La terapia dell'ADPKD

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Ospedale certificato ISO 9001:2008

Polycystic Kidney Disease
GIVE PKD THE BUMP
Lottiamo contro il Rene Policistico

30 settembre – 1 ottobre 2016
PKD International Day
partecipa anche tu alla battaglia contro il Rene Policistico

- Scopri di più sul sito www.BumpPKD.com
- Registra anche tu il tuo video e postalo sul tuo profilo social usando nel messaggio di testo **#BumpPKD** e invitando 3 amici a fare altrettanto

- Supporta la ricerca scientifica con una donazione

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Polycystic Kidney Disease
GIVE PKD THE BUMP
Lottiamo contro il Rene Policistico

ADPKD - Dati di scenario

Malattia policistica del rene autosomica dominante (ADPKD), Ereditaria nel 90% dei casi

12,5 milioni
di persone nel mondo

Geni
ADPK1
ADPK2

Formazione di cisti renali bilaterali che crescono in modo lento, graduale e costante – con conseguente progressivo incremento di volume dei reni, associato a:

- Ipertensione arteriosa
- Tensione e dolore addominale
- Episodi di emorragia delle cisti
- Macro-ematuria
- Nefrolitiasi ed infezioni delle cisti

Continuo incremento del numero e del volume delle cisti

Progressiva perdita di funzione renale per

- Compressione del parenchima renale
- Sclerosi vascolare
- Infiammazione/fibrosi interstiziale
- Apoptosi delle cellule tubulari epiteliali

La progressione della malattia determina nel tempo la comparsa di insufficienza renale

I **costi** di gestione dei pazienti **aumentano** sensibilmente al **decrescere della funzionalità renale**, con ricadute economiche ingenti legate al peggioramento irreversibile della malattia renale cronica.

30-40 anni
COMPARSA DEI SINTOMI

50% ESDR
ENTRO 60 ANNI

- La **gestione clinica** dei pazienti con ADPKD (diagnosi, prevenzione e cura) **varia a seconda delle aree geografiche**
- **Non esistono linee guida condivise per la pratica clinica**
- **Non vi sono trattamenti "eziologici" che prolunghino la sopravvivenza renale in corso di ADPKD**
- È convinzione condivisa che **qualsiasi terapia debba iniziare il prima possibile,** quando il parenchima è ancora relativamente preservato, **prima dell'inizio del declino del GFR**

Chapman AB, et al. Kidney International 2015; 88:17–27. Ying-Cai T. BBA - Molecular Basis of Disease 2011;1812(10):1202–12.

Scenario terapeutico

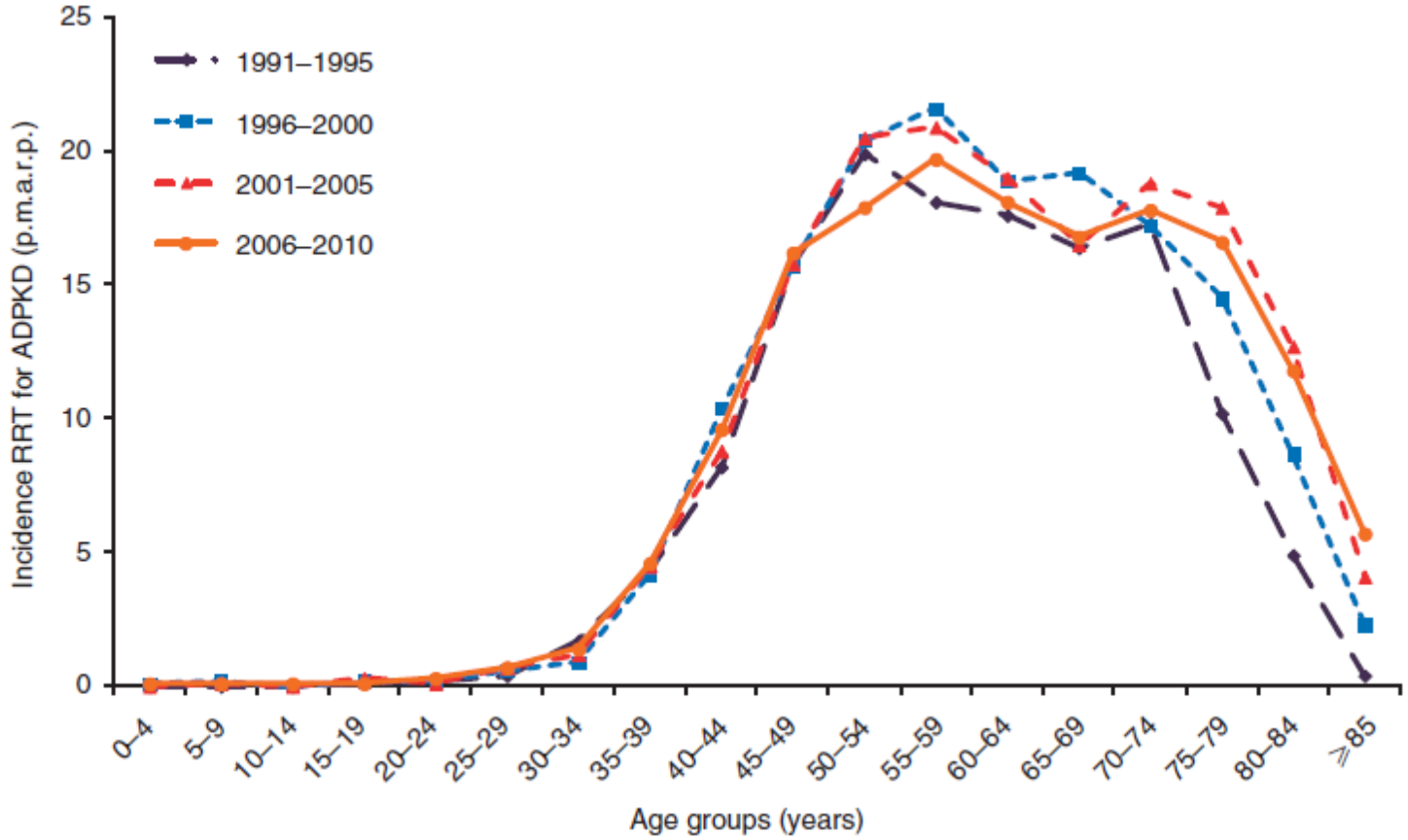
- Allo stato attuale **non ci sono linee guida** per la pratica clinica che siano universalmente accettate e **non esistono trattamenti in grado di prolungare la sopravvivenza renale in corso di ADPKD**; tuttavia è opinione condivisa che un trattamento dovrebbe iniziare nelle fasi precoci della malattia, quando il parenchima renale è ancora parzialmente preservato

- **Qualità e durata della vita dei pazienti con ADPKD sono migliorate** grazie a strategie che comprendono **cambiamento dello stile di vita**, **trattamento dell'ipertensione, delle complicanze renali ed extra-renali e connesse alla malattia renale cronica**

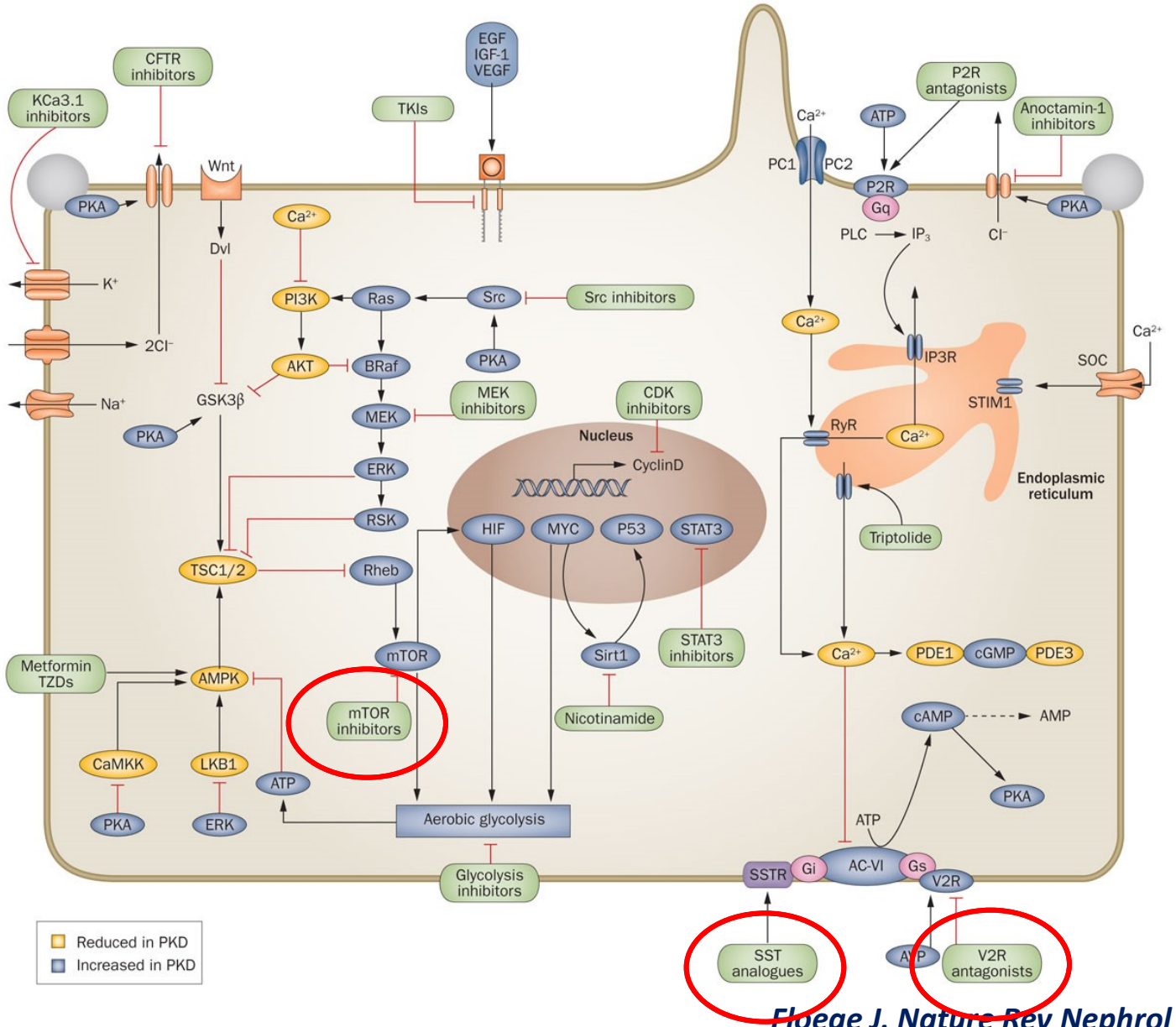
- Al momento non vi sono trattamenti "eziologici" che prolunghino la sopravvivenza renale in corso di ADPKD e sono attualmente oggetto di studio alcune classi farmacologiche per valutarne il potenziale impiego nell'ADPKD

Chapman AB, et al. Kidney International 2015; 88:17–27

Analysis of data from the ERA-EDTA Registry indicates that conventional treatments for chronic kidney disease do not reduce the need for renal replacement therapy in autosomal dominant polycystic kidney disease



Pathways aberranti della ADPKD e farmaci potenzialmente interferenti



Floege J, Nature Rev Nephrol 2015

Lancet, 2013

Effect of longacting somatostatin on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial

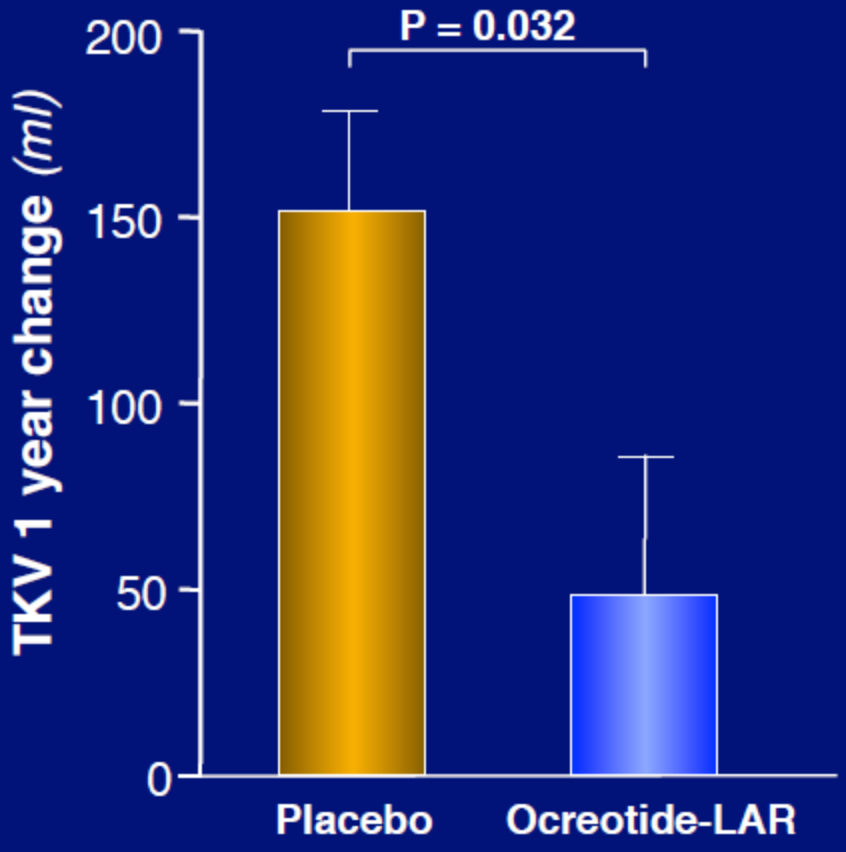
Anna Caroli, Norberto Perico*, Annalisa Perna*, Luca Antiga, Paolo Brambilla, Antonio Pisani, Bianca Visciano, Massimo Imbriaco, Piergiorgio Messa, Roberta Cerutti, Mauro Dugo, Luca Cancian, Erasmo Buongiorno, Antonio De Pascalis, Flavio Gaspari, Fabiola Carrara, Nadia Rubis, Silvia Prandini, Andrea Remuzzi, Giuseppe Remuzzi*, Piero Ruggenenti*, for the ALADIN study group†*

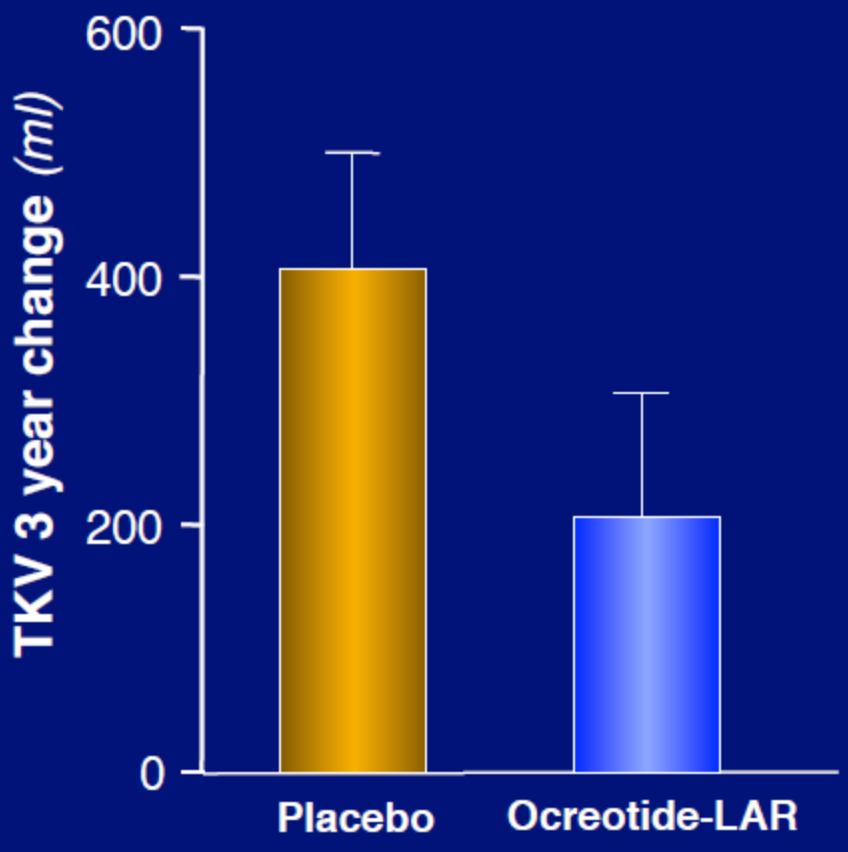
Effect of **A** Long **A**ctin somatostatin on **D**isease progression **I**n **N**ephropathy due to ADPKD: The **ALADIN** Study

Selection criteria	ADPKD Estimated GFR > 40 ml/min Age > 18 yrs
Design	Academic, multicenter, prospective, randomized, parallel-group, placebo controlled, single-blind
Population and setting	79 patients referred to 5 Nephrology Units in Italy
Treatment	**Ocreotide LAR** (40 mg/28 days) **Placebo** (0.9 % NaCl/28 days)
Follow-up	3 years
Main outcome	Total kidney volume (NMR) Cystic and non-cystic volume (NMR) GFR (Iohexol plasma clearance) Safety
Registration	ClinicalTrial.gov: NCT 00309283

Caroli et al, ***Lancet***, 2013

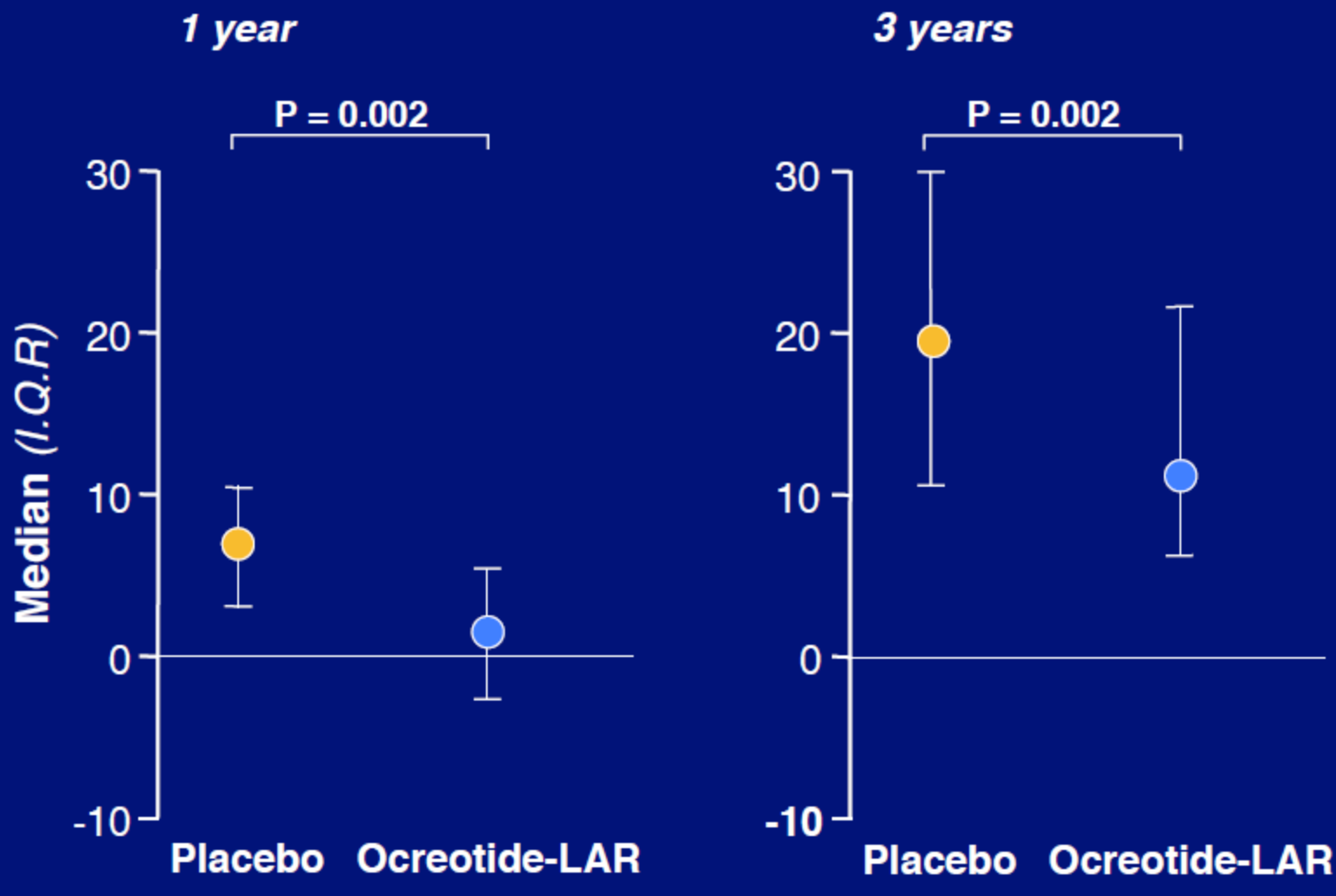
ABSOLUTE CHANGE IN TOTAL KIDNEY VOLUME DURING PLACEBO OR OCTREOTIDE-LAR TREATMENT





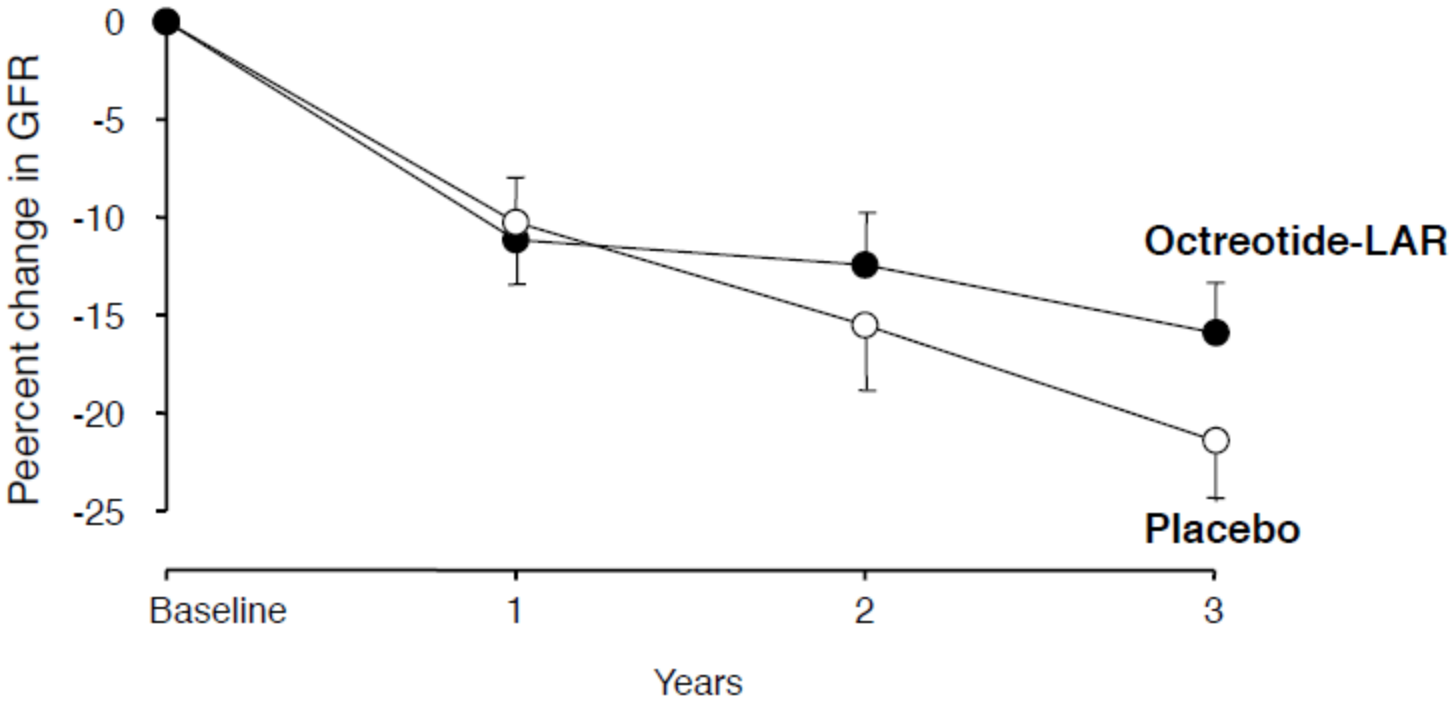
Caroli et al, ***Lancet***, 2013

PERCENT CHANGES IN TKV VS BASELINE



Caroli et al, ***Lancet***, 2013

GFR CHANGES VS. BASELINE



Cxaroli A et al, ***Lancet*** 2013

Treatment-related adverse events

- Asymptomatic cholelithiasis *(n =10)*

  Five participants fully recovered with ursodeoxycholic acid therapy

- Self-limited diarrhea (n =14)

- Hypoglycemic episodes (n =2)

  Treatment withdrawal in one case

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*Uterine leyomioma observed in five women on Octreotide LAR was probably a casual finding, since leyomioma has never been reported as a possible treatment-related effect, and somatostatin is among pharmacological treatments used for this disorder**

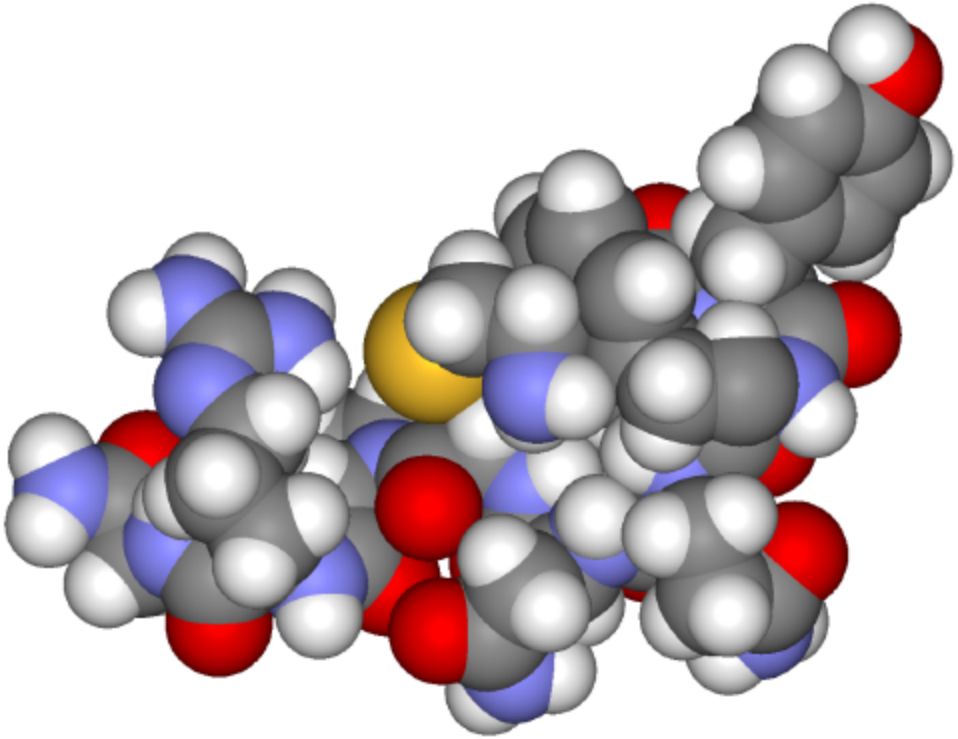
* De Leo et al., *Fertil Steril*, 2001

Caroli et al, *Lancet*, 2013

Three-year Octreotide-LAR therapy effectively limited kidney volume growth in participants with ADPKD, an effect that was largely explained by blunted growth of kidney cysts and associated with almost complete protection against renal function loss over time

Ocreotide reduced liver volumes, an effect that was sustained 2-years after treatment withdrawal

These findings, combined with remarkably good safety profile, are encouraging on the way to identify a new effective and safe treatment to limit the uncontrolled growth of polycystic kidneys and, hopefully, of polycystic livers that so frequently associate with ADPKD

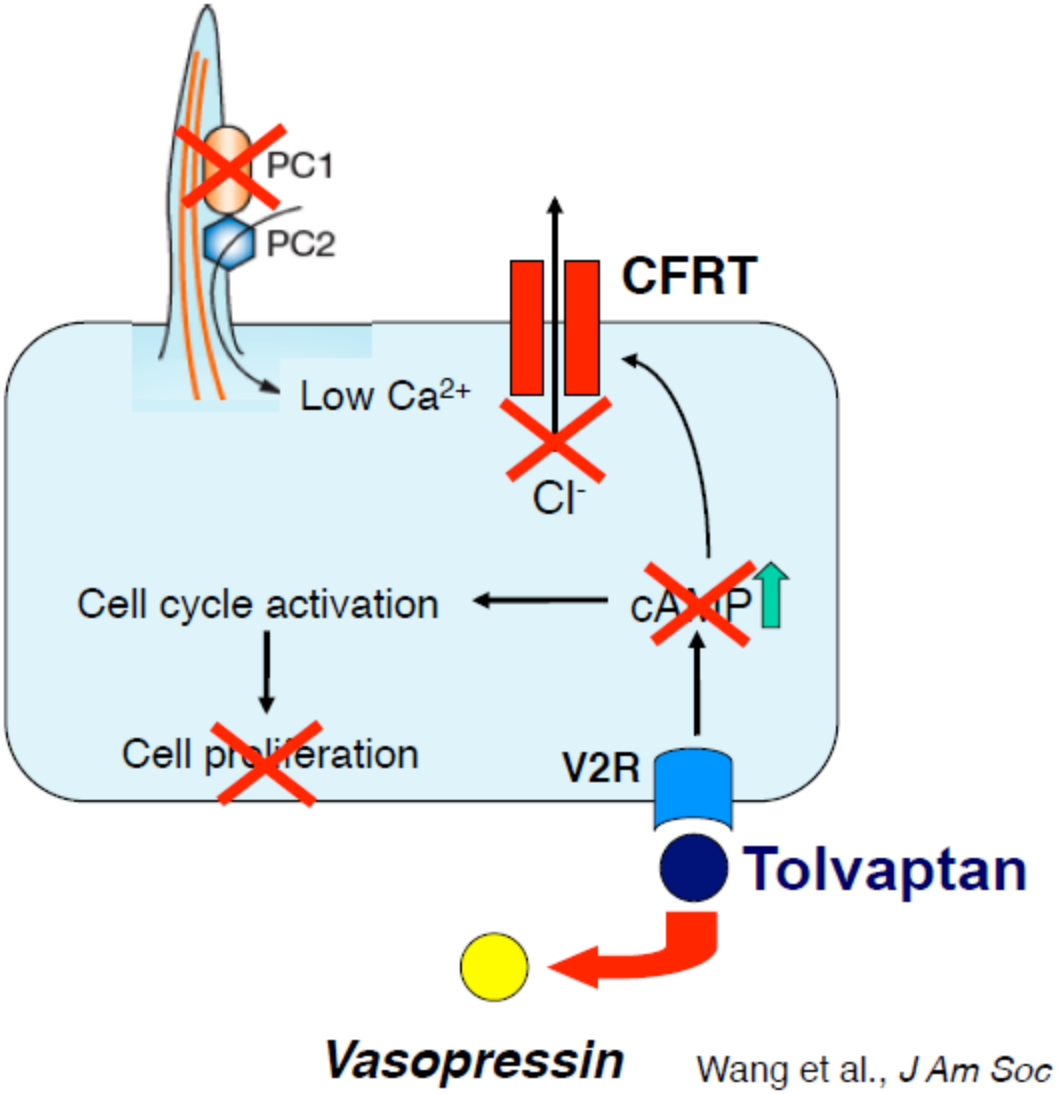


Vasopressin

Plasma vasopressin levels are increased in animal models and in human ADPKD and might represent the body's attempts to compensate for the reduced concentrating capacity of the polycystic kidneys

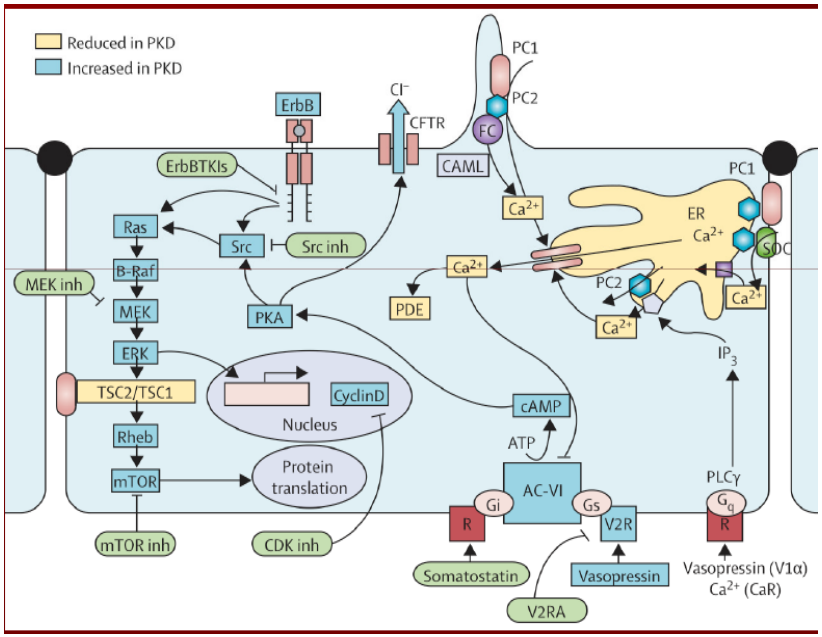
Torres et al., ***Kidney Int***, 2005

VASOPRESSIN PROMOTES CYST GROWTH IN PKD BY INCREASING cAMP



Wang et al., *J Am Soc Nephrol*, 2008

Vasopressina e ADPKD



1. **AVP è ↑ nei pazienti ADPKD ed è inibita dall'assunzione di grandi quantità di liquidi (> 3L/Die)**

2. **Gli antagonisti del Rec. V2 ↓ i livelli di cAMP intracellulare:**

- **Inibiscono cistogenesi e preven-gono ingrandimento e disfunzione renale**
- **Inibiscono proliferazione cellule epiteliali**
- **Inibiscono accumulo di fluidi**

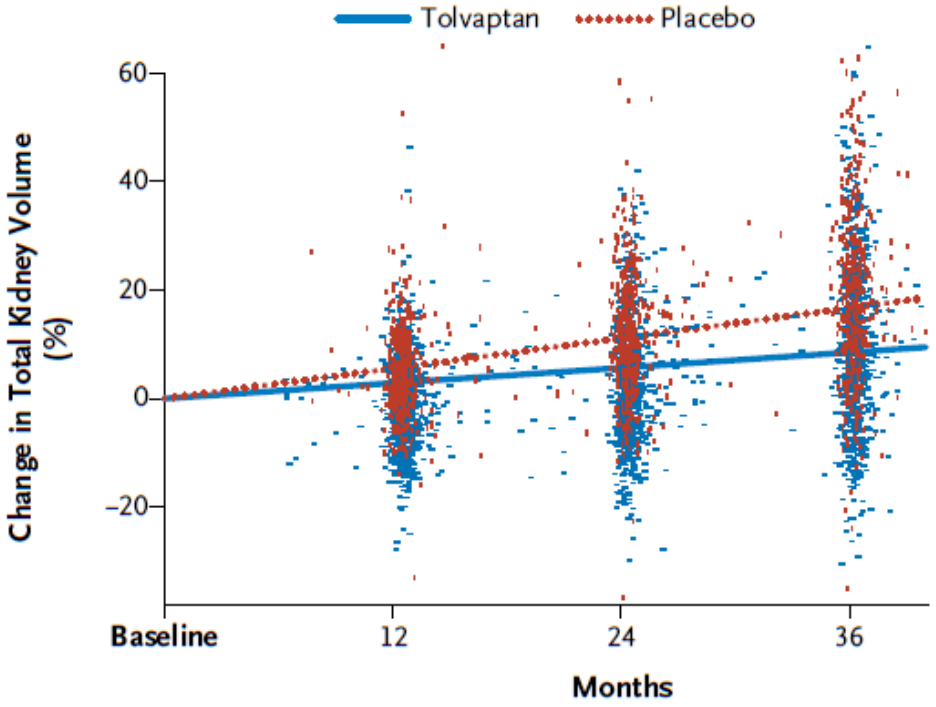
ORIGINAL ARTICLE

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*

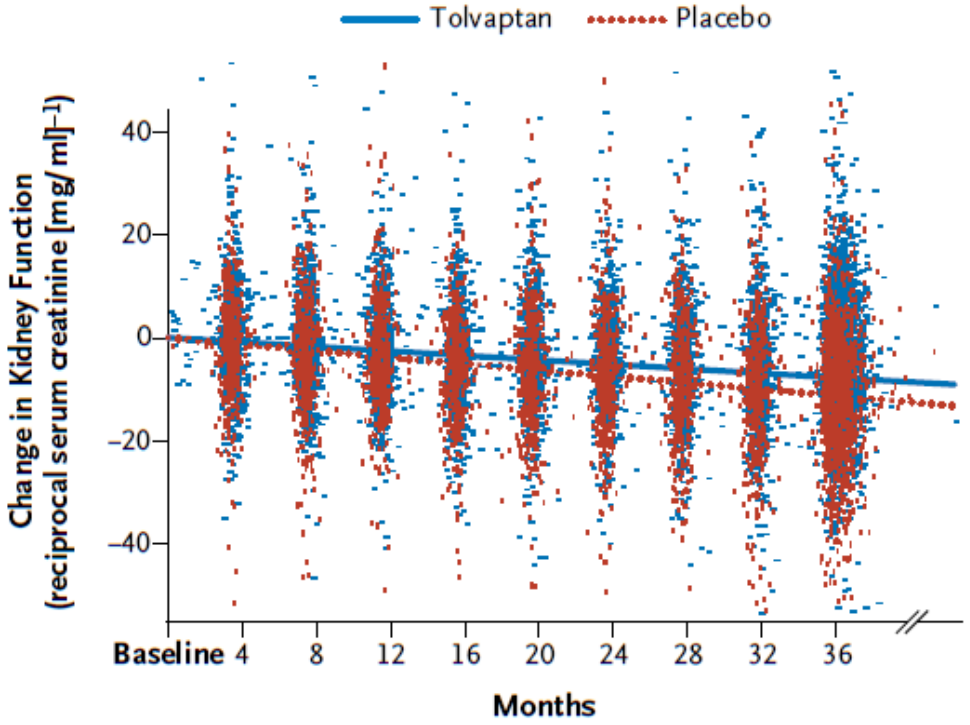
- Phase 3, multicenter, randomized, double-blind, placebo-controlled trial
- 1445 ADPKD pts, 18-50 yrs old, KV>750 ml, eGFR>60 ml/min.
- Randomized 2:1 to receive tolvaptan or placebo
- Tolvaptan given at the highest dose found tolerable, starting from 45 mg+15 mg, up to 90+30 mg.
- F-U: 36 months

The NEW ENGLAND JOURNAL of MEDICINE DECEMBER 20, 2012

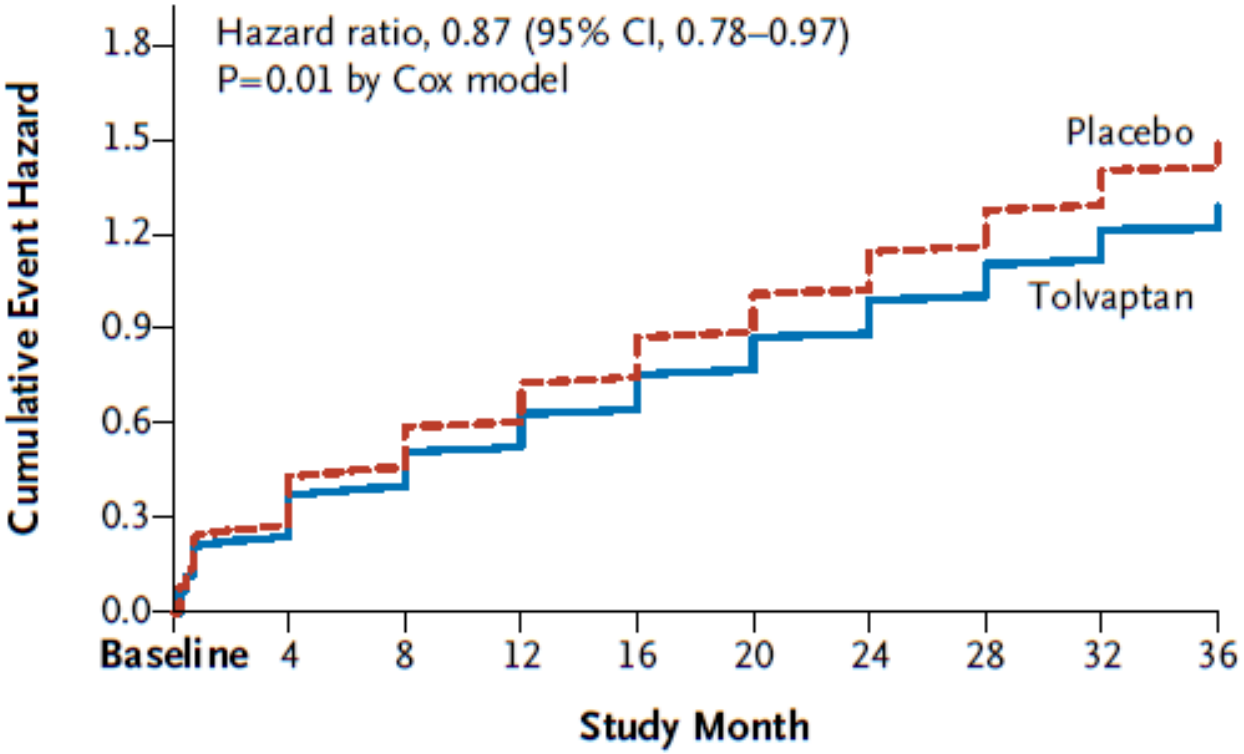


The increase in total kidney volume in the tolvaptan group was 2.8% per year, versus 5.5% per year in the placebo group (P<0.001)

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



Risk of ADPKD-Related Composite Events

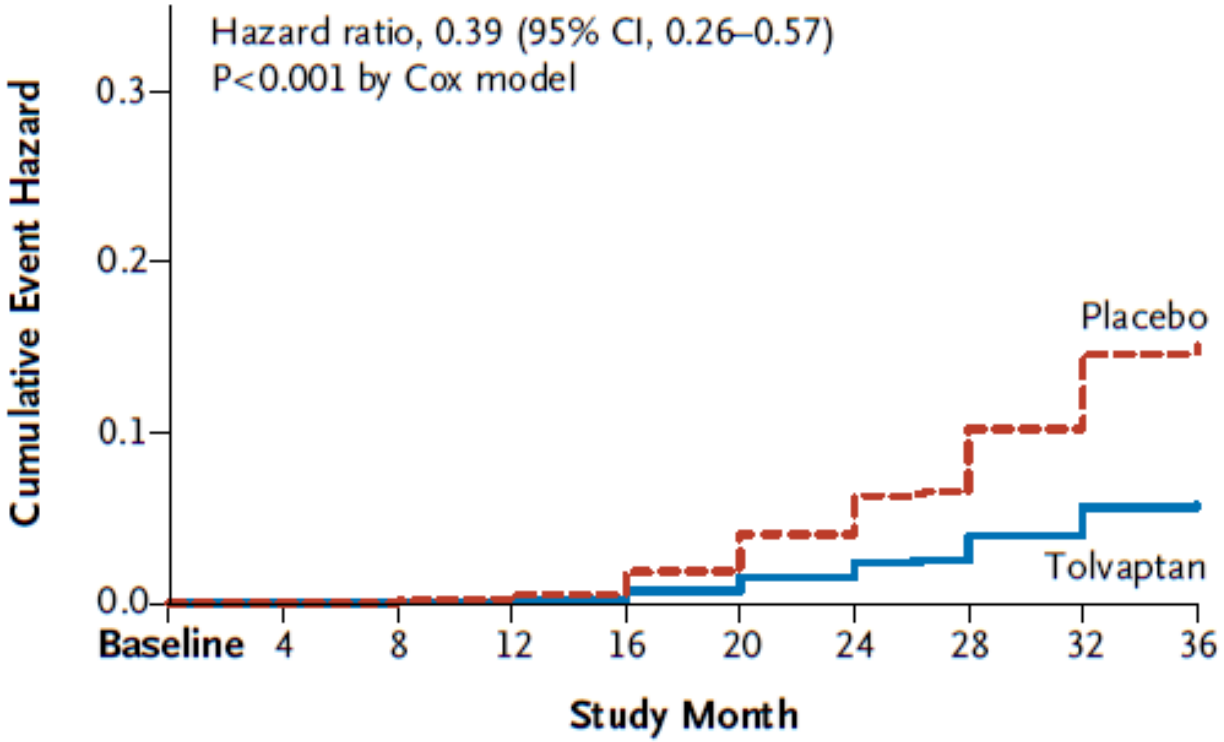


No. at Risk										
Tolvaptan	961	870	835	811	792	776	763	752	744	642
Placebo	483	472	463	454	446	438	428	422	418	359

Sequential secondary end points included a composite of time to clinical progression (defined as worsening kidney function, kidney pain, hypertension, and albuminuria) and rate of kidney-function decline

Torres V, NEJM 2012

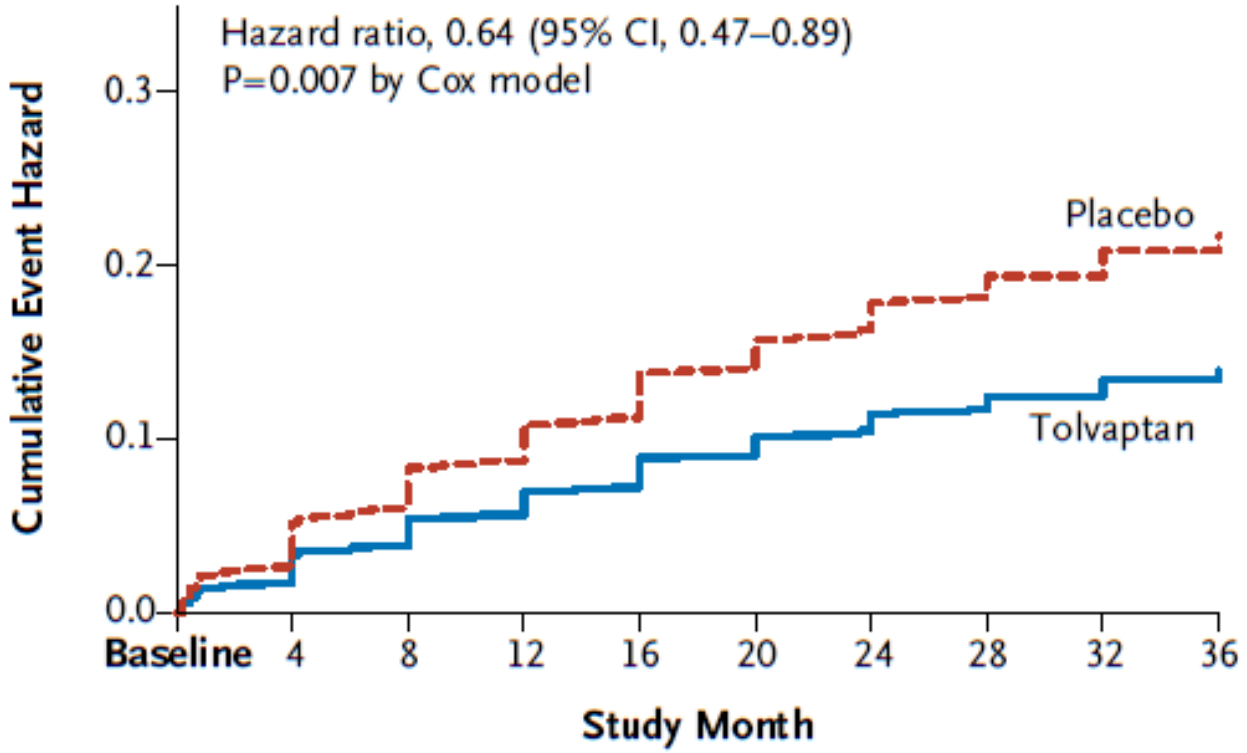
Risk of worsening Kidney Function



No. at Risk										
Tolvaptan	918	868	833	809	791	775	762	751	743	641
Placebo	476	470	461	452	444	436	426	420	416	357

Torres V, NEJM 2012

Risk of Clinically Significant Kidney Pain



No. at Risk										
Tolvaptan	961	870	835	811	792	776	763	752	744	642
Placebo	483	472	463	454	446	438	428	422	418	359

Torres V, NEJM 2012

Most Common Adverse Events and Serious Adverse Events

Table 2. Most Common Adverse Events and Serious Adverse Events.*

Event	Tolvaptan (N=961)	Placebo (N=483)
	no. of patients with event (%)	
Adverse events more common in tolvaptan group		
Thirst	531 (55.3)†	99 (20.5)
Polyuria	368 (38.3)†	83 (17.2)
Nocturia	280 (29.1)†	63 (13.0)
Headache	240 (25.0)	120 (24.8)
Pollakiuria‡	223 (23.2)†	26 (5.4)
Dry mouth	154 (16.0)	59 (12.2)
Diarrhea	128 (13.3)	53 (11.0)
Fatigue	131 (13.6)	47 (9.7)
Dizziness	109 (11.3)	42 (8.7)
Polydipsia	100 (10.4)†	17 (3.5)
Adverse events more common in placebo group		
Hypertension	309 (32.2)	174 (36.0)
Renal pain	259 (27.0)§	169 (35.0)
Nasopharyngitis	210 (21.9)	111 (23.0)
Back pain	132 (13.7)	88 (18.2)
Increased creatinine level	135 (14.0)	71 (14.7)
Hematuria	75 (7.8)†	68 (14.1)
Urinary tract infection	80 (8.3)§	61 (12.6)
Nausea	98 (10.2)	57 (11.8)
Serious adverse events more common in tolvaptan group		
Alanine aminotransferase elevation	9 (0.9)	2 (0.4)
Aspartate aminotransferase elevation	9 (0.9)	2 (0.4)
Chest pain	8 (0.8)	2 (0.4)
Headache	5 (0.5)	0
Serious adverse events more common in placebo group		
Pyelonephritis	5 (0.5)	5 (1.0)
Renal-cyst infection	6 (0.6)	4 (0.8)
Renal-cyst hemorrhage	3 (0.3)	4 (0.8)
Renal pain	1 (0.1)	4 (0.8)
Appendicitis	1 (0.1)	4 (0.8)
Nephrolithiasis	2 (0.2)	3 (0.6)
Urinary tract infection	1 (0.1)	3 (0.6)
Hypertension	1 (0.1)	3 (0.6)

* Adverse events were categorized according to the *Medical Dictionary for Regulatory Activities* (MedDRA).
† P<0.001 by Fisher's exact test, as compared with the placebo group.
‡ Pollakiuria is more commonly called urinary frequency.
§ P<0.05 by Fisher's exact test, as compared with the placebo group.

Torres V, NEJM 2012

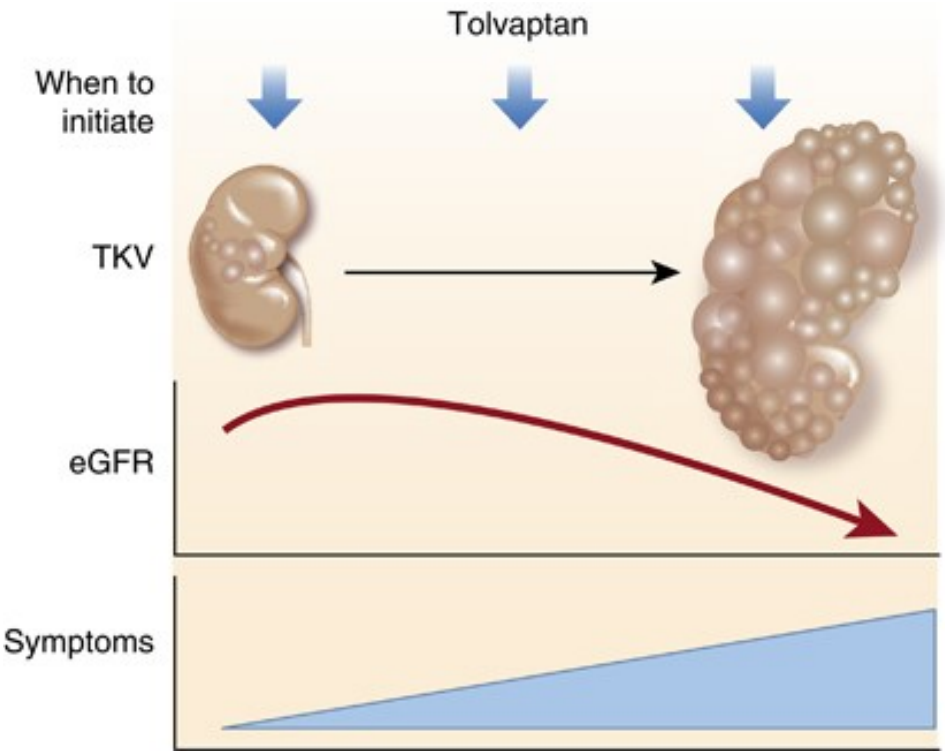
Conclusioni

- La somministrazione di Tolvaptan (60-120 mg) a pazienti di 18-50 anni (media: 40), con eGFR >60 ml/min (media: 81 mL/min) e volume renale totale > 750 mL (media: 1705 mL) ha dimezzato l'incremento di volume totale dei reni rispetto al placebo ed ha rallentato il declino della funzione renale, in un F-U a 3 anni
- La somministrazione di Tolvaptan si è associata ad una quota significativamente più elevata di interruzioni del trattamento, per la comparsa di eventi avversi

The NEW ENGLAND JOURNAL of MEDICINE

Tolvaptan in clinical practice

Horie S, Kidney Int 2015



Al presente, sembra ragionevole iniziare precocemente l'inibizione dei recettori V2, a parenchima relativamente conservato.

Non è chiaro se sia opportuno raccomandarlo a pazienti con GFR normale e senza sintomi.

L'analisi dello Studio TEMPO 3:4 suggerisce che **i maggiori benefici sono attesi in pazienti>35 anni, ipertesi e con TKV> 1500 ml.**

Andrebbero identificati i markers genetici specifici comuni ai pazienti responsivi alla terapia

Secondo una estrapolazione dallo Studio TEMPO 3:4, Tolvaptan sembra **ritardare l'inizio della RRT di 6,5 anni e aumentare l'aspettativa di vita di 2,6 anni**: "*Offsetting the high cost of therapy may be the fact that medical expenditure soars rapidly when CKD progresses from stage G3 to G4*"

(***Erickson KF, Ann Intern Med 2013***)

TREATMENT COSTS

	Tolvaptan	Octreotide LAR
Recommended posology	90 + 30 mg/day	40 mg/28 days
Average daily dose *(mg/day)*	120*	1,42 mg/day
Cost per mg *(Euros)*	6.45	64.4
Daily cost *(Euros)*	**774**	**91.4**
Yearly costs *(Euros)*	**282510**	**33361**
Cost Ratio (Tolv/Octr)	**8.5**	

*** in TEMPO *(Torres VE, NEJM 2012)* and **ALADIN *(Caroli A, Lancet 2013)* studies**

GTND
ISSN 0394-9362

Giornale di Tecniche Nefrologiche e Dialitiche 2016; 28 (2): 139
DOI: 10.5301/GTND.2016.15858

IL RENE POLICISTICO E AIRP ONLUS

Il Tolvaptan negato. L'impegno di AIRP contro la decisione dell'Aifa

Luisa Sternfeld Pavia

Cari amici,

notizie buone e meno buone in questa primavera 2016, che sboccia mentre vi scrivo queste righe.

Le notizie buone sono quelle che riguardano le nostre attività, sempre intense e di costante impegno.

AIRP è stata presente alla **Giornata Mondiale del Rene**, che si è celebrata il 10 Marzo in tutto il mondo e che, in questa edizione, era dedicata alle malattie renali nei bambini.

Per l'occasione, siamo stati presenti con postazioni dedicate a **Milano** (Ospedale San Raffaele), a **Treviso** (Ospedale Ca' Foncello) e a **Salerno**, presso l'Università degli Studi. I nostri *desk* hanno diffuso

"Dobbiamo far conoscere alla gente il problema dei malati di rene policistico come me, la mia famiglia (tre figli malati) e tutti gli altri. Non si può far pagare un farmaco che permette a chi lo assume di salvargli la vita", scrive C.M. una paziente affetta da rene policistico, 54 anni, di Arese, Milano. *"Io lo sto già assumendo, perché faccio parte del protocollo al Policlinico di Milano, ma non voglio ritenermi una dei pochi fortunati. Deve essere per tutti"*.

Con la sua decisione, Aifa dimostra di considerare di serie B i pazienti affetti da rene policistico, ai quali è negata l'unica cura in grado, oggi, di dare una nuova speranza di vita più dignitosa e un miglioramento delle condizioni di salute.

Tolvaptan è, infatti, il primo trattamento in grado di rallentare la crescita delle cisti, preservando la funzionalità renale. AIRP chiede, quindi, che una decisione così ingiusta venga prontamente modificata ed è impegnata a sollevare il problema presso le massime au-

Nephrol Dial Transplant (2016) 0: 1–12
doi: 10.1093/ndt/gfv456

ndt
Nephrology Dialysis Transplantation

NDT Perspectives

Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice

Ron T. Gansevoort[1], Mustafa Arici[2], Thomas Benzing[3], Henrik Birn[4,5], Giovambattista B. Capasso[6], Adrian Covic[7], Olivier Devuyst[8,9], Christiane Drechsler[10], Kai-Uwe Eckardt[11], Francesco Emma[12], Bertrand Knebelmann[13], Yannick Le Meur[14], Ziad Massy[15,16,17], Albert C.M. Ong[18], Alberto Ortiz[19], Franz Schaefer[20], Roser Torra[21,22], Raymond Vanholder[23], Andrzej Więcek[24], Carmine Zoccali[25] and Wim Van Biesen[23]

Need for guidance on identifying patients for treatment

According to the EMA label tolvaptan *"is indicated to slow the progression of cyst development and renal insufficiency of ADPKD in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease."*

This indication incorporates two issues that need clarification:

1. The CKD stage and age that qualify patients for treatment

2. How to define "*evidence of rapidly progressing disease*".

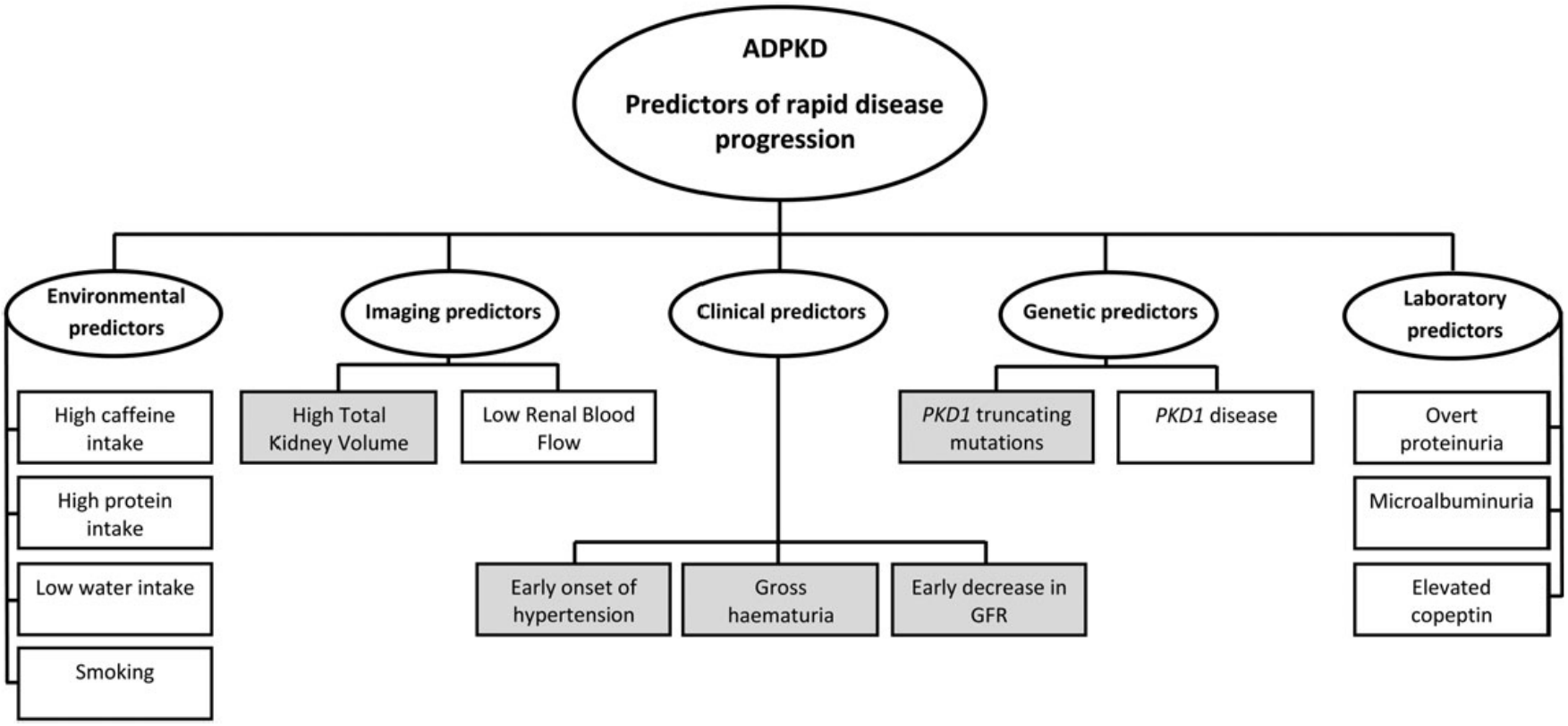
CKD stage and age at initiation of treatment

Recommendation 1.1	*We suggest that tolvaptan can be prescribed to adult ADPKD patients aged <50 years with CKD stages 1 to 3a (eGFR >45 ml/min/1.73m²) who have demonstrated or who are likely to have rapidly progressing disease, but that CKD stage must be interpreted in conjunction to age.*
Recommendation 1.2	*We recommend not starting tolvaptan in patients at age 30-40 with CKD stage 1 (eGFR >90 ml/min/1.73m²).*
Recommendation 1.3	*We recommend not starting tolvaptan in patients aged 40-50 with CKD stages 1 or 2 (eGFR >60 ml/min/ 1.73m²).*

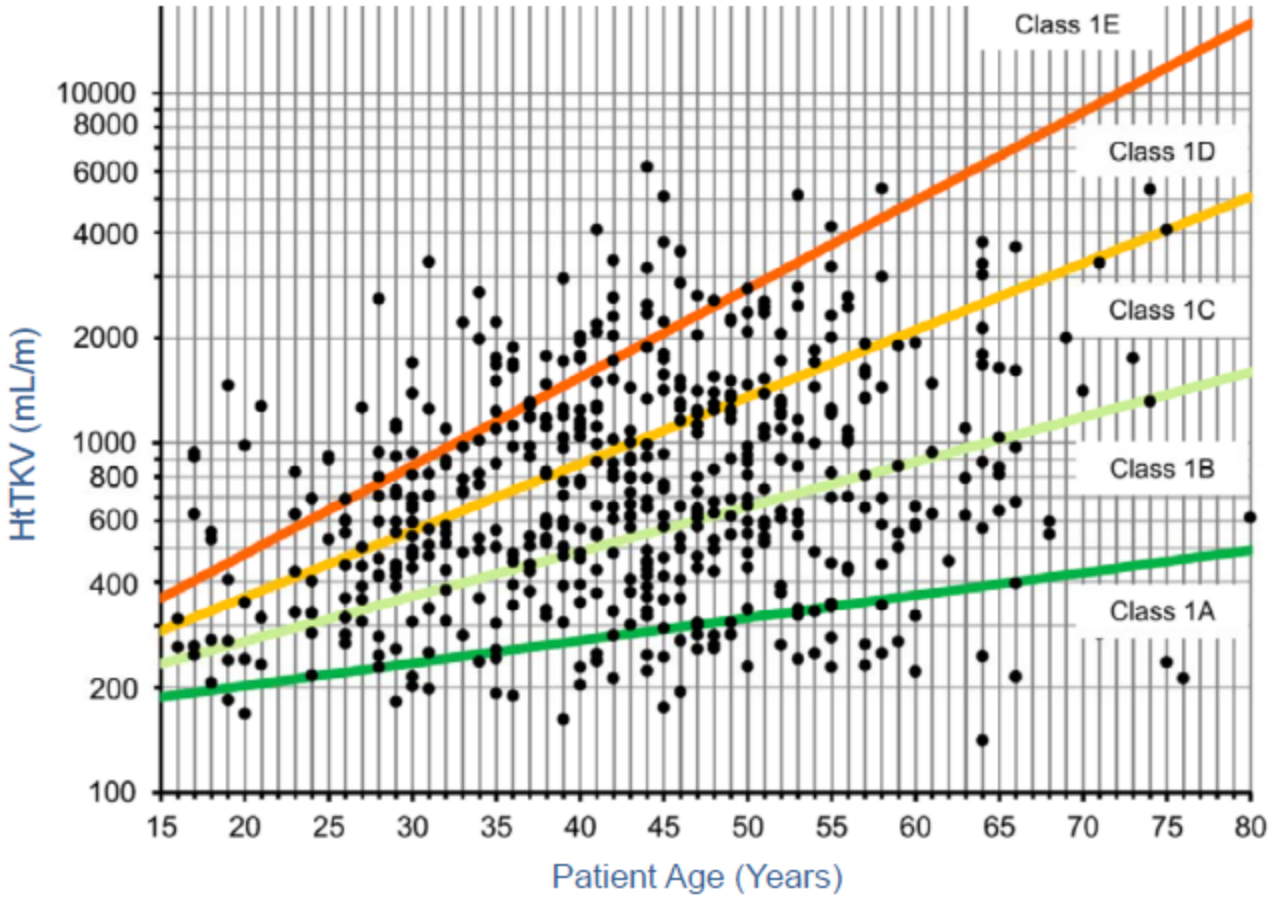
Documented change in GFR and TKV to define rapid disease progression

Reccomendation 2	*A confirmed annual eGFR decline ≥5 mL/min/1.73 m^2 in one year and/or ≥2.5 mL/min/1.73 m^2 per year over a period of 5 years, defines rapid progression.*
Reccomendation 3	*A TKV increase of more than 5% per year by repeated measurements (preferably ≥3, each at least 6 months apart and by MRI), defines rapid progression.*

Markers used to assess prognosis in ADPKD.



The Mayo classification for prediction of disease progression in ADPKD by height adjusted TKV and age



Grantham JJ, et al CJASN 2006

Mayo ADPKD Class Calculator

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

Risk prediction using a single TKV value

Reccomendation 4.1	*We recommend the use of the Mayo classification of ADPKD, that makes a distinction in "typical" and "atypical" morphology and adjusts TKV in patients with "typical" morphology for age and height to define five classes of patients according to prognosis (1A-1E).*
Reccomendation 4.2	*We suggest that in ADPKD patients with Mayo class 1C-1E disease (corresponding to a predicted eGFR decrease ≥2.5ml/min/1.73m² per year) rapid disease progression is likely.*
Reccomendation 4.3	*We suggest that in patients with atypical morphology of ADPKD, as described in the Mayo classification, rapid disease progression is unlikely.*
Reccomendation 4.4	*We suggest that in a patient with age <45 years and a kidney length of >16.5 cm as assessed by ultrasound, rapid disease progression is likely.*

The PRO-PKD Score to assess prognosis in ADPKD

Begin male	**1 point**
Hypertension before 35 years of age	**2 points**
First urologic event before 35 years age	**2 points**
PKD2 mutation	**0 points**
Non-truncating PKD1 mutation	**2 points**
Truncating PKD1 mutation	**4 points**

- **A score ≤3 points** excludes progression to ESRD before the age of 60 with a negative predictive value of 81.4%
- **A score >6 points** predicts rapid disease progression with ESRD onset before the age of 60 years with a positive predictive value of 90.9%.
- **For intermediate scores (4–6 points)** the prognosis is unclear.

(Cornec-Le Gall et al. JASN 2015)

Risk prediction using genetic and clinical factors

Recommendation 5	*We suggest that in patients with a truncating PKD 1 mutation in conjunction with early onset of clinical symptoms, consistent with a PRO-PKD score >6, rapid disease progression is likely.*

Risk prediction using family history

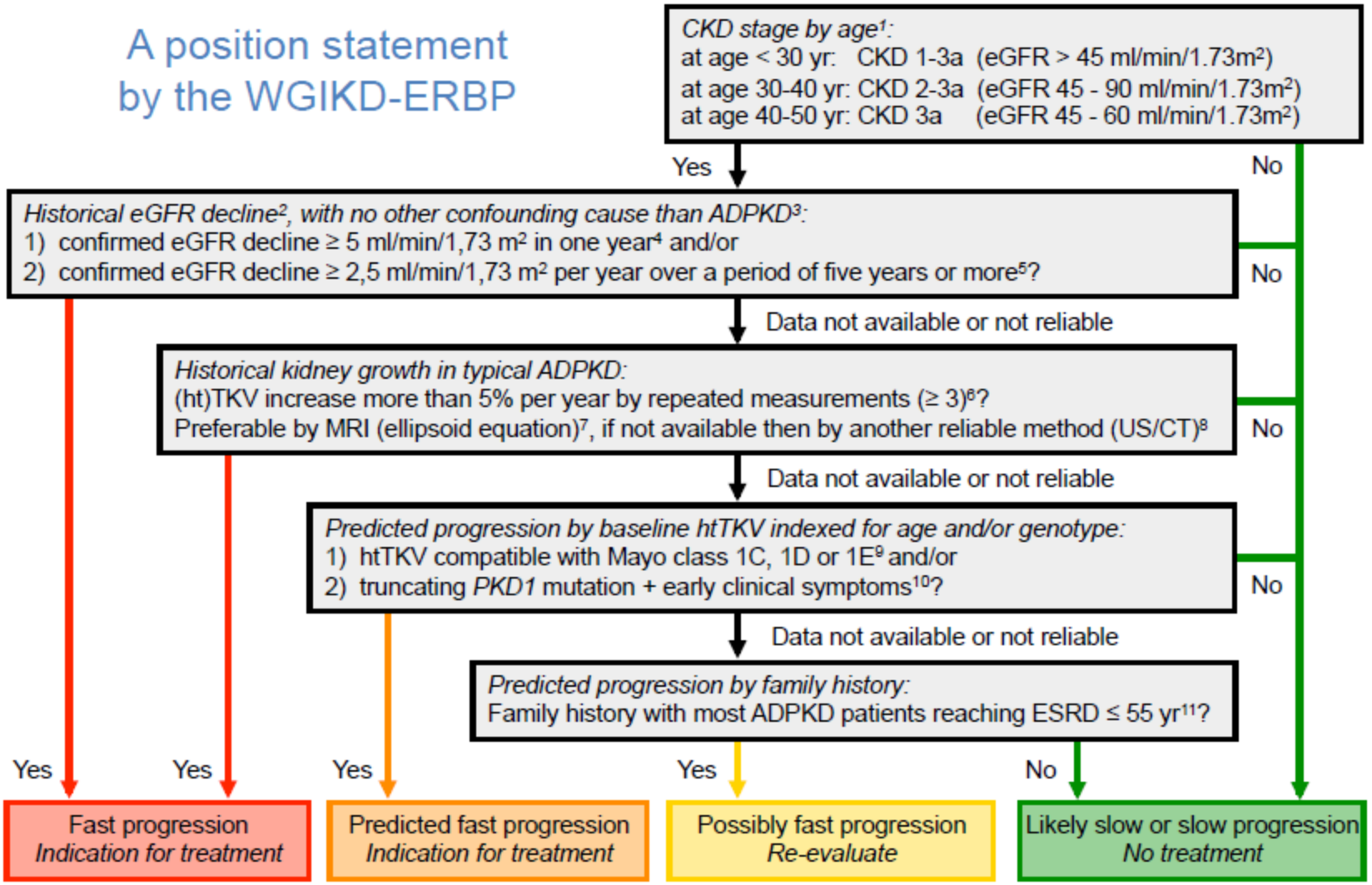
Recommendation 6	*We suggest patients with a family history of ESRD before age 58 years be re- assessed for rapid disease progression on a 3 to 5 yearly basis.*

An algorithm to assess eligibility for Tolvaptan treatment in ADPKD

Recommendation 7	We suggest to use a hierarchical decision algorithm to assess whether ADPKD patients are rapid progressors or likely to be rapid progressors, and accordingly may qualify for treatment.

Assessment of renal progression and progression risk in ADPKD

A position statement
by the WGIKD-ERBP



Contraindications, Special Warnings and Precautions

Recommendation 8.1	We recommend discussing adverse effects and impact on lifestyle with patients when considering starting tolvaptan.
Recommendation 8.2	We recommend taking into account contra-indications and adverse effects such as hepatic toxicity and other precautions when considering starting tolvaptan.
Recommendation 8.3	We recommend that prescription and documentation of safety monitoring of tolvaptan is performed under supervision of physicians with expertise in managing ADPKD.

Initiation, Titration and Maintenance of Treatment

Recommendation 9.1	We suggest tolvaptan treatment to be started with a dose of 45 mg in the morning and 15 mg in the evening.
Recommendation 9.2	We suggest to uptitrate the dose of tolvaptan to 60/30 mg and 90/30 mg when tolerated.
Recommendation 9.3	We suggest tolvaptan treatment to be discontinued when patients approach ESRD.

Contra-indications

- Hypersensitivity to the active substance or to any of the excipients
- Elevated liver enzymes and/or signs or symptoms of liver injury prior to initiation of treatment
  - ✓ Volume depletion
  - ✓ Hypernatremia
  - ✓ Patients who cannot perceive or respond to thirst
  - ✓ Pregnancy
  - ✓ Breast-feeding

Ambulatorio dedicato per ADPKD

Organizzazione della SC di Nefrologia e Dialisi della Casa Sollievo della Sofferenza

1. Cadenza bimestrale (due giovedì / mese)
2. Gestione del Nefrologo con US in sede
3. Rilevazione QoL , Score dolore ,

   Rilevazione psicologica
4. Collaborazioni:

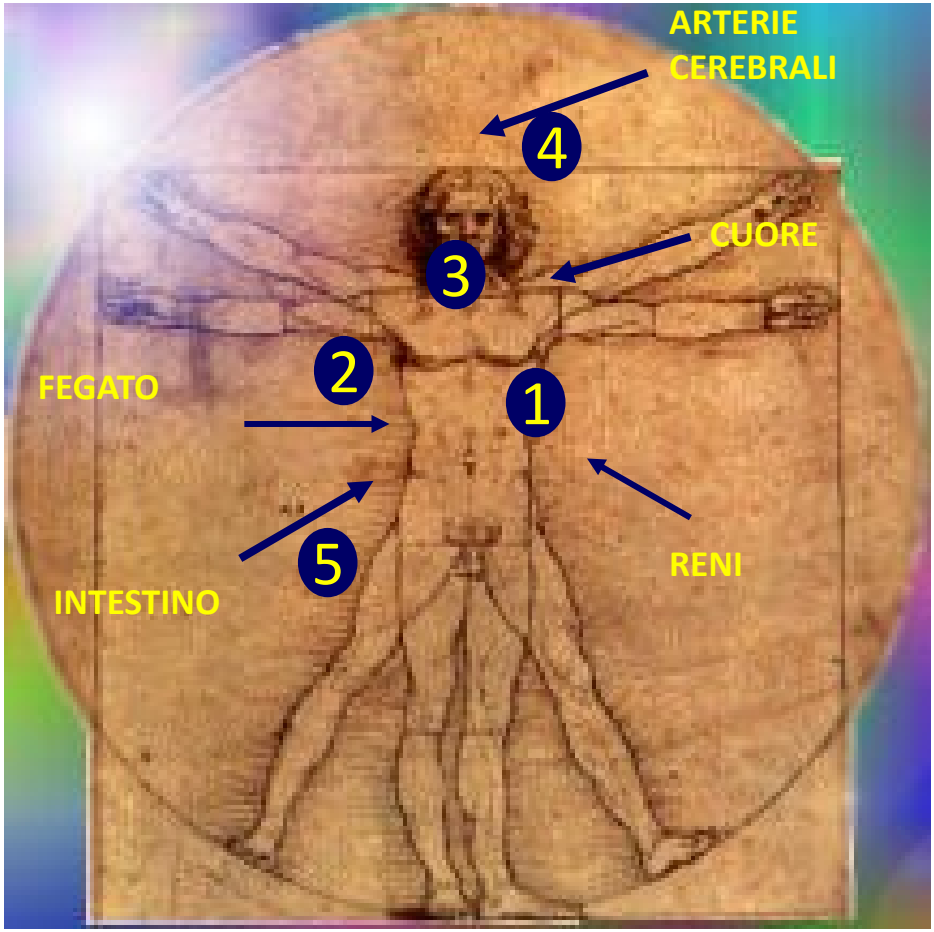
   GENETICA Dr.ssa Accadia, Dr. Melchionda

   RADIOLOGIA Dr Palladino, Dr Dragone

   TERAPIA DEL DOLORE Dr Visconti

   Dietologia e **Servizio di Psicologia**

   Epatologo, Cardiologo e Neurochirurgo
5. **MMG : Coordinamento Dr R Sammarco**
6. Opzioni organizzative: ***day-service***



Inizio attività 1 gennaio 2016

Polycystic Kidney Disease

GIVE PKD THE BUMP

Lottiamo contro il Rene Policistico