95% confidence interval [CI], 2.5 to 3.1), versus 5.5% per year in the placebo group (95% CI, 5.1 to 6.0; $P<0.001$).

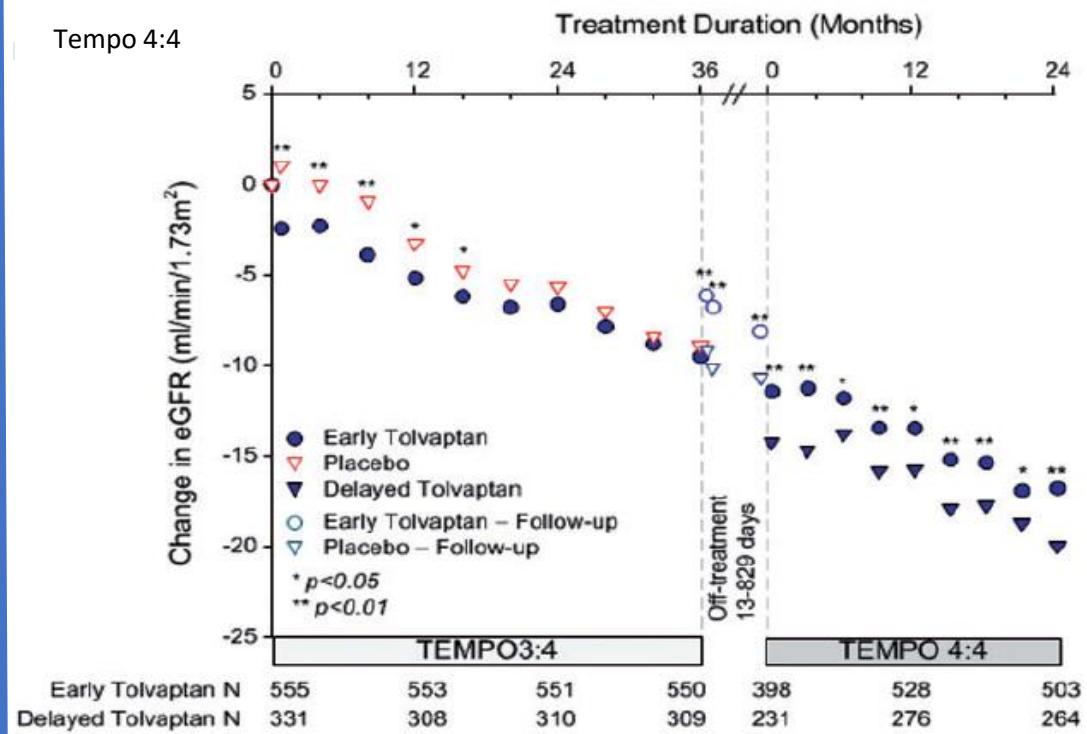
Tempo 3:4 and 4:4 trials

Tolvaptan was associated with a milder decline of kidney function than in controls over 3 and 5 years

Tempo 3:4



Tempo 4:4



Tolvaptan was associated with a slower decline in kidney function (reciprocal of the serum creatinine level)
-2.61 [mg/milliliter]⁻¹ per year vs. -3.81 [mg/milliliter]⁻¹ per year; P<0.001.

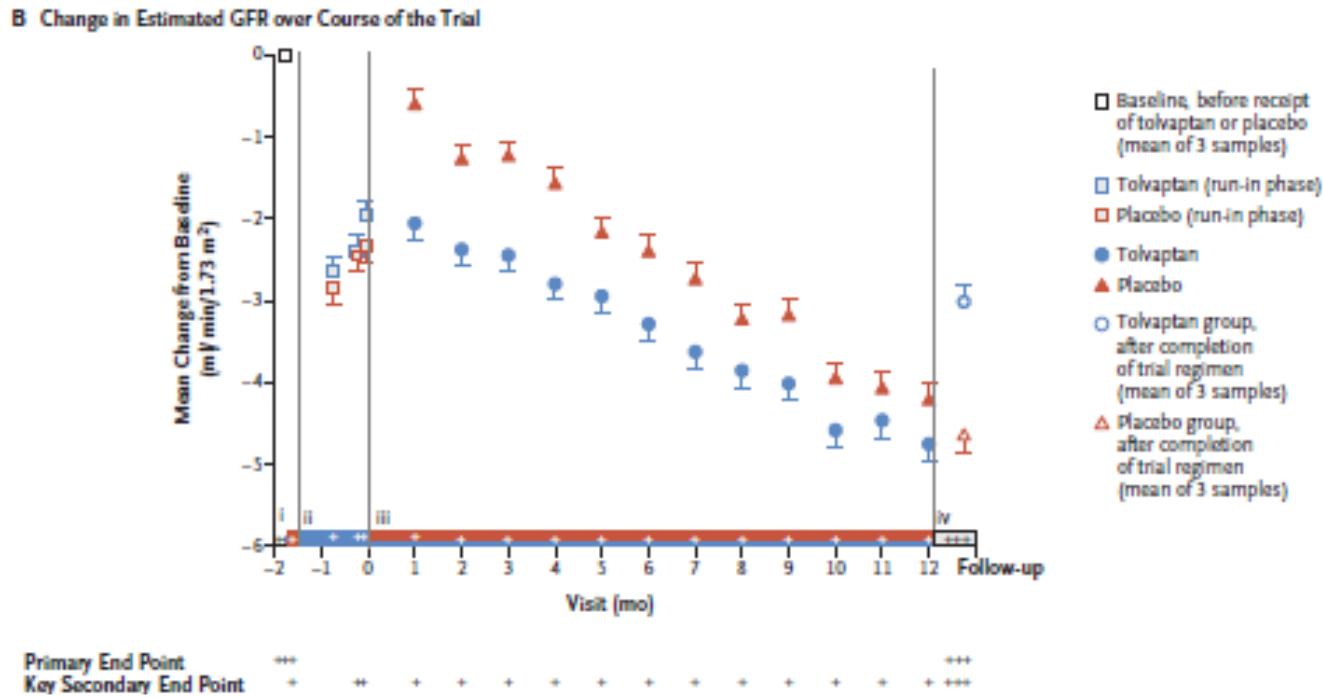
Analysis of secondary eGFR endpoints demonstrated a persistent effect on eGFR (3.15mL/min/1.73 m², P<0.001)

Tolvaptan received a [marketing authorisation](#) valid throughout the European Union on 27 May 2015

Tolvaptan is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults (18-50y) with CKD stage 1 to 3 (GFR 45-89 ml/min) at initiation of treatment with evidence of rapidly progressing disease.

Reprise trial

1370 patients with ADPKD who were either 18 to 55 years of age with an estimated GFR of 25 to 65 ml per minute per 1.73 m² of body-surface area or 56 to 65 years of age with an estimated GFR of 25 to 44 ml per minute per 1.73 m².



Tolvaptan resulted in a slower decline than placebo in the estimated GFR over a 1-year period in patients with later-stage ADPKD.

In August 2018, EMA approved the following extension of indication: "Tolvaptan is indicated to slow the progression of cyst development and renal failure associated with autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 4 at the start of treatment, with evidence of rapidly progressing disease"

Nephrologists may consider the option of Tolvaptan for ADPKD.

CONTRARY TO USE

Problems that may impact decisions to treat.

DOES TOLVAPTAN AFFECT QUALITY OF LIFE?

VARIABLE EFFECTS OF TOLVAPTAN ON TKV

HEPATOTOXICITY AND DOSING OF TOLVAPTAN

WORSENING OF GFR DURING TOLVAPTAN THERAPY

SHOULD TOLVAPTAN BE STOPPED BEFORE ESRD?

THE COST-EFFECTIVENESS OF TOLVAPTAN IS BORDERLINE

Arguments against tolvaptan...

*" Patients have to drink at least
10 litres of water per day...
This is not possible... "*

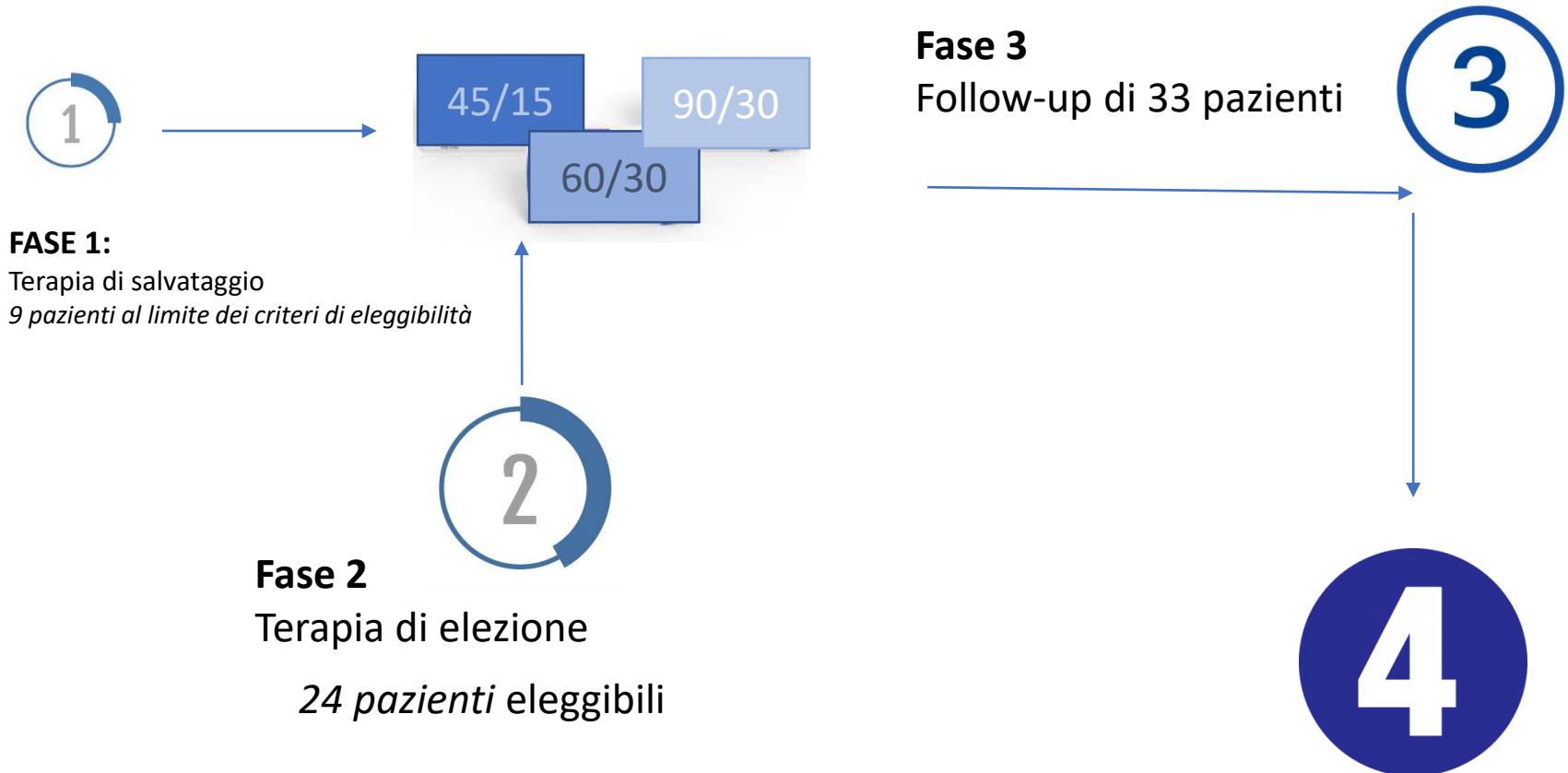
*“adherence to treatment is
difficult in the long run...”*

*“ Uptitration
... who should do it and how?
surely it is difficult.... ”*

*“ Feasibility of therapy ...
surely the patients will have problems”*

La nostra esperienza

Tolvaptan ha ricevuto l'autorizzazione alla commercializzazione in Italia a Dicembre 2017



La nostra esperienza:

Eleggibilità dei pazienti

Eleggibilità	FASE 1	FASE 2
	Terapia di salvataggio (n=9)	Terapia di elezione (N=24)
Eta <50 anni %	9 (100)	24(100)
IRC legato all ADPKD %	9 (100)	24 (100)
Test genetico %	0	2(8)
eGFR _{CKD-EPI} (mL/min/1.73 m ²), media± SD	45.5 ± 0,6	56 ± 13
Valutazione TKV	9	16
Rm > 750 ml	5	10
Eco Lunghezza reni >16.7 cm	8	6
Anuria/danno renale ostruttivo	9	24
Ipersodiemia	NO, n	24
Valori transaminasi anomali		
Normale risposta allo stimolo della sete	9	24

La nostra esperienza:

Eleggibilità dei pazienti

Eleggibilità	FASE 1	FASE 2
	Terapia di salvataggio (n=9)	Terapia di elezione (N=24)
Malattia rapidamente progressiva definita come		
Perdita di GFR >5ml/min in 12 mesi n %	9 (100)	12 (50)
Perdita di GFR >2,5 ml/min in 5 anni n %	0	10 (42)
Aumento di TKV >5% all anno n %	4 (44)	2 (8)

La nostra esperienza:

caratteristiche basali dei pazienti

Parametri	FASE 1 Terapia di salvataggio (n=9)	FASE 2 Terapia di elezione (N=24)
Donne , n (%)	3 (33)	11 (45)
Età, media ± DS	39.2 ± 6.3	37.8 ± 16.5
Anni dalla diagnosi, media ± SD	19.2 ± 2.0	17.4 ± 1.6
eGFR _{CKD-EPI} (mL/min/1.73 m ²), media± SD	45,5 ± 0,6	65,5 ± 11
Diametro renale massimo cm	21.9± 5,7	20.6± 6,6
Sodiemia	140.3 ± 1.9	141 ± 0,5
Alt	18 ± 4.7	15 ± 3
Ast	16 ± 4.8	16 ± 4.5

**What to do once a
decision has been made
to initiate the therapy?**



How to start tolvaptan – patient toolkit

- Regular water intake is absolutely essential:
always carry along a bottle of water
do not wait too long until getting thirsty
stop tolvaptan in cases of dehydration,
diarrhoea, vomiting, lacking access to water ...
- To be discussed with the patient:
do not compensate the water deficit with
calorie-rich drinks (milk, soft drinks)



How to start tolvaptan – patient toolkit

- Take the first pill at ~7 am in the morning and the second pill 8 hours later
- Start therapy on a weekend rather than a working day
- Take advantage of helpful tools (apps, patient groups...)
- Stop tolvaptan and seek medical advice in case of symptoms pointing towards liver damage (e.g. fatigue, brown urine, jaundice, complaints of the upper abdomen)



Indicazioni modificate da

Position Statement sull'impiego del Tolvaptan nei pazienti con Rene Policistico Autosomico Dominante (ADPKD)

Roman-Ulrich Müller, UP TO SPEED with Rapid Disease Progression in ADPKD (EDTA 2018) meeting organized and funded by Otsuka

How to start tolvaptan – patient toolkit

- Avoid salt
- Avoid grapefruit juice
- Stop 4 weeks before trying to get pregnant
- Do not take during pregnancy or breastfeeding



Indicazioni modificate da

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How to start tolvaptan – nephrologist

- LFT check-up monthly before handing out new prescription for the first 18 months, then every 3 months
- Also check serum creatinine, uric acid and electrolytes
- Check Uosm (adherence)
- Stop therapy when reaching ESRD

Do not forget about supportive strategies,
especially blood pressure control



How should uptitration be done?

Which answer do you consider most appropriate?

1. All patients have to be uptitrated to 90/30 mg
2. Seeing the data 60/30 mg is sufficient
3. Uptitration should be the target, however, lower doses may be sufficient in case of problems

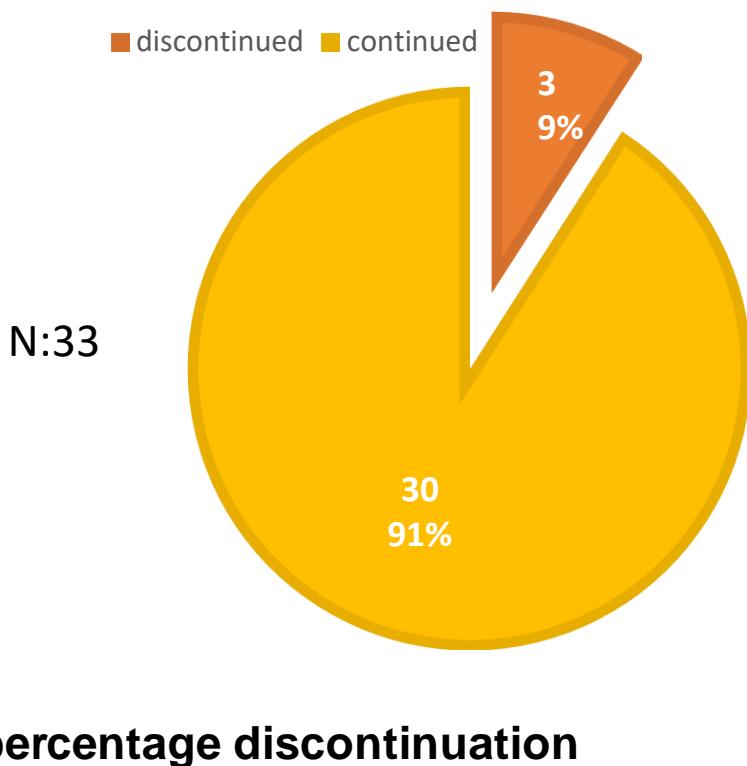


**How does this actually
work in the real-life
setting?**



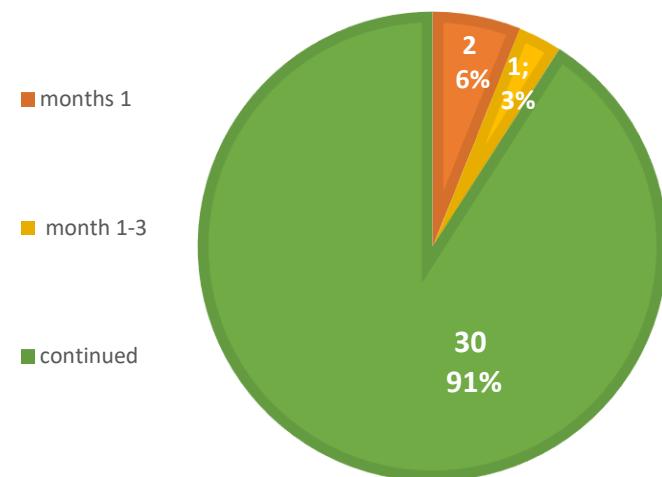
Arguments against tolvaptan

“adherence to treatment is difficult in the long run...”



Adherence in real life

Time of discontinuation

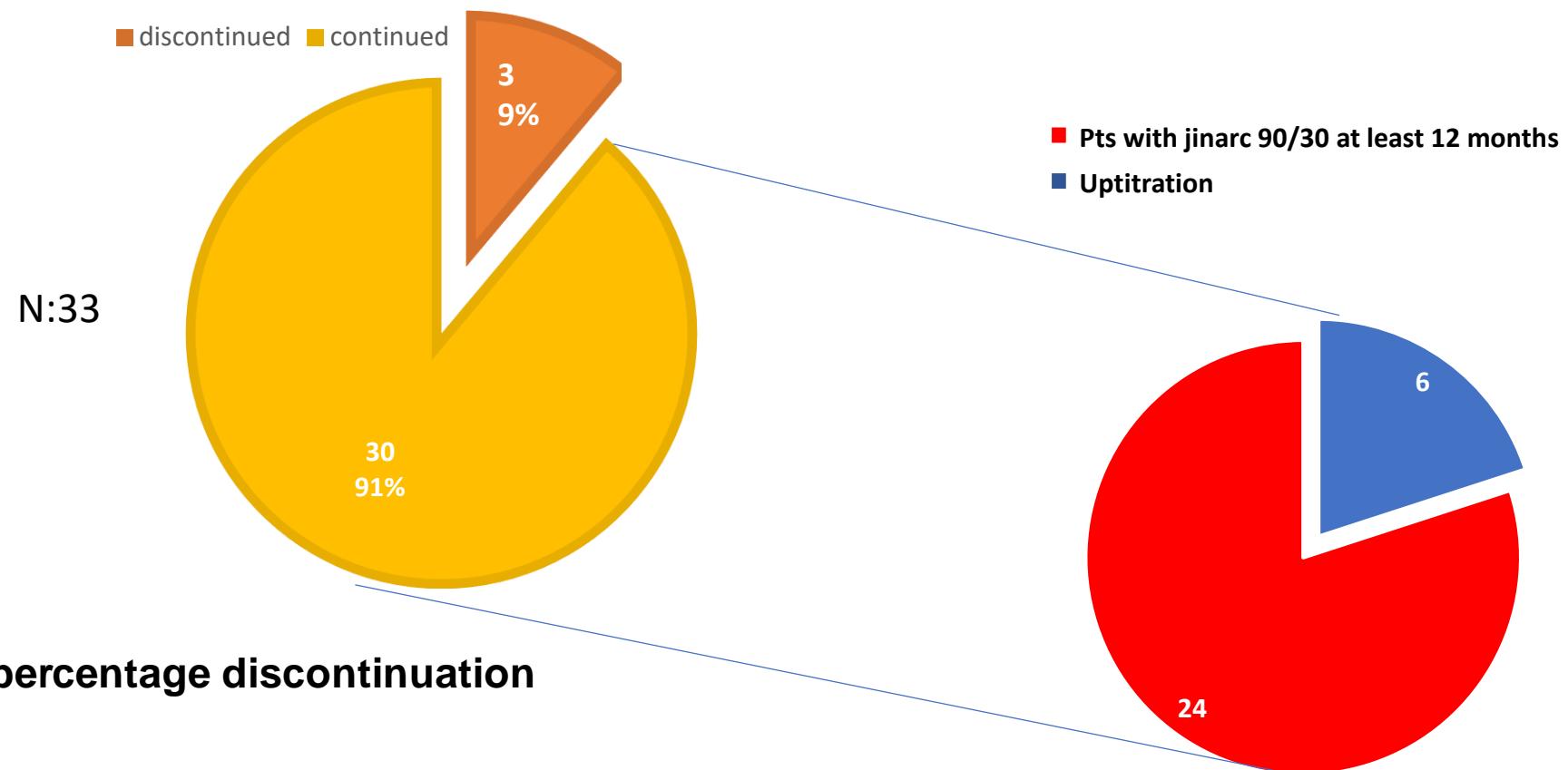


Arguments against tolvaptan

“ Uptitration

..... surely it is difficult.... ”

Adherence in real life

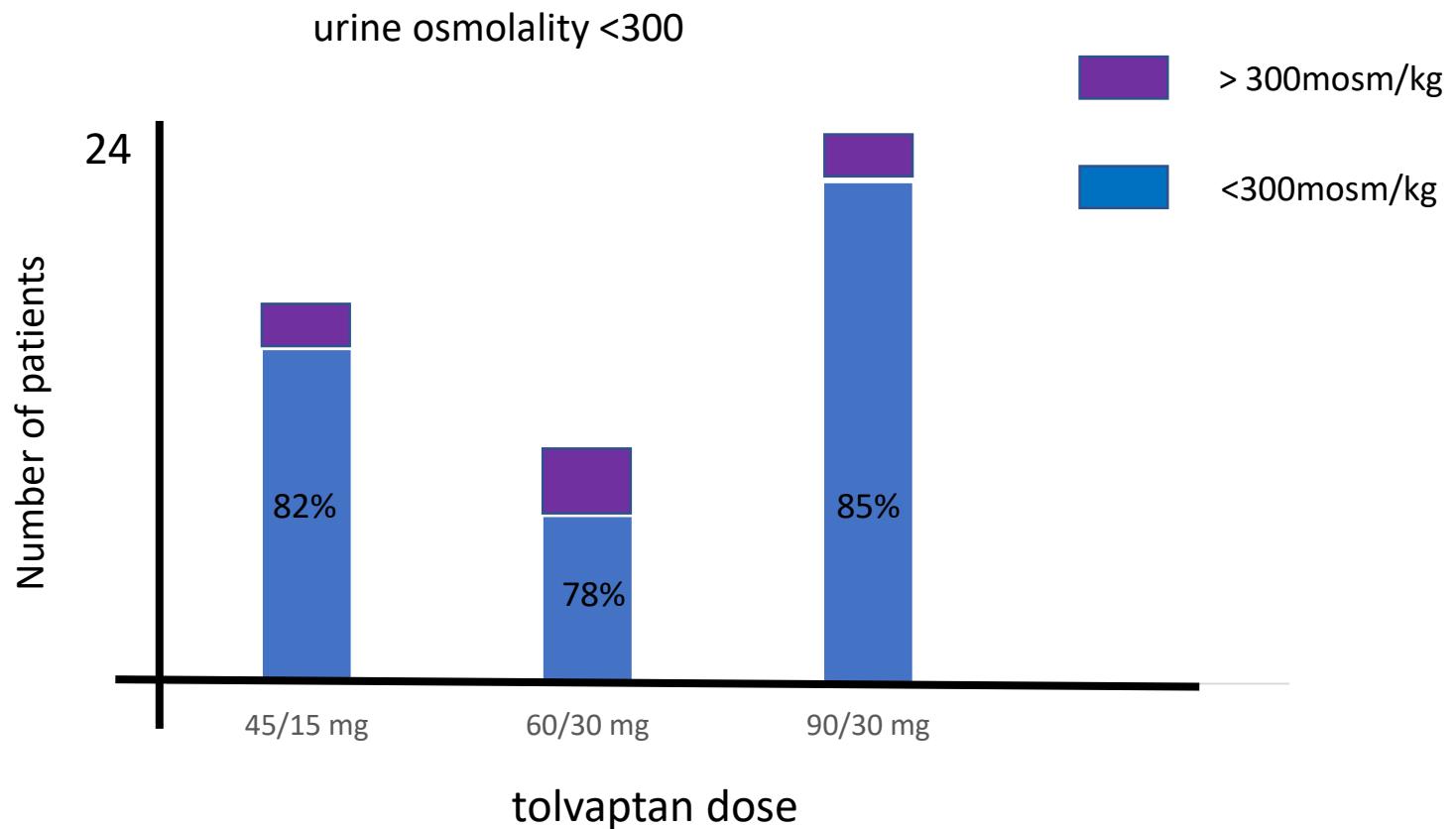


La nostra esperienza:

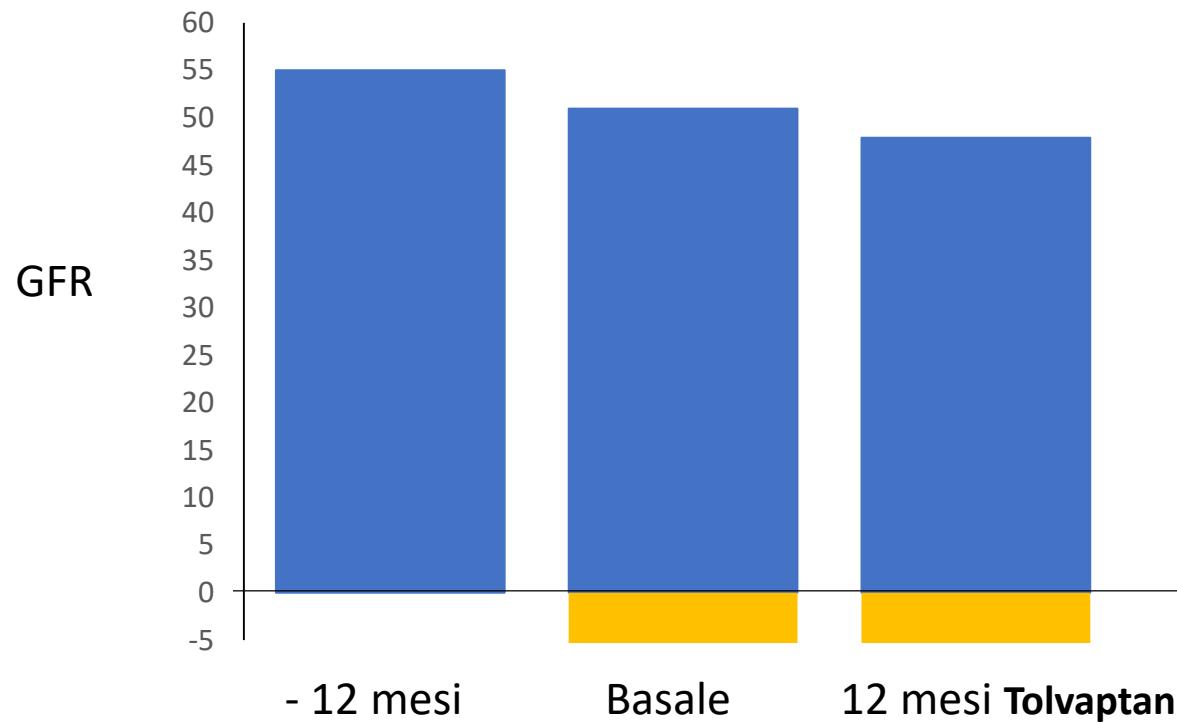
Caratteristiche basali dei 24 pazienti arruolati con almeno 12 mesi **al dosaggio 90/30 mg**

Parametri	PZ con almeno 12 mesi di jinarc 90/30 (N=24)
Donne , n (%)	11 (46)
Età, media ± DS	35.8 ± 7,8
Anni dalla diagnosi, media ± SD	19.4 ± 2.3
eGFR _{CKD-EPI} (mL/min/1.73 m ²), media± SD	55 ± 15
Diametro renale massimo cm	21.8 ± 3,8
Sodiemia	140.9± 1,8
Alt	15 ± 4.8
Ast	16 ± 4
Mesi di terapia renge	12-18

Real-life urine osmolality



Change in Kidney Function



eGFR mean±SD, mL/min/1.73 m ²	55±15	51±10	48±14
Mean of Annualized Change in eGFR mL/min		- 4	-3

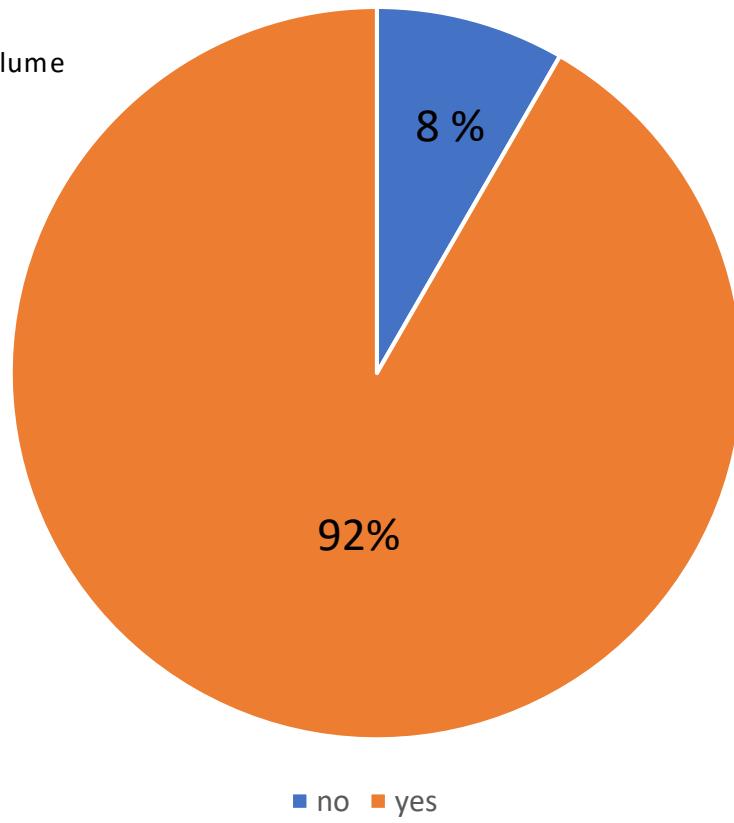
Arguments against tolvaptan...

" tolvaptan makes urinating very much
...Patients have to drink at least 10 litres of water per day...
This is not possible..."

Real-life urine volume...

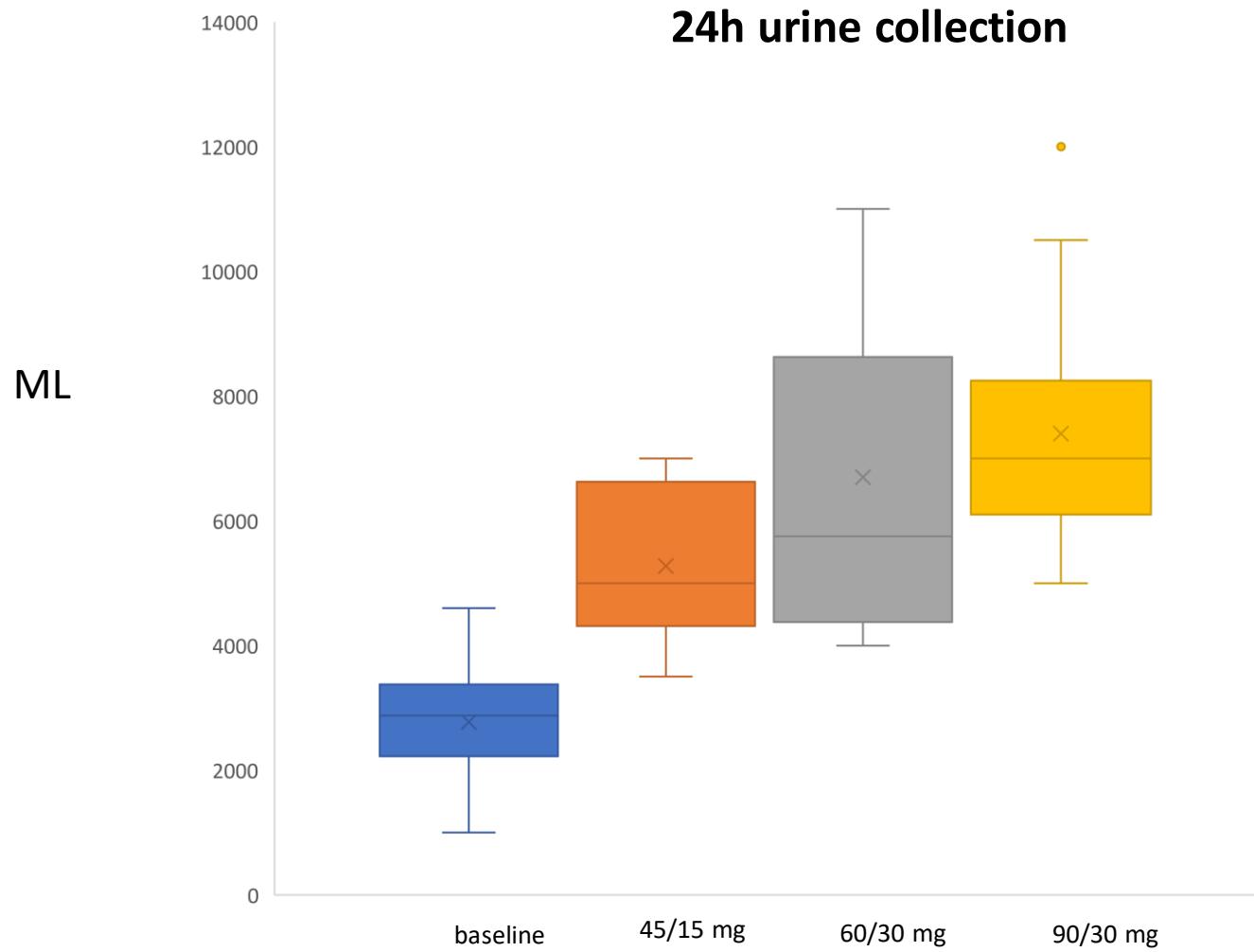


complete feedback on urine volume



n = 24

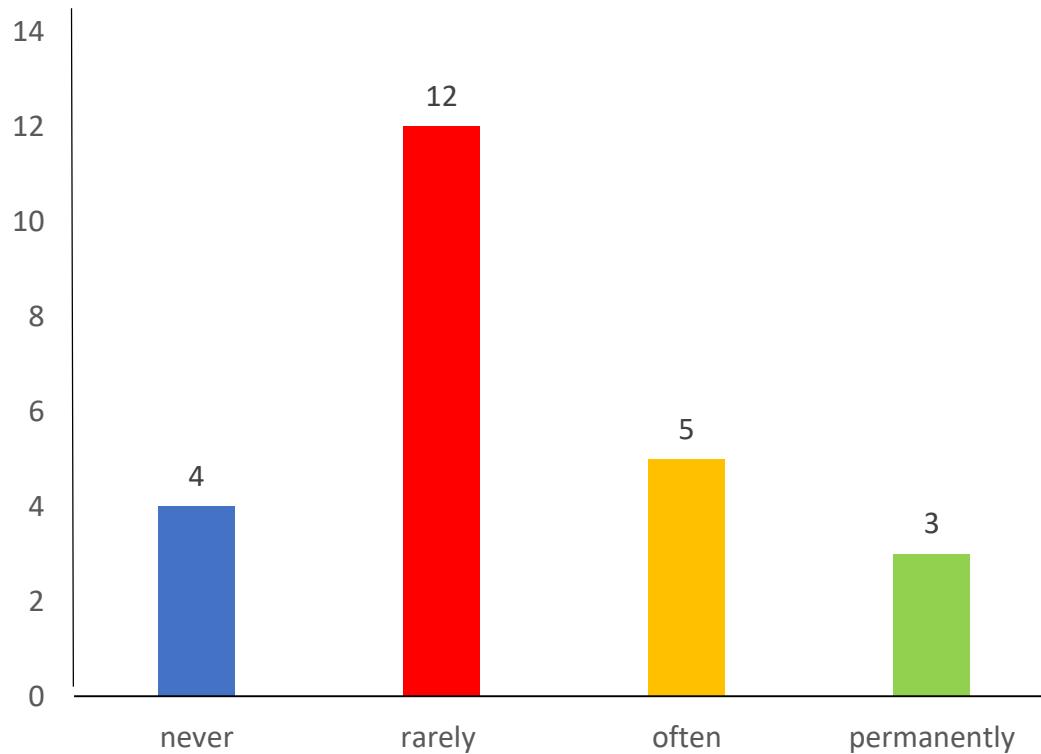
Real-life urine volume...



$n = 24$

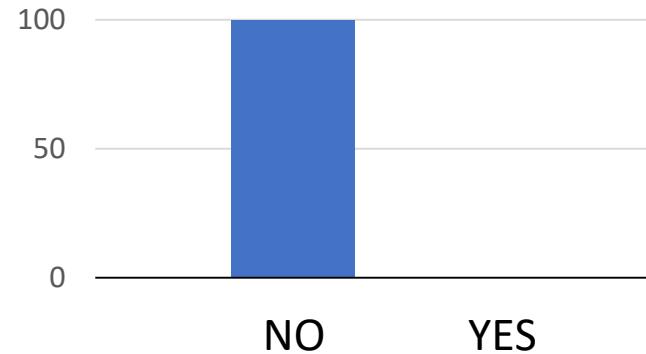
Feasibility of the therapy...

Do you consider the increased urine volume a burden?

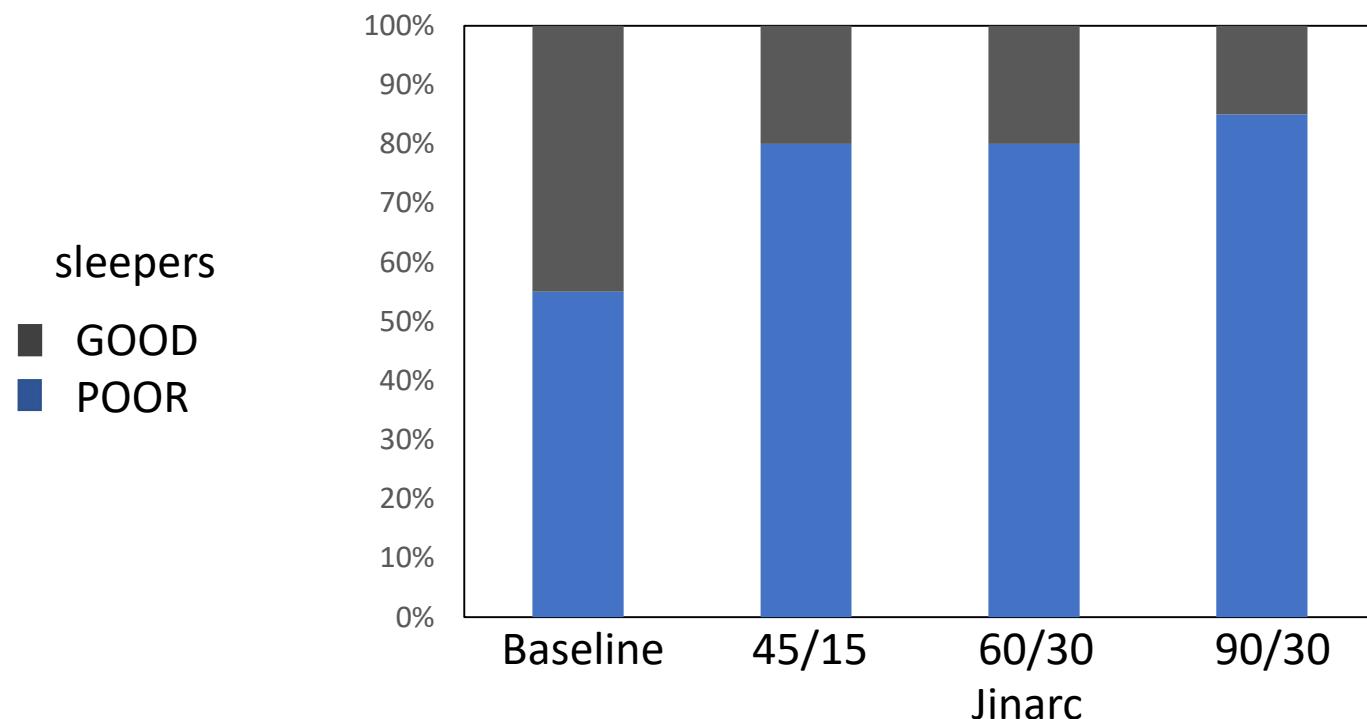


Impact of urinary volume on sleep quality

Do you sleep all the time in bed?



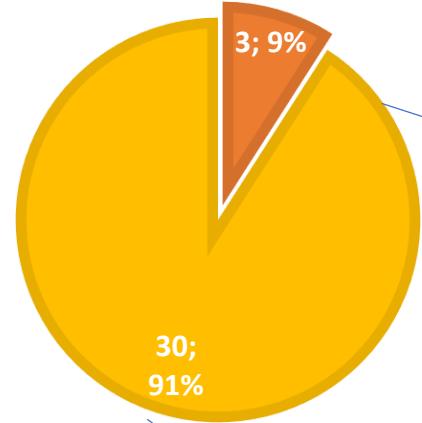
Pittsburgh Sleep Quality Index



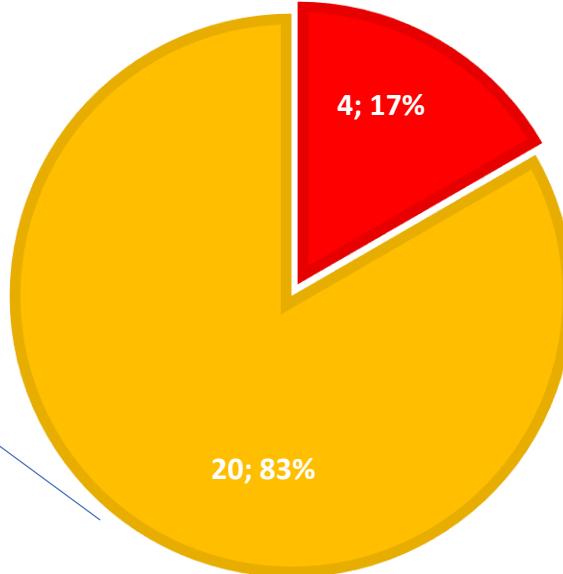
Adherence in Real life

percentage discontinuation

■ discontinued ■ continued

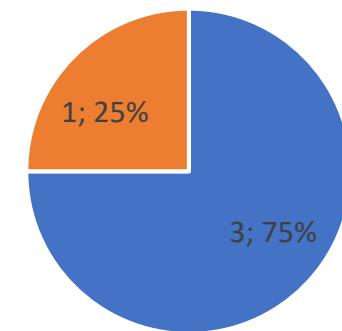


n = 24

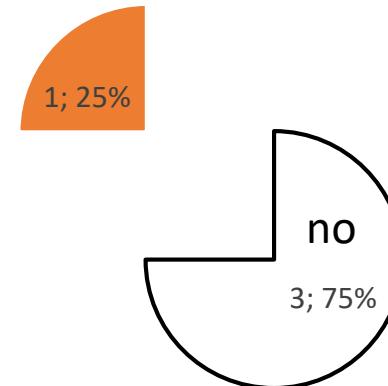


temporary drug interruption

reasons for temporary drug interruption



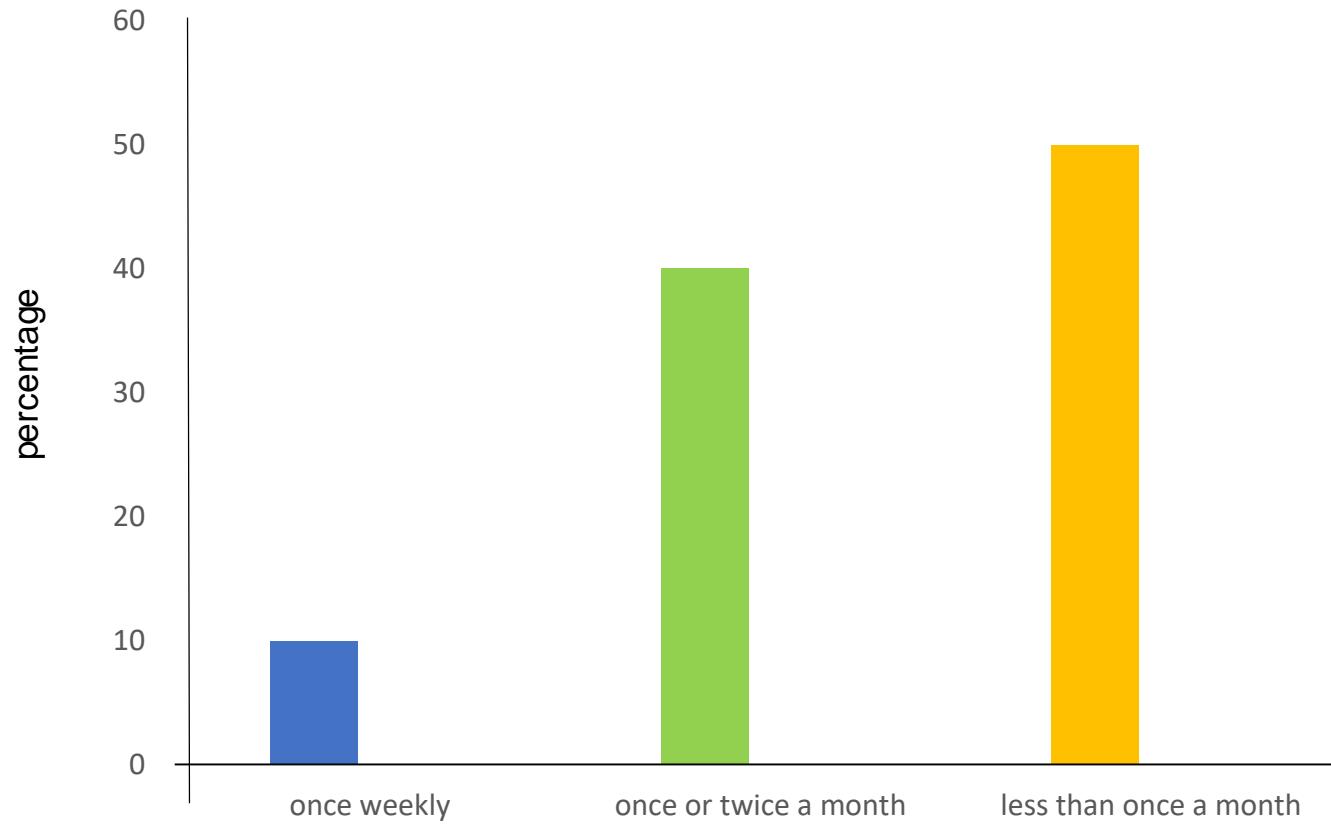
■ liver value ■ iperNa



Continued after temporary drug interruption

Feasibility of the therapy...

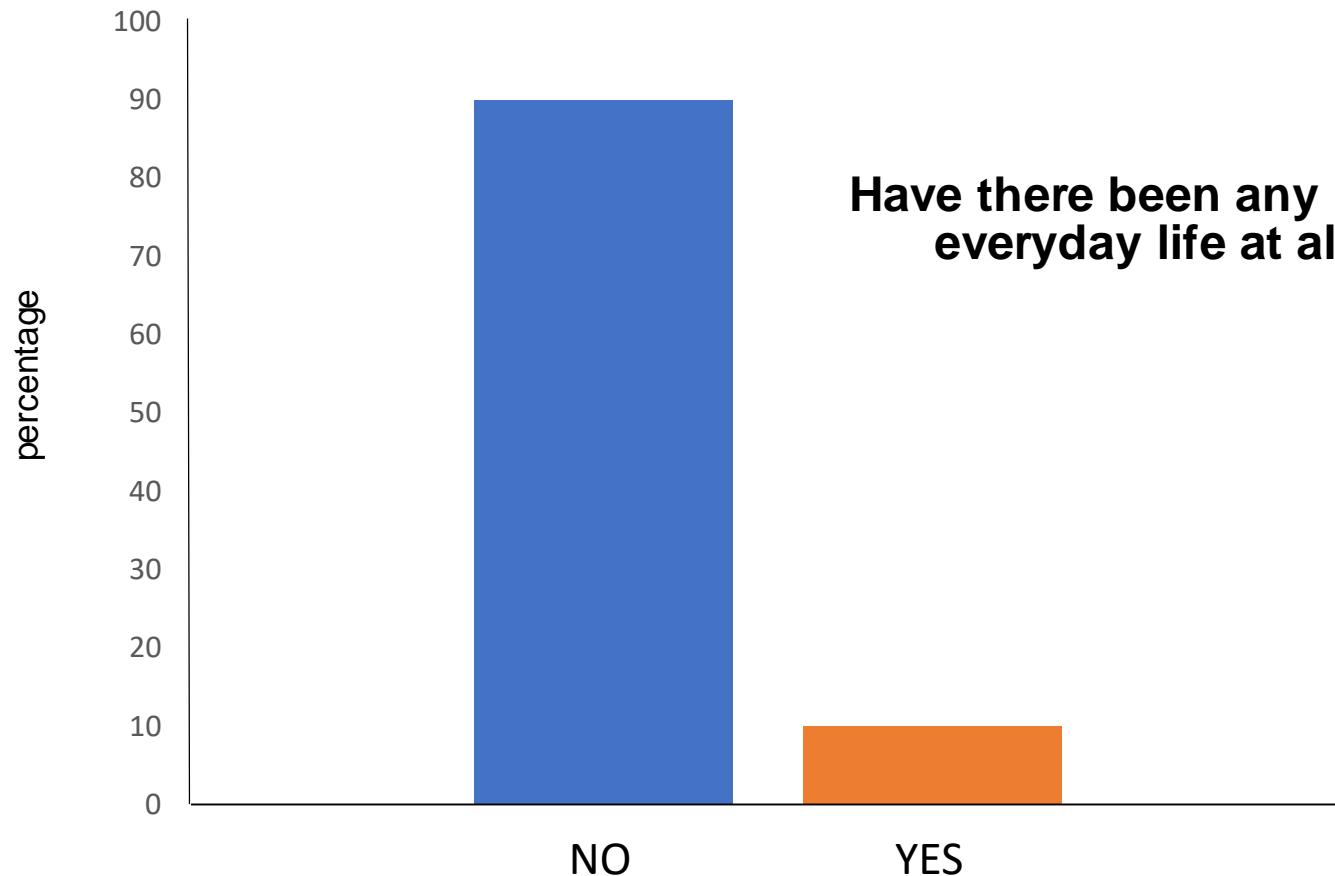
**How often did you interrupt
the treatment?**



Arguments against tolvaptan...

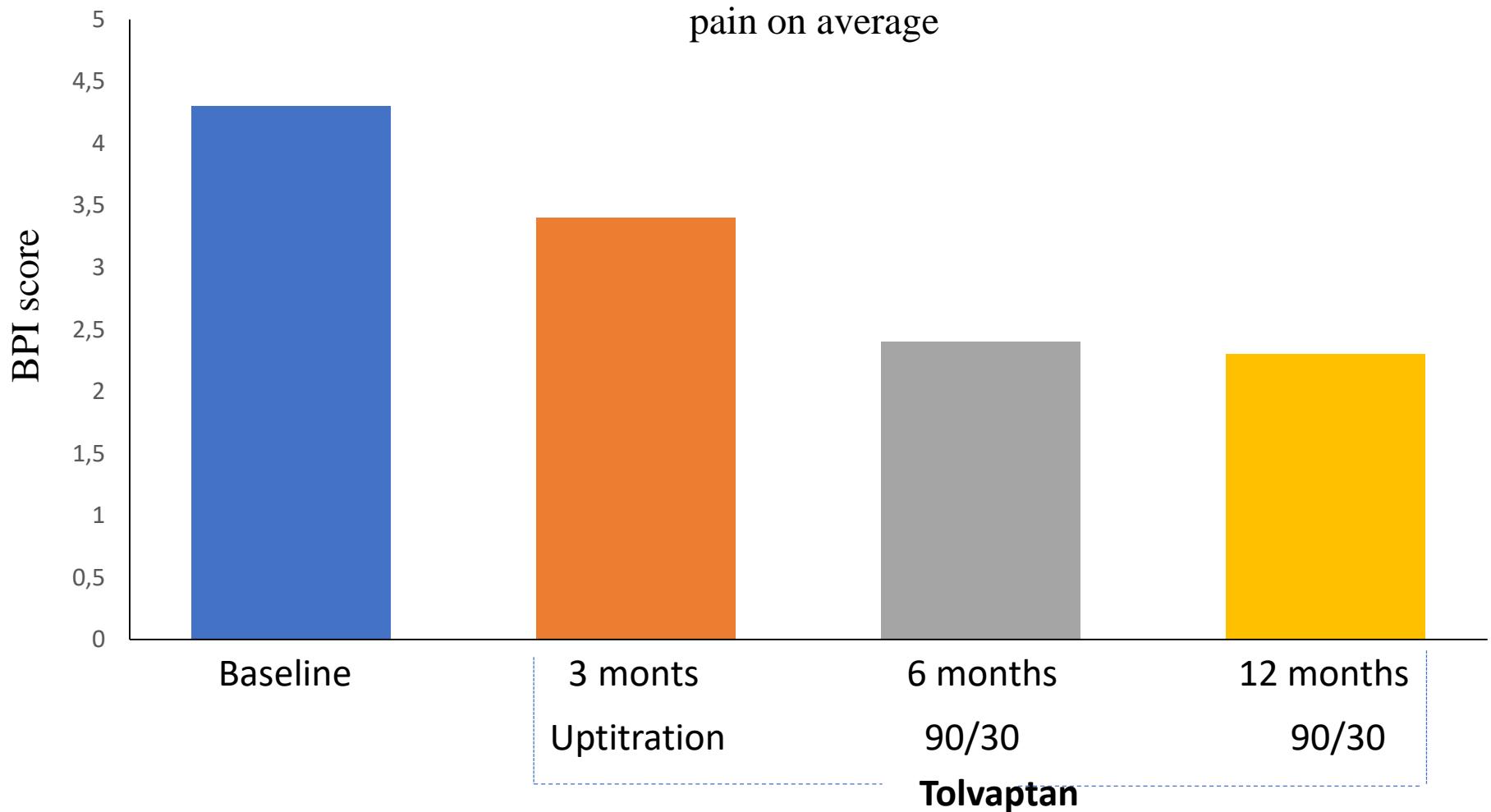
*“Feasibility of therapy ...
surely the patients will have problems”*

Feasibility of the therapy...



Have there been any problems in everyday life at all?

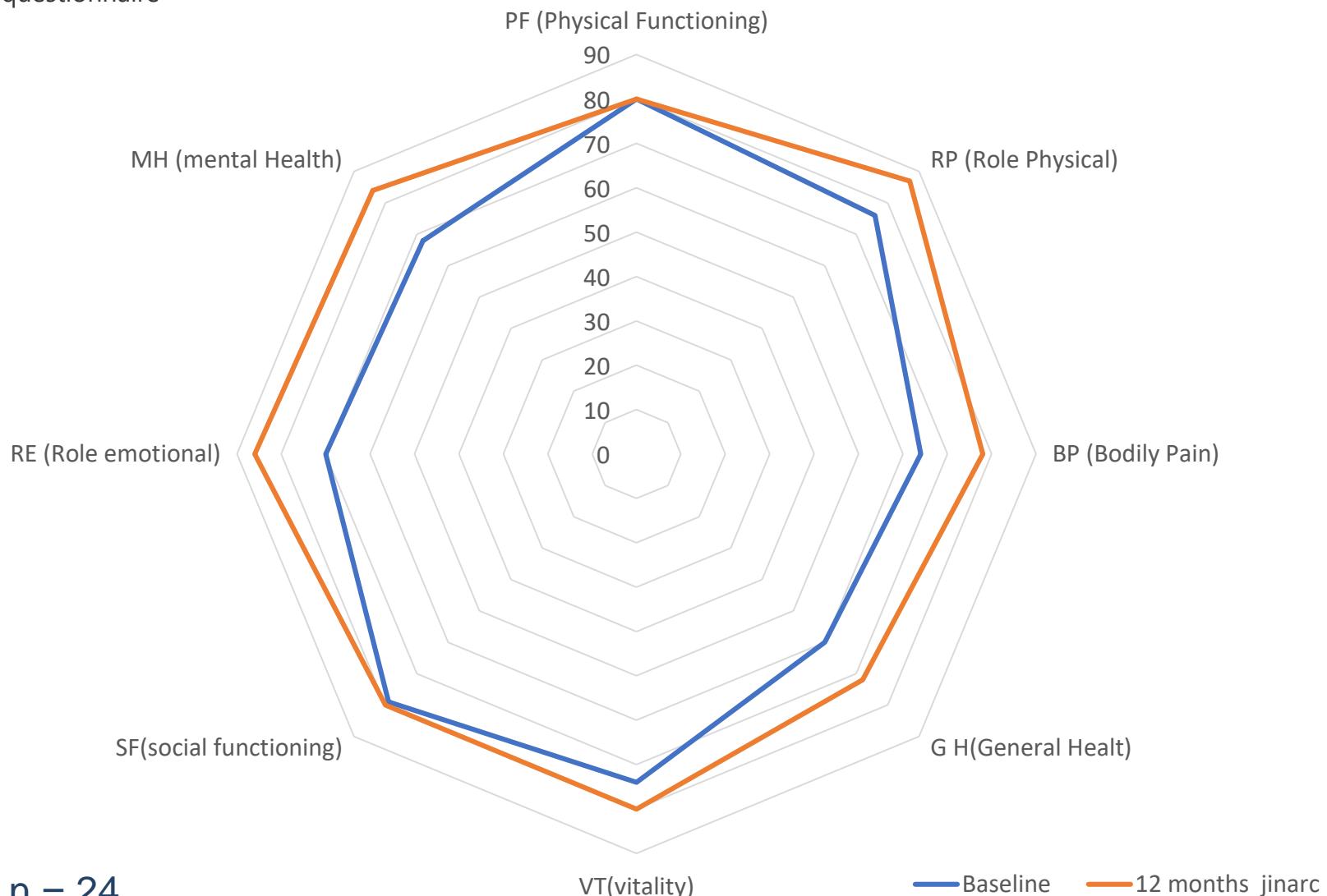
Changes in Brief Pain Inventory (BPI) score for pain



Values are means \pm SEM

Changes in Quality of Life

SF36 questionnaire



First year experience **TOLVAPTAN- ADPKD**

- Real-life adherence is it is high and very similar to the trials
- Uptitration is not difficult
- Hepatotoxicity is an infrequent and manageable problem
- Urine volume in patients treated is as high as expected (4-8 litres per day in the majority of patients)
- Most patients report few problems regarding the therapy
the increase in urinary volume impacts the quality of sleep
- treatment with Tolvaptan appears to reduce abdominal pain symptom

A longer observation time is necessary for a correct evaluation of the real effects on TKV and GFR

