Società Medico Chirurgica di Ferrara

Tolvaptan nel trattamento del rene policistico (ADPKD)

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End Stage Polycystic Kidney (ADPKD)

PKD Foundation, www.pkdcure.com

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- **1/500-1/1000** of the general population

- Characterized by **bilateral renal cysts formation.**

-Systemic Disease:
liver and pancreatic cysts.
Cardiovascular defects, **Intracranial** and **aortic aneurysms.**

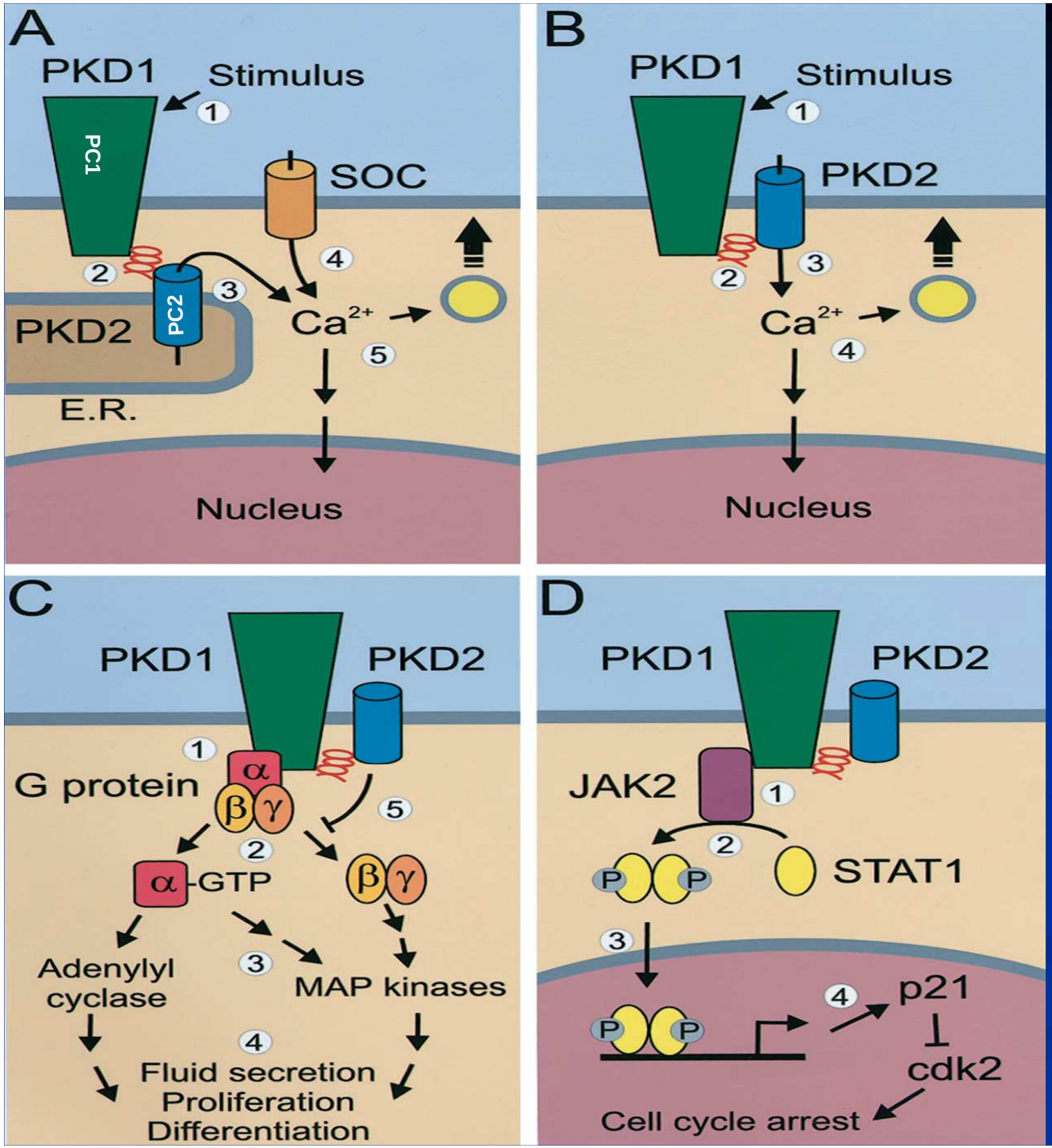
- Important cause of End Stage Renal Disease (ESRD), which occurs by age 50 in 50% of the patients (but a significant fraction is already present in infants) **10% dialysis patients**

- Mutations of 2 genes:

PKD1: 85% of all cases, chromosome 16p13.3

PKD2: 15% of cases, chromosome 4q22

2 genes encodes for Polycystin-1 and Polycystin-2

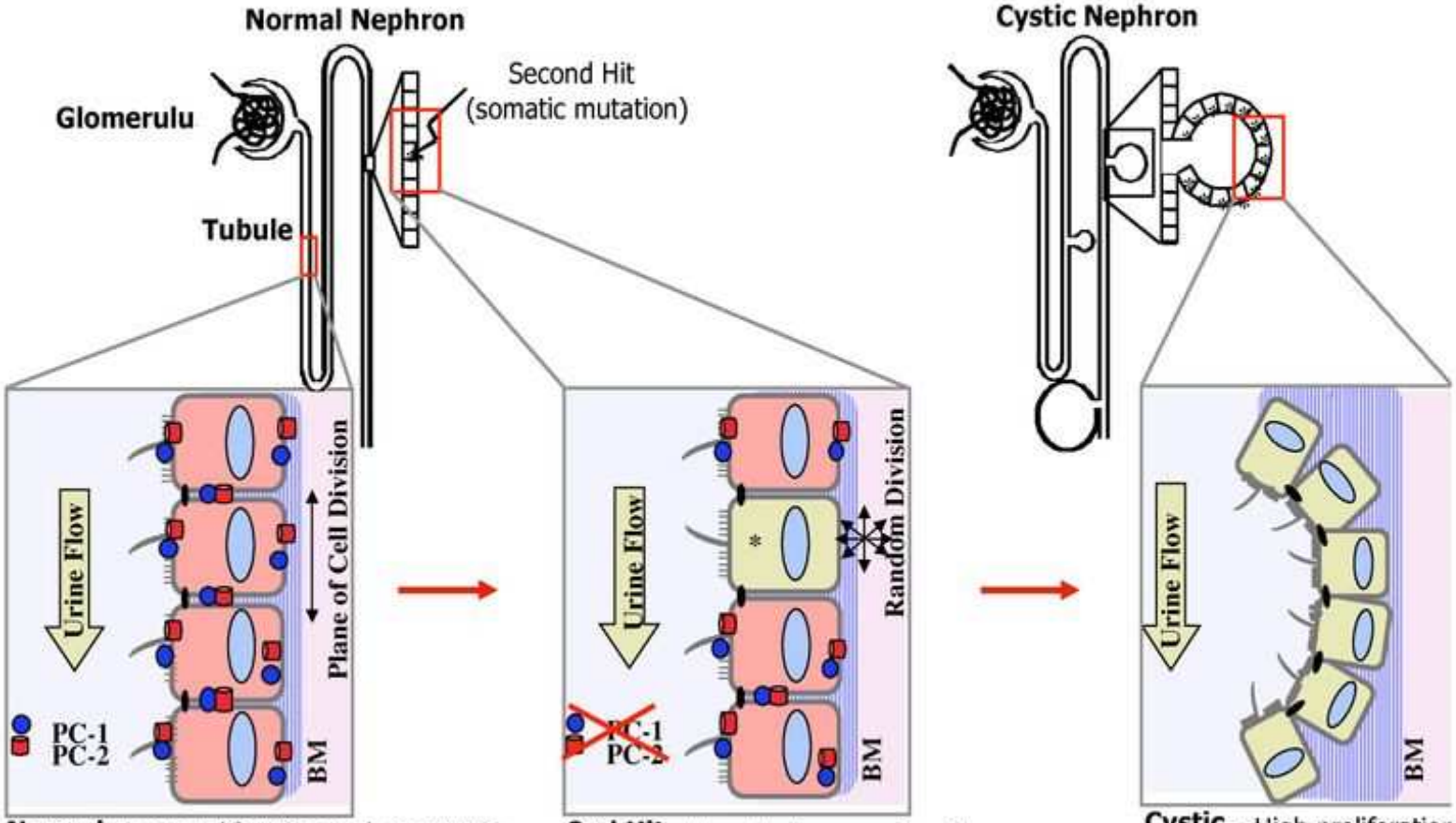


Le policistine 1 e 2 sono proteine la cui interazione porta ad una cascata di fenomeni

Regolano:

- il segnale del calcio intracellulare
- lo sviluppo e riparazione epiteliale
- il fenotipo della cellula renale differenziato

ADPKD is a loss-of-function disease (Two-hit/threshold model)

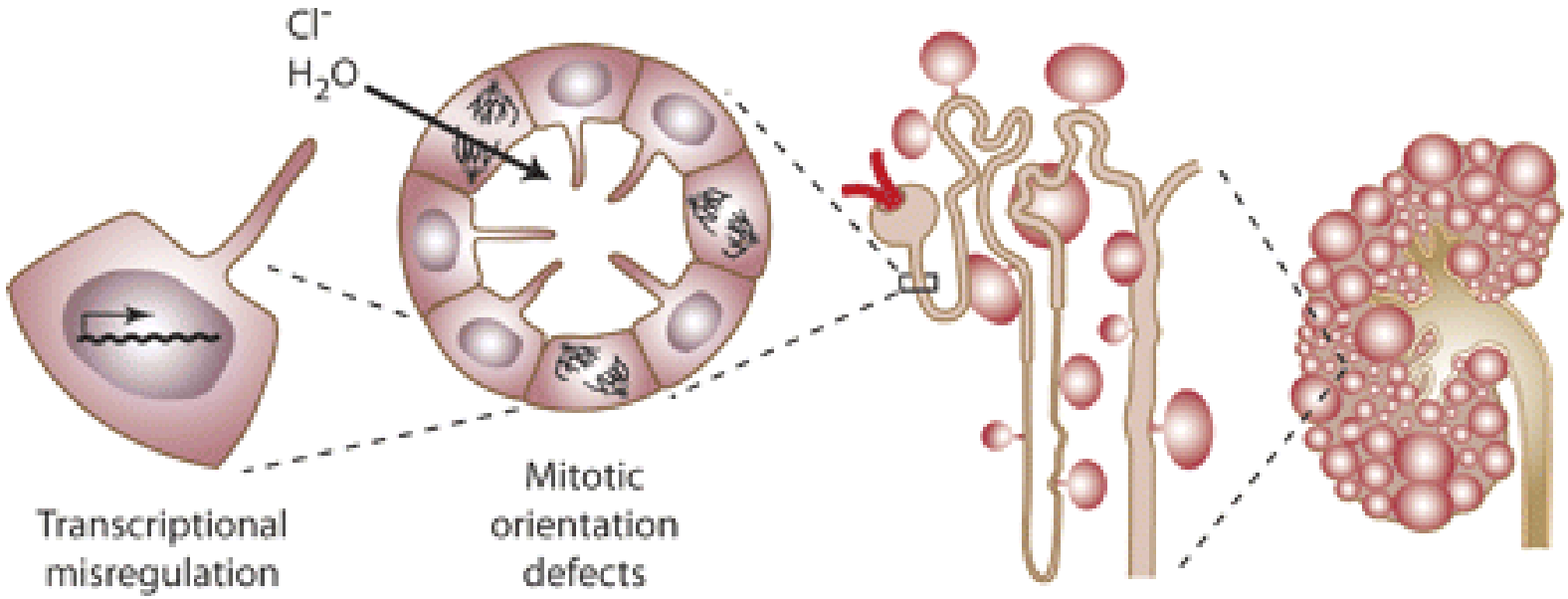


Normal - Low proliferation and apoptosis
- Absorption, Flow sensing
- Oriented Cell Division

2nd Hit - Un-able to sense flow ?
- Mis-Oriented Cell Division?

Cystic - High proliferatior
- High apoptosis
- Fluid secretion
-Glycolysis

Formazione delle cisti a livello della cellula, nefrone e rene.



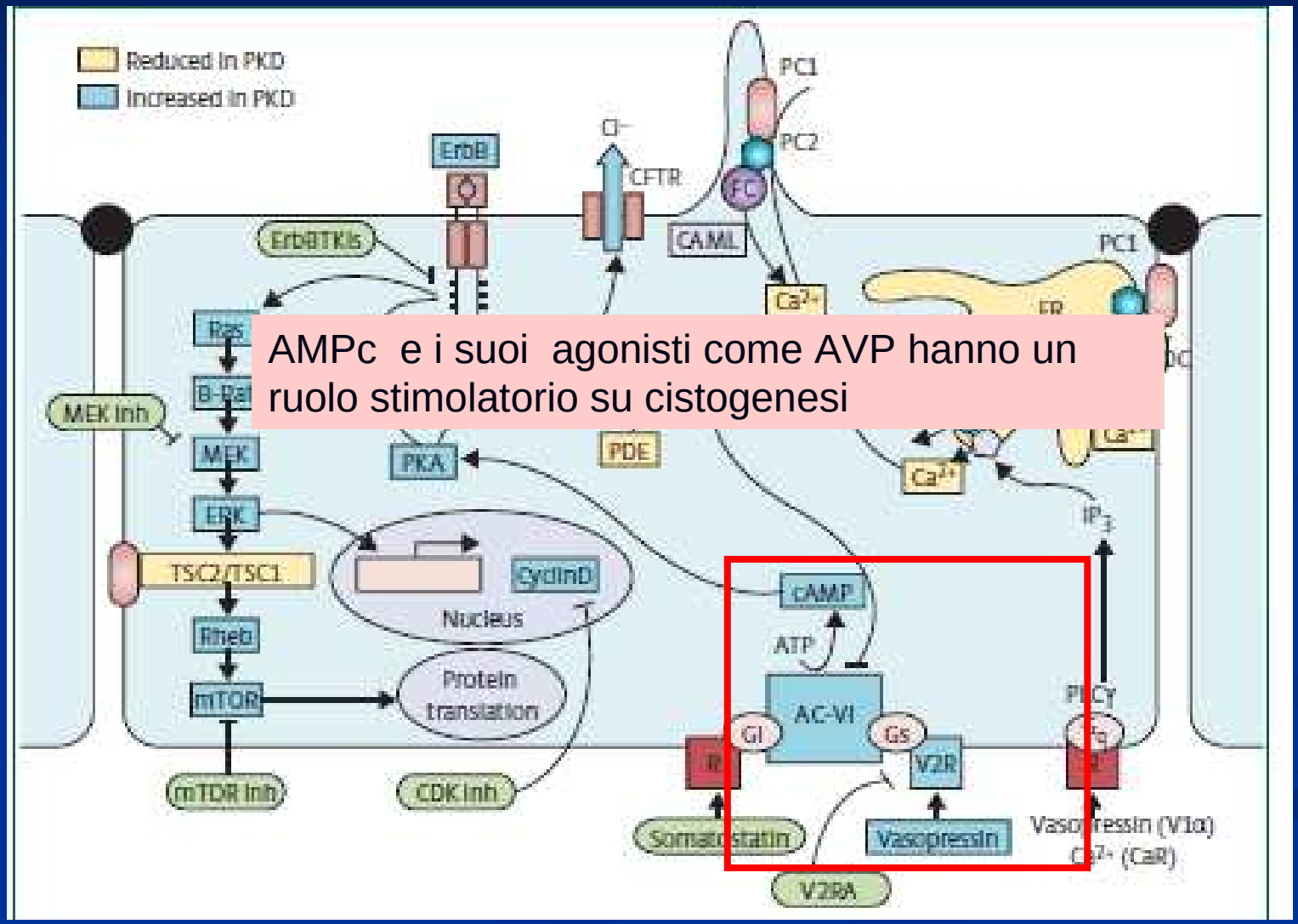
Difetti nei geni che codificano per PC1 e PC2 portano a trascrizioni geniche aberranti, proliferazione cellulare, secrezione degli ioni, con conseguente formazione di fluido nelle cisti. L'espansione delle cisti oltre il tubulo porta a dislocazione del parenchima renale e riduzione della funzione renale

Chapin et al, The Journal of cell biology, 2010

Autosomal dominant polycystic kidney disease

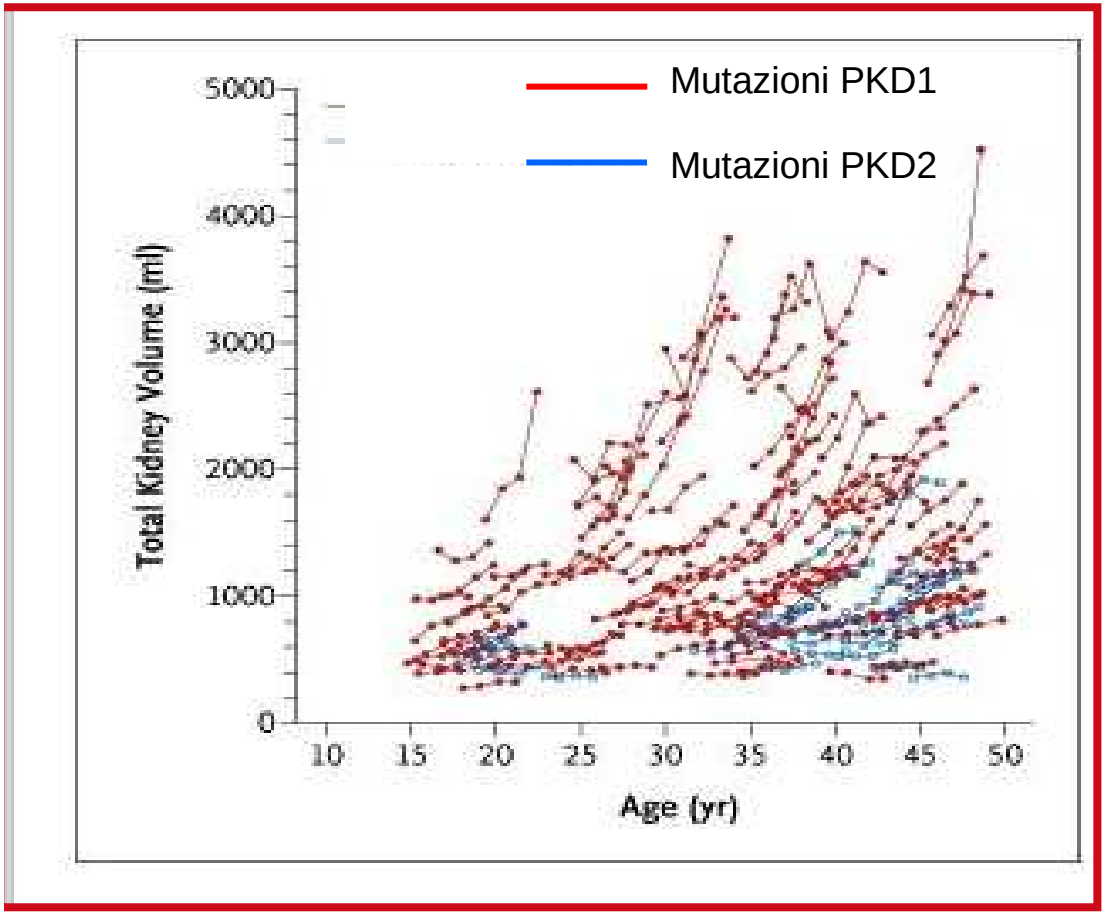
Vicente E Torres, Peter C Harris, Yves Pirson

Autosomal dominant polycystic kidney disease is the most prevalent, potentially lethal, monogenic disorder. It is associated with large interfamilial and intrafamilial variability, which can be explained to a large extent by its genetic heterogeneity and modifier genes. An increased understanding of the disorder's underlying genetic, molecular, and cellular mechanisms and a better appreciation of its progression and systemic manifestations have laid out the foundation for the development of clinical trials and potentially effective treatments.



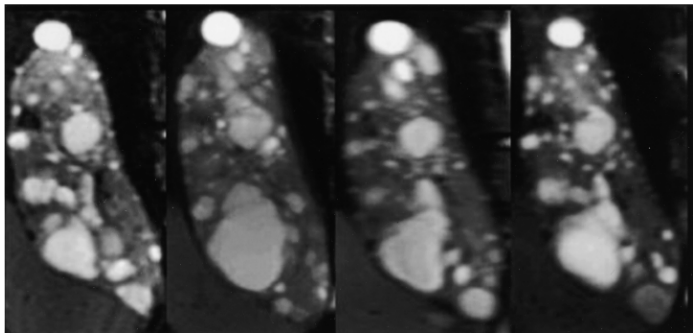
AMPc e i suoi agonisti come AVP hanno un ruolo stimolatorio su cistogenesi

Volume renale totale in relazione all'età in 185 pazienti con mutazioni identificate in PKD1 e PKD2

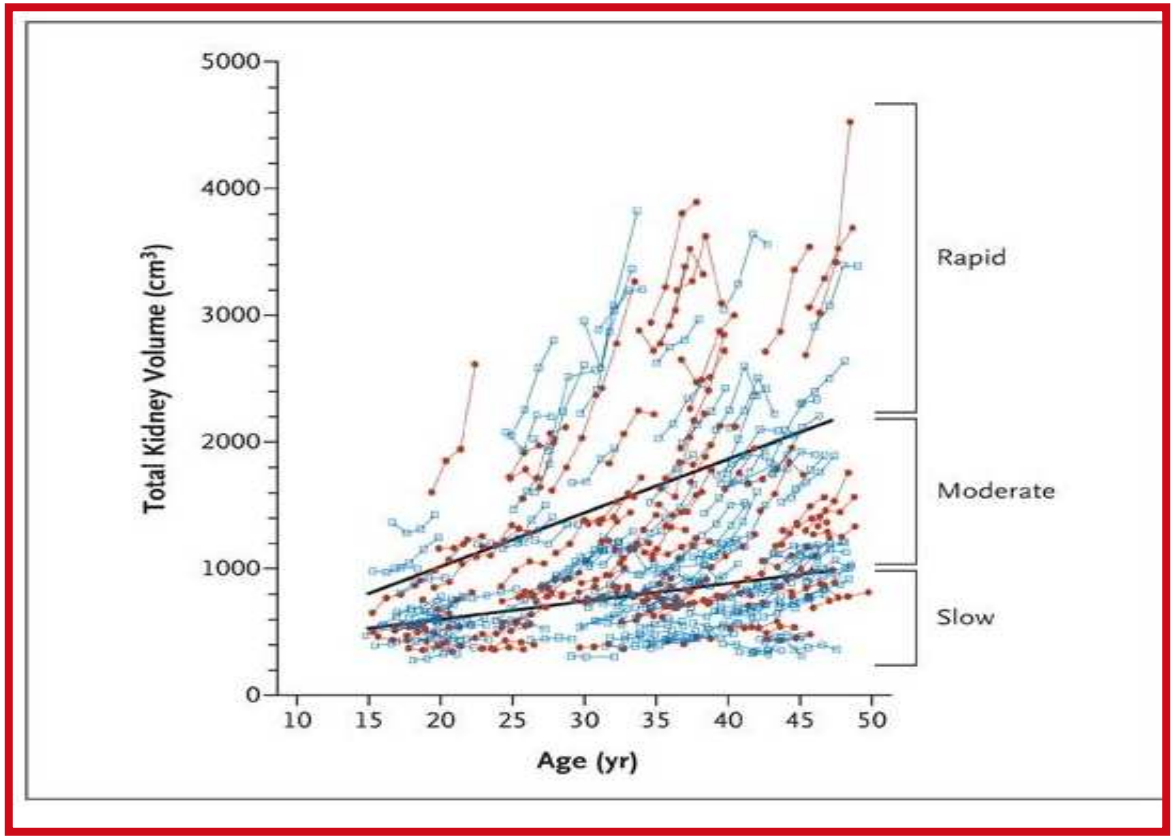


Le mutazioni di PKD1 si associano a un maggior numero di cisti renali e conducono a insufficienza renale in media 20 anni prima rispetto a PKD2

Grantham JJ et al. N Engl J Med 2006;354:2122-2130



CRISP Study



- TKV < 1500 ml
- TKV > 1500 ml

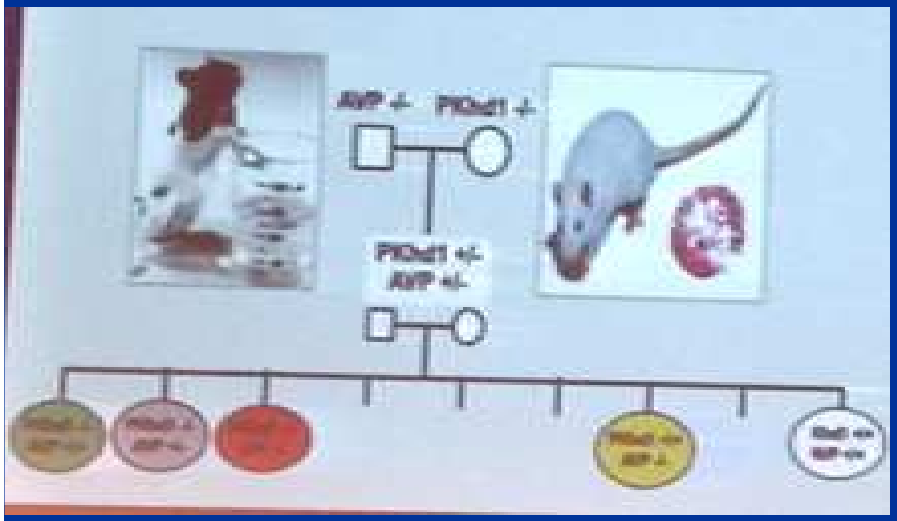
Gli studi di imaging, in particolare la RM, sembrano utili nel prevedere la progressione dell'insufficienza renale in relazione all'incremento del volume totale renale (TKV)

Grantham JJ et al. N Engl J Med 2006;354:2122-2130

Wang et al JASN 2008

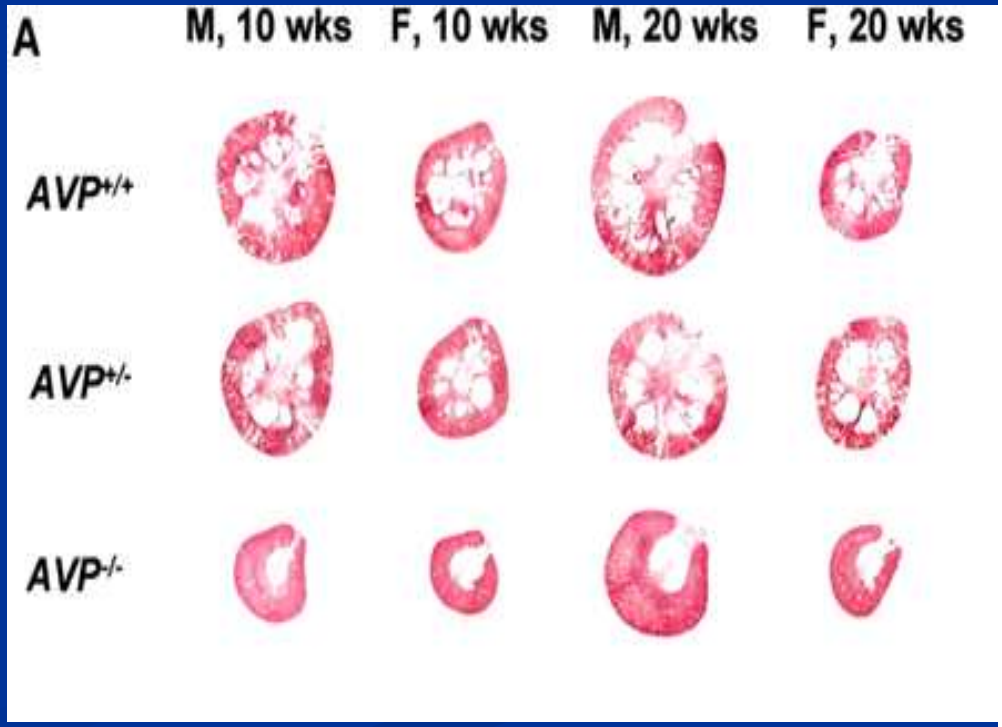
PCK rats +

Brattelboro Rats



10 and 20 week-old

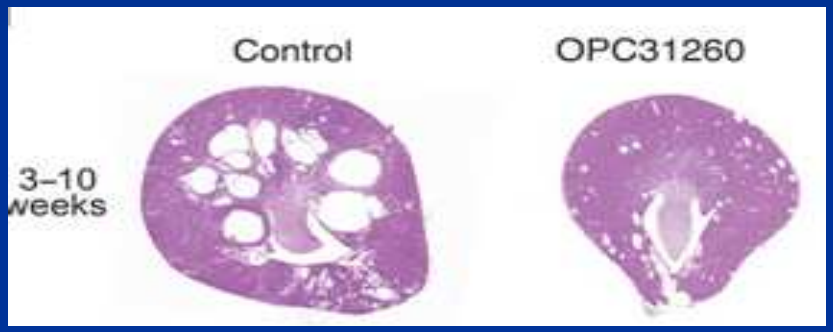
PCK - Brattelboro Rats



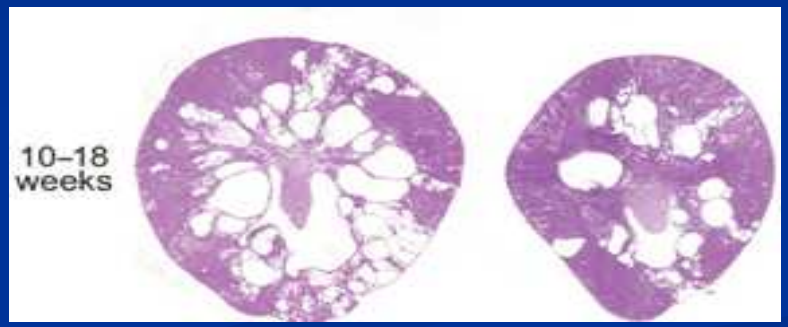
Gattone VH et Al Nat Med 2003
Torres VE et Al. Nat Med 2004

Effetti dell'OPC 31260 su tre modelli animali con policistosi

recessive PCK rats



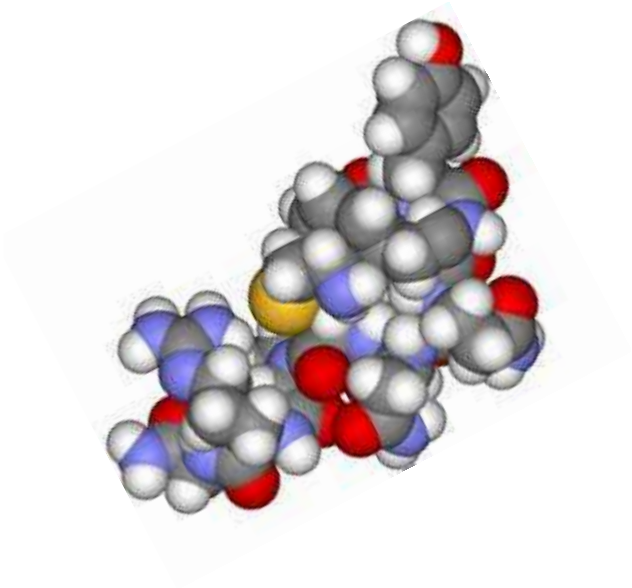
PCY mice nephronophthisis



***Pkd2*-/tm1Som** ADPKD

Nei modelli animali le terapie rallentano la crescita del volume renale e rallentano parallelamente il declino della funzione renale

Vaptani

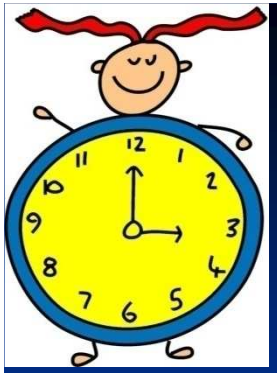


vasopressina

I Vaptani costituiscono una classe di farmaci che vengono definiti "acquaretici“ antagonisti non peptidici dei V1 e V2 della vasopressina.

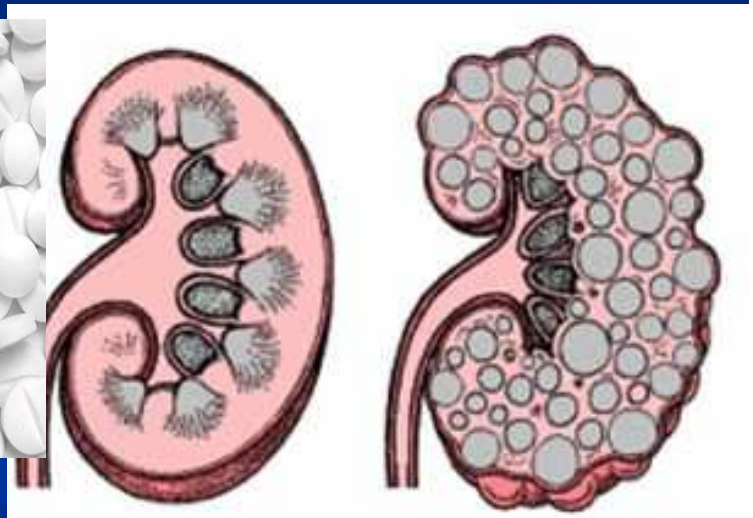
Tolvaptan: blocca in modo selettivo i recettori V2 della Vasopressina localizzati principalmente nel dotto collettore

Tolvaptan riduce la sintesi e l'espressione di acquaporina-2 sulla membrana luminale e riduce il riassorbimento "opzionale" di acqua



TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes)

ADPKD E Tolvaptan



TEMPO 2:4

TEMPO 3:4

TEMPO 4:4

2006 - 2007 2010 - 2011 - 2012 2016

Tolvaptan in Autosomal Dominant Polycystic Kidney Disease: Three Years' Experience

TEMPO 2:4 Trial

TEMPO 2:4 (156-04-250)
47 Patients underwent screening
46 Subjects met inclusion criteria

46 Entered titration period

46 Entered fixed dose period

156-05-002
18 Patients underwent screening
17 Subjects met inclusion criteria

22 Assigned to 45/15 mg split-dose daily regimen tolvaptan

24 Assigned to 60/30 mg split-dose daily regimen tolvaptan*
(*5 Down-titrated during this period)

17 Assigned to 15/15 mg split-dose daily regimen tolvaptan

4 Withdrew* prior to month 36
3 Due to Adverse Event
1 Met Withdrawal Criteria

5 Withdrew* prior to month 36
2 Due to Adverse Event
1 Met Withdrawal Criteria
2 Subjects Withdrew Consent

3 Withdrew* prior to month 36
1 Lost to Follow-up
1 Due to Adverse Event
1 Subject Withdrew Consent
(1 Withdrawn subject had down-titrated)

18 Assigned to 45/15 mg tolvaptan completed 36 months of therapy

21 Assigned to 60/30 mg tolvaptan completed 36 months of therapy
(4 Previously down-titrated subjects completed)

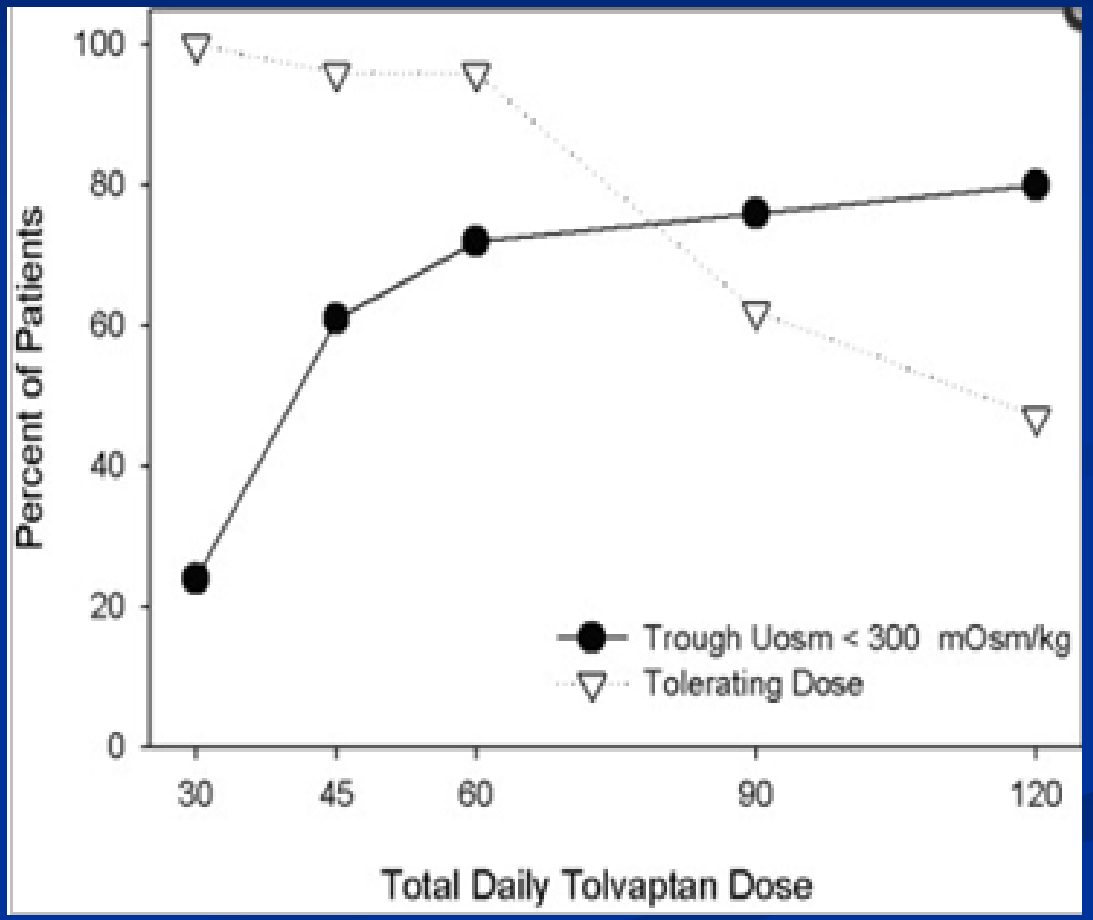
12 Assigned to 15/15 mg tolvaptan completed 36 months of therapy

*Detailed withdrawal information may be found in Supplementary Material

Higashihare E et al clin J Am Soc Nephrol 2011; 6 (10):2499-507

TEMPO 2:4 Trial

- Confermare la *sicurezza* e la tollerabilità a lungo termine del Tolvaptan
- Acquisire dati pilota sull'*efficacia*: modificazioni di osmolarità urinaria,TKV,GFR, stato ipertensivo
- Analisi farmacocinetiche e farmacodinamiche



Higashihare E et al clin J Am Soc Nephrol 2011; 6 (10):2499-507

Tolvaptan in Autosomal Dominant Polycystic Kidney Disease: Three Years' Experience

Eiji Higashihara,[*†] Vicente E. Torres,[‡§] Arlene B. Chapman,[‖] Jared J. Grantham,[¶] Kyongtae Bae,[#] Terry J. Watnick,[**] Shigeo Horie,[††] Kikuo Nutahara,[†] John Ouyang,[‡‡] Holly B. Krasa,[§§] Frank S. Czerwiec,[‡‡] for the TEMPO[3:4] and 156-05-002 Study Investigators

Table 3. Annualized progression rate of TKV and eGFR in completing subjects projected over 3 years

		Annualized TKV Growth Rate[a]		
Group	*N*	Annual Change (%/yr)[b]	RGM[c]	*P*-Value
TKV control	102	5.8 (4.3)	0.96 (0.95 to 0.97)	<0.01
Tolvaptan	51	1.7 (3.5)		

		Annualized eGFR Slope[d]		
Group	*N*	Annual Change (ml/min per 1.73 m^2 per year)[b]	LS Mean Difference (ml/min per 1.73 m^2 per year)[c]	*P*-Value
eGFR control	102	−2.1 (3.1)	1.1 (0.24 to 1.92)	=0.01
Tolvaptan	51	−0.7 (2.2)		

Tolvaptan in Autosomal Dominant Polycystic Kidney Disease: Three Years' Experience

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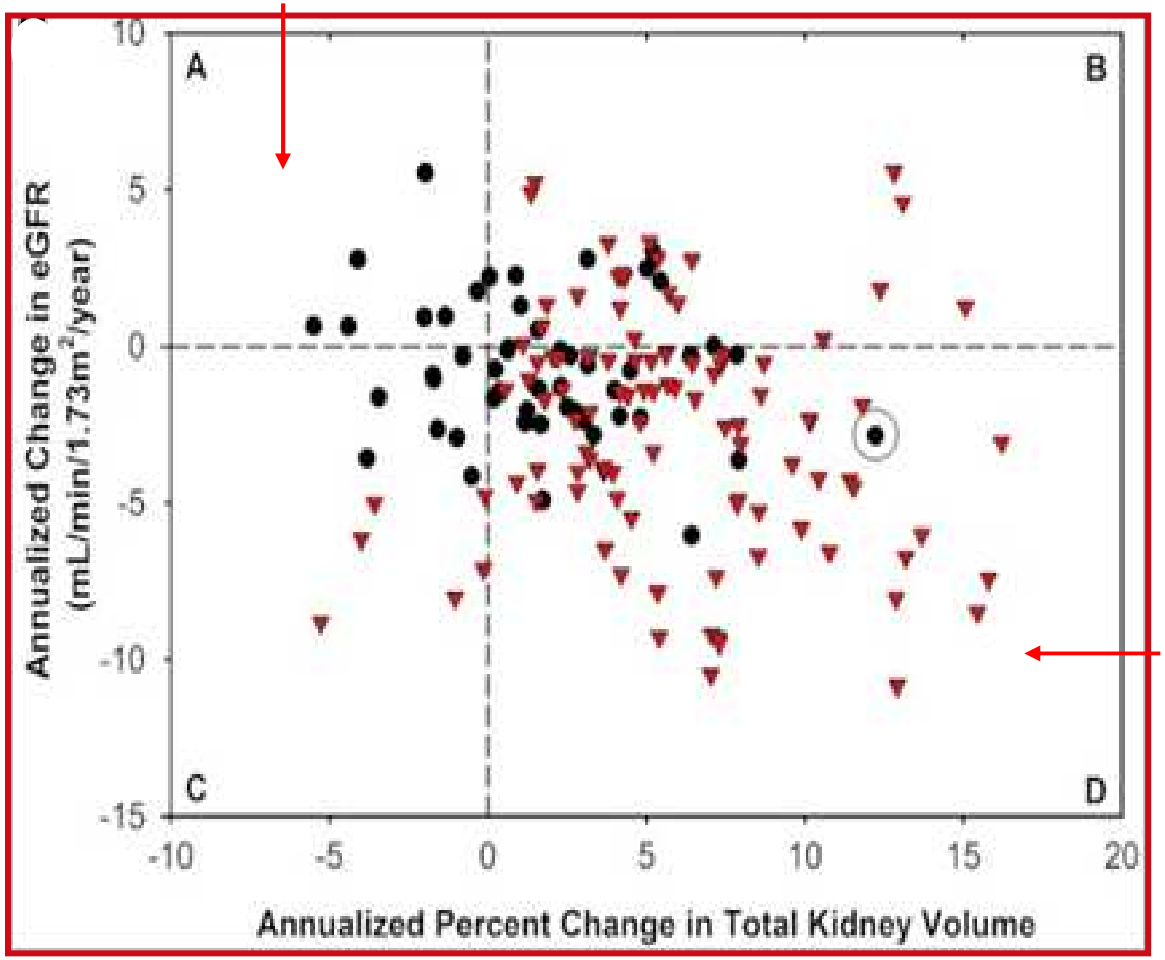
Gruppo tolvaptan

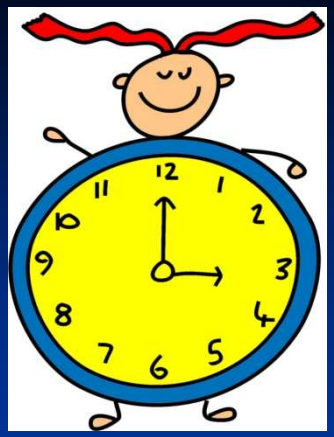
Gruppo controllo

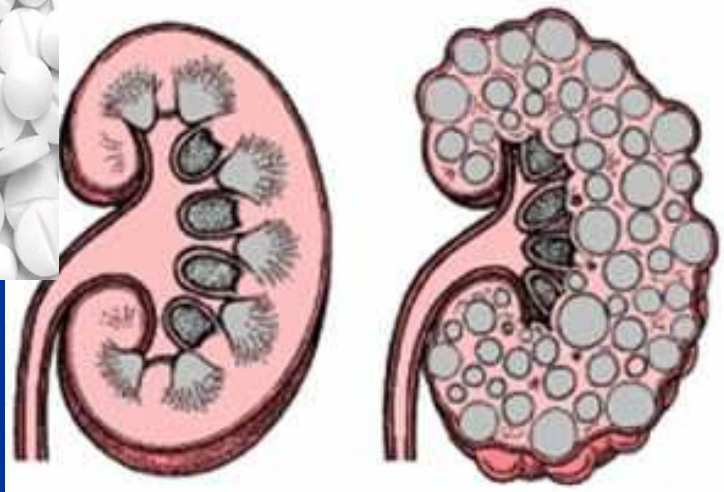
Miglioramento sia GFR che TKV



Peggioramento sia di GFR che TKV

ADPKD E Tolvaptan





TEMPO 2:4

TEMPO 3:4

TEMPO 4:4

2006 - 2007 2010 - 2011 - 2012 2016

TEMPO 3:4 TRIAL

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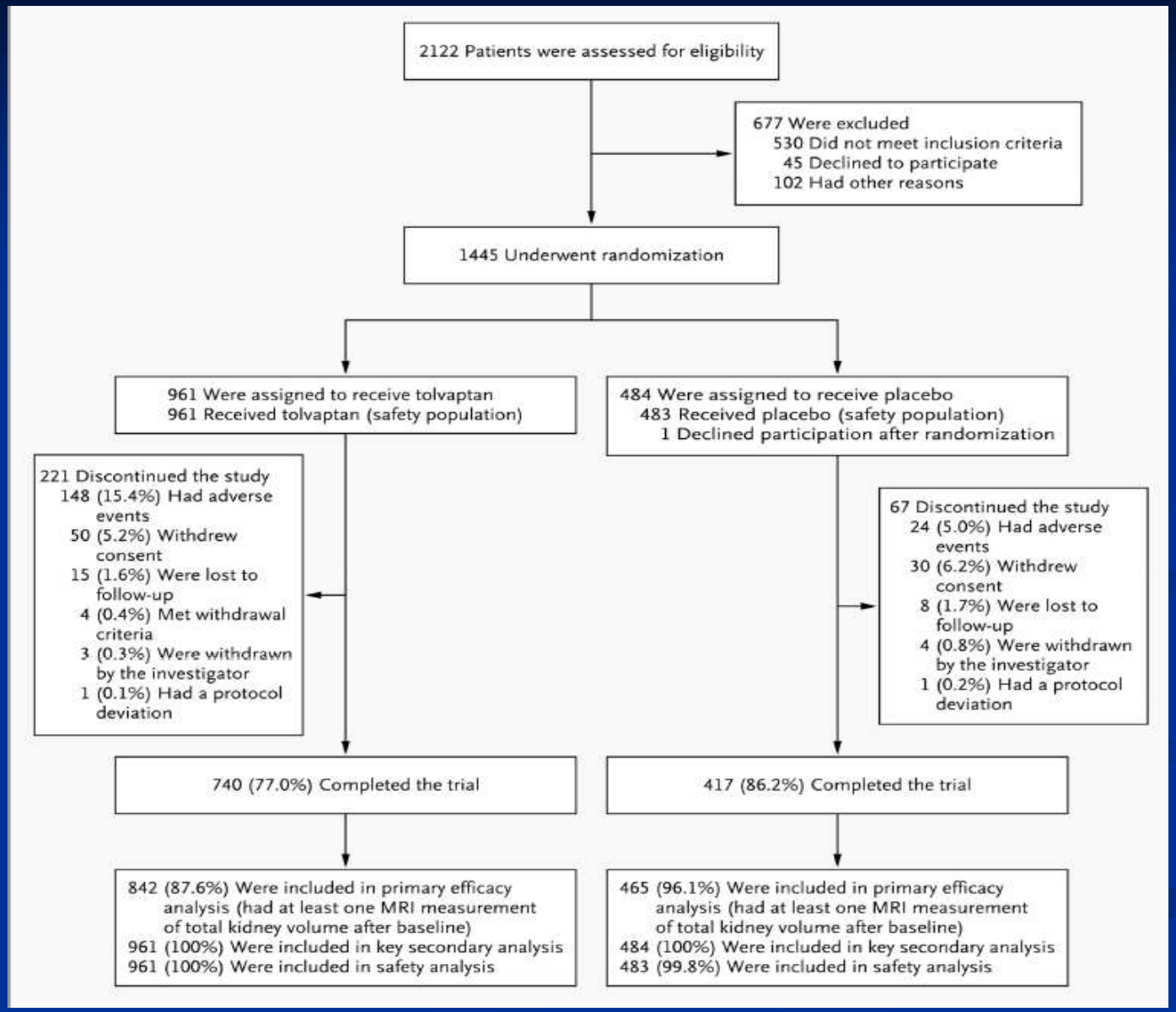
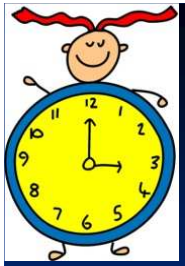


Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease Torres V E. et al 2012



TEMPO 3:4

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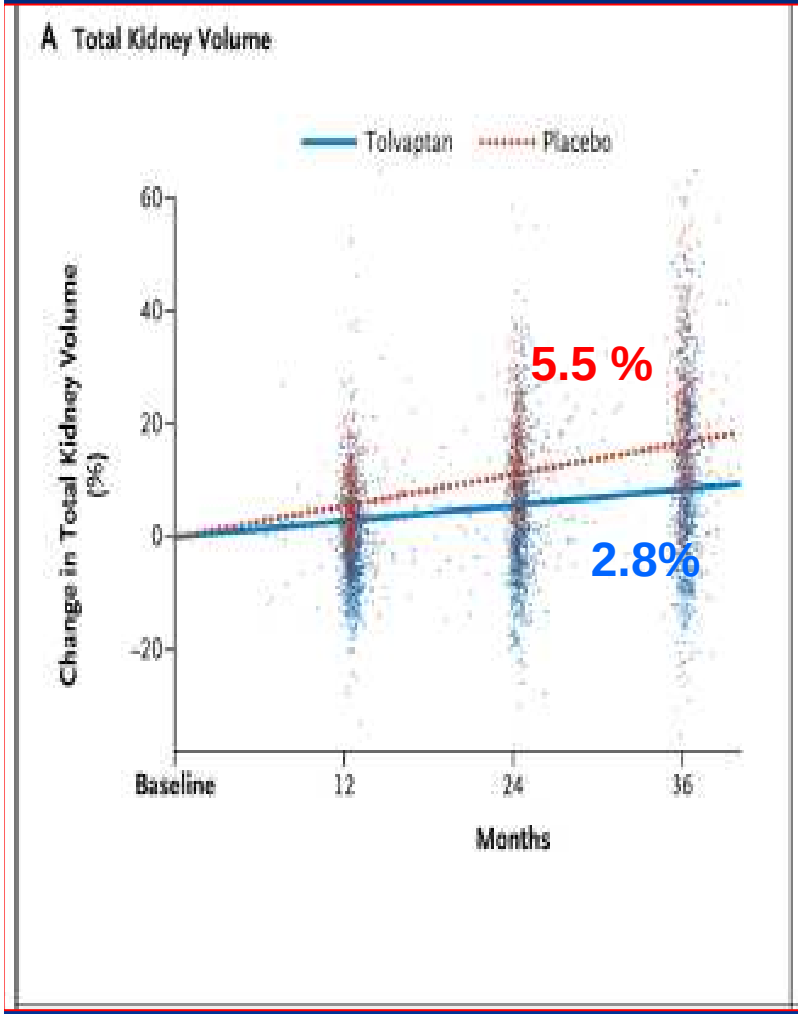
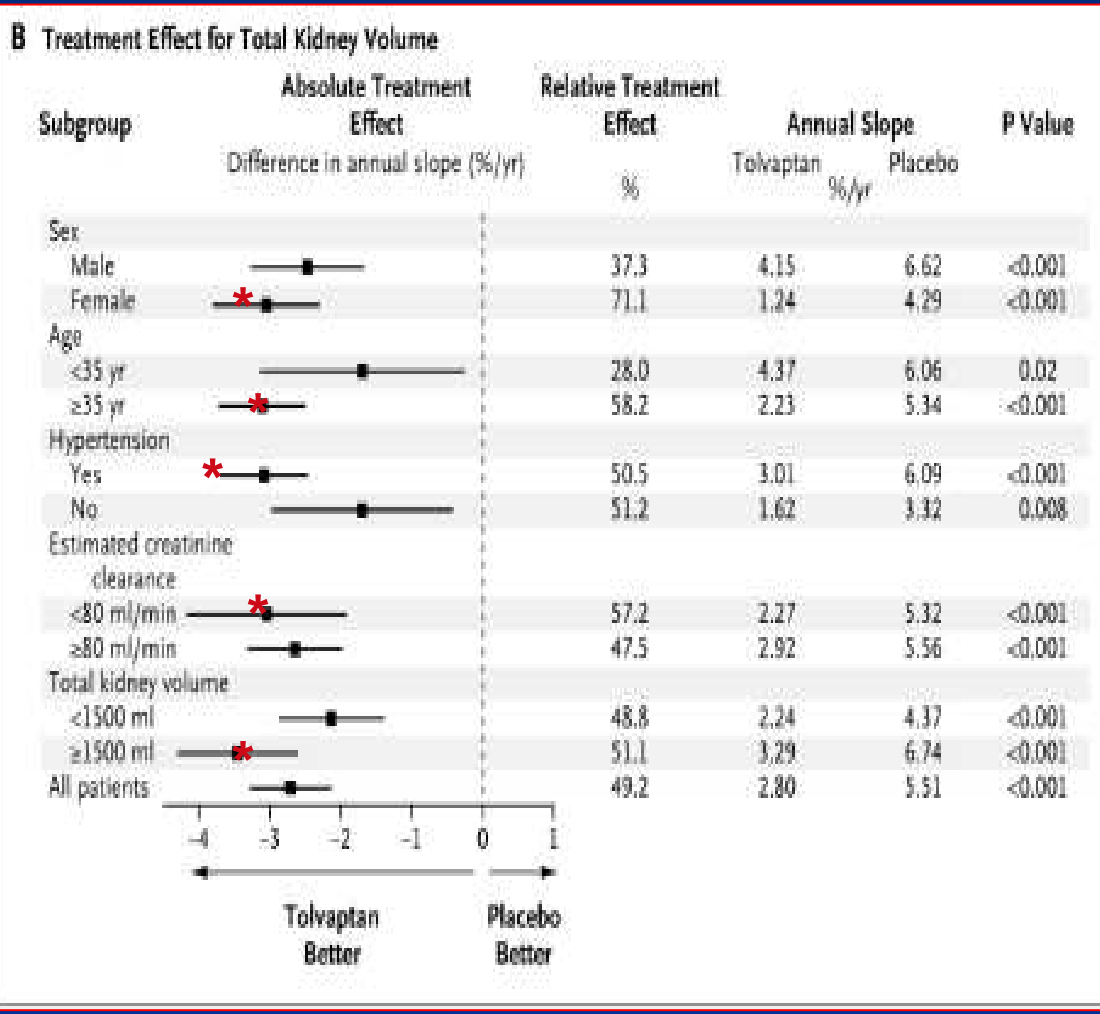
The primary end point was the annual rate of percentage change in total kidney volume





Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease Torres V E. et al 2012

Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease

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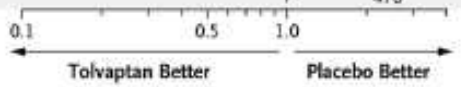
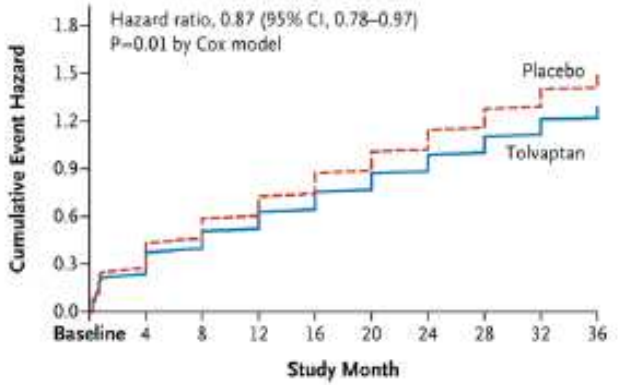
A Effects of Tolvaptan

End Point	Hazard Ratio (95% CI)	No. of Subjects	No. of Total Events	Events/100 Person-Yr	P Value
ADPKD-related composite					0.01
Tolvaptan group		961	1049	44	
Placebo group		483	665	50	
Worsening hypertension					0.42
Tolvaptan group		961	734	31	
Placebo group		483	426	32	
Worsening albuminuria					0.74
Tolvaptan group		961	195	8	
Placebo group		483	103	8	
Clinically significant kidney pain					0.007
Tolvaptan group		961	113	5	
Placebo group		483	97	7	
Worsening kidney function					<0.001
Tolvaptan group		918	44	2	
Placebo group		476	64	5	

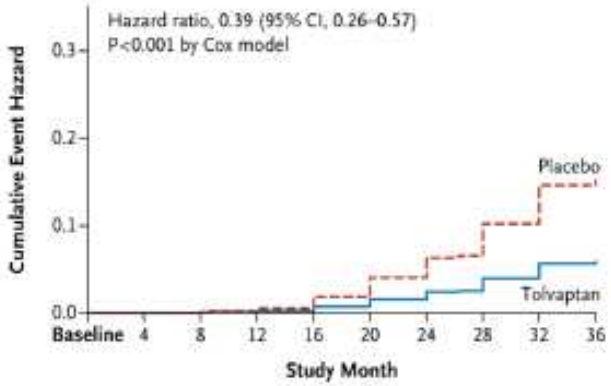


B Risk of ADPKD-Related Composite Events



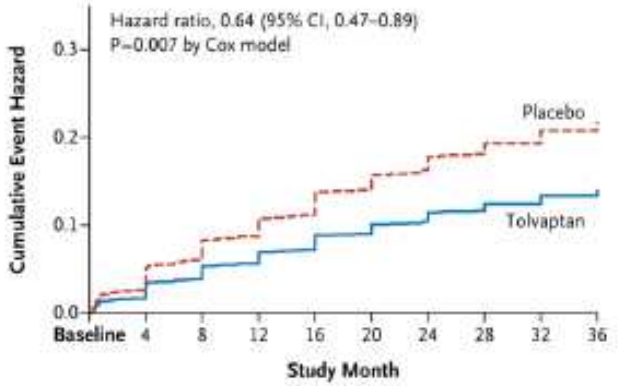
No. at Risk										
Tolvaptan	961	870	835	811	792	776	763	752	744	642
Placebo	483	472	463	454	446	438	428	422	418	359

C 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

D Risk of Clinically Significant Kidney Pain



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Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease Torres V E. et al 2012

Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease
Torres V E. et 2012

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Avventi avversi e anomalie di laboratorio

	Tolvaptan (n 961) %	Placebo (n 483)%
Any adverse event	97.9	97.1
Any serious adverse event	18.4	19.7
AEs >10% and significantly more common in Tolvaptan group		
Thirst	55.3	20.5
Polyuria	38.3	17.2
Nocturia	29.1	13.0
Pollakiuria	23.2	5.4
AEs >10% and significantly more common in Tolvaptan group		
Pain renal	27.0	35.0
Haematuria	7.8	14.1
Urinary tract infection	8.3	12.6
Elevated laboratory values at any visit		
Serum sodium > 150 mEq/l	4.0	1.4
Serum uric acid > 7.5 mg/dl	6.2	1.7
ALT or AST 3 x	4.7	1.7
ALT or AST 5 x	2.4	0.6

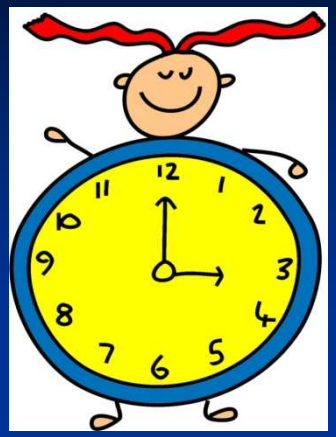
Review of Tolvaptan for Autosomal Dominant Polycystic Kidney Disease

Brian P. Baur and Calvin J. Meaney*
University at Buffalo School of Pharmacy and Pharmaceutical Sciences, Buffalo, New York

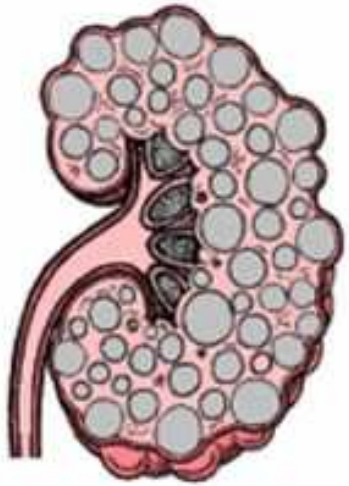
Table 2. Comparison of Adverse Events of Tolvaptan and Placebo during Two Large Clinical Trials[57, 58, 62]

Adverse event	Tolvaptan TEMPO 2:4[a] (n=63)[57]	Tolvaptan TEMPO 3:4[b] (n=961)[58, 62]	Placebo TEMPO 3:4 (n=483)[52, 62]
Aquaresis-related effects			
Thirst	33 (52.4)	531 (55.3)[c]	99 (20.5)
Polydipsia	NA	100 (10.4)[c]	17 (3.5)
Dry mouth	3 (4.8)	154 (16.0)	59 (12.2)
Dehydration	5 (7.9)	18 (1.9)	11 (2.3)
Renal system			
Kidney pain	19 (30.2)	259 (27.0)[c]	169 (35.0)
UTI	10 (15.9)	80 (8.3)[c]	61 (12.6)
Pollakiuria (frequent urination)	26 (41.3)	223 (23.2)[c]	26 (5.4)
Polyuria	15 (23.8)	368 (38.3)[c]	83 (17.2)
Nocturia	14 (22.2)	280 (29.1)[c]	63 (13.0)
Gastrointestinal system			
Elevated AST	NA	36 (3.7)	16 (3.3)
Elevated ALT	2 (3.2)	39 (4.1)	17 (3.5)
Constipation	6 (9.5)	81 (8.4)[c]	12 (2.5)
Diarrhea	11 (17.5)	128 (13.3)	53 (11.0)
Nausea	6 (9.5)	98 (10.2)	57 (11.8)
Miscellaneous adverse effects			
Back pain	11 (17.5)	132 (13.7)	88 (18.2)
Headache	13 (20.6)	240 (25.0)	120 (24.8)
Fatigue	15 (23.8)	131 (13.6)[c]	47 (9.7)
Hypertension	13 (20.6)	309 (32.2)	174 (36.0)
Increased uric acid/hyperuricemia	8 (12.7)	37 (3.9)[c]	9 (1.9)
Gout	NA	28 (2.9)	7 (1.4)

TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes)



ADPKD E Tolvaptan



TEMPO 2:4

TEMPO 3:4

TEMPO 4:4

2006 - 2007 2010 - 2011 - 2012 2016

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Phase 3, multi-center, open-label, extension study to evaluate the long-term efficacy and safety of oral tolvaptan tablet regimens in subjects with ADPKD

Study Start Date: May 2010

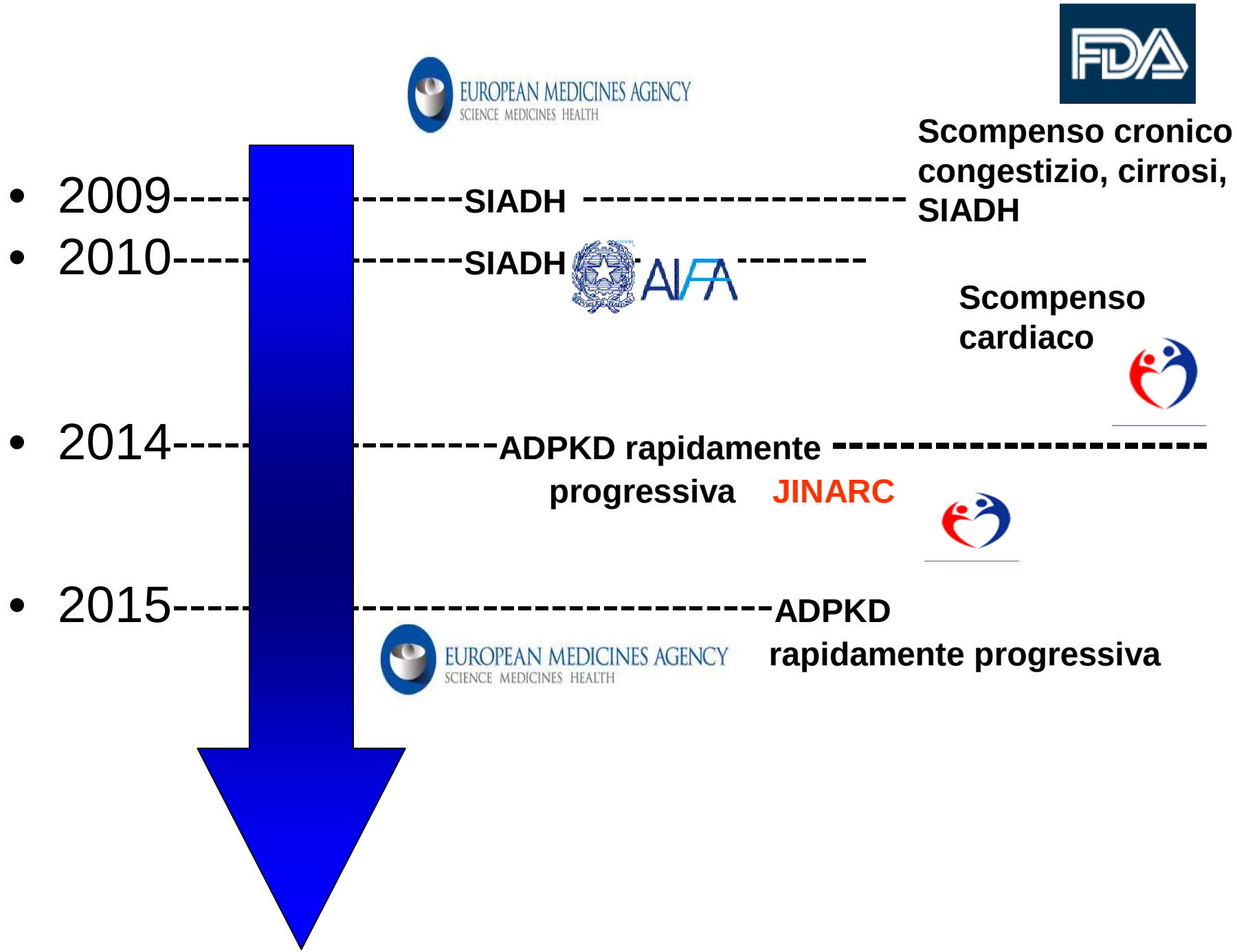
Estimated study completation date: March 2016

Primary outcome:

Percent Change in Total Kidney Volume (TKV): for subjects continuing from protocol 156-04-251: change from 251 baseline TKV at month 24 of 156-08-271 comparing those previously treated with tolvaptan to those previously treated with placebo

Secondary outcome:

- **Change in Estimated Glomerular Filtration Rate (**eGFR) For subjects randomized to tolvaptan and placebo in 156-04-251 and enrolled and treated in 156-08-271 as early treated and delayed treatment groups: change from 251 baseline eGFR at month 24 of 156-08-271
- **Slope of Total Kidney Value (TKV)** For subjects randomized to tolvaptan and placebo in 156-04-251 and enrolled and treated in 156-08-271 as early treated and delayed treatment groups
- **Slope of eGFR (CKD-EPI)** For subjects randomized to tolvaptan and placebo in 156-04-251 and enrolled and treated in 156-08-271 as early treated and delayed treatment groups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SCIENCE MEDICINES HEALTH
FDA
Scompenso cronico congestizio, cirrosi, SIADH
2009
SIADH
2010
SIADH
AIFA
Scompenso cardiaco
2014
ADPKD rapidamente progressiva
JINARC
2015
ADPKD rapidamente progressiva
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Tolvaptan

Assorbimento

- Rapido assorbimento dopo somministrazione orale
- Biodisponibilità 56%
- Picco plasmatico dopo 2 h
- Emivita 8 h

Distribuzione

legato (99%) a proteine plasmatiche

Metabolismo

- prevalentemente a livello epatico CYP3A 4/5

Escrezione

-99% fecale

Tolvaptan: dosaggio del protocollo

Tolvaptan viene somministrato in due dosi:

-mattina (dosaggio maggiore)

-pomeriggio (circa 8 h) dosaggio minore (favorire il riposo notturno del paziente)

Dosaggio iniziale → 45 mg/15 mg

Aumento successivo → 60 mg/30 mg

Dose target → 90 mg/30 mg

Intervallo di aumento → almeno 1 settimana

Ulteriori suggerimenti

- Counselling sul tipo di fluidi per compensare la poliuria con calcolo delle calorie
- Evitare diuretici per rischio di alterazioni elettrolitiche
- Sconsigliato l'uso in gravidanza

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JINARC (TOLVAPTAN)

- Rallentare [illegible] isti e dell'insuffi

- In adulti c [illegible] ento con evidenza [illegible] ***gressiva…***

Non necessarie modificazioni con insufficienza renale o epatica di grado lieve-moderato

limitate informazioni in pazienti con severa disfunzione epatica

informazioni non disponibili in pazienti con clearence della creatinina < 10 ml/min

European Medic ines A gency, 2015.

…malattia rapidamente progressiva…

Non esiste una definizione universalmente accettata di “ADPKD rapidamente progressiva”

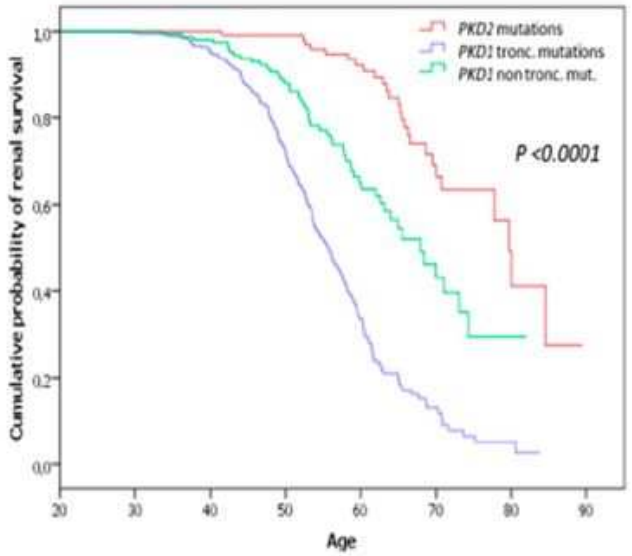
Criteri … MPO potrebb…

Elevated TKV, particularly when used together with age and kidney function, identifies individuals who are at-risk for progression to ESRD
AB Chapman et al.: ADPKD: A KDIGO executive summary report
2015 International Society of Nephrology

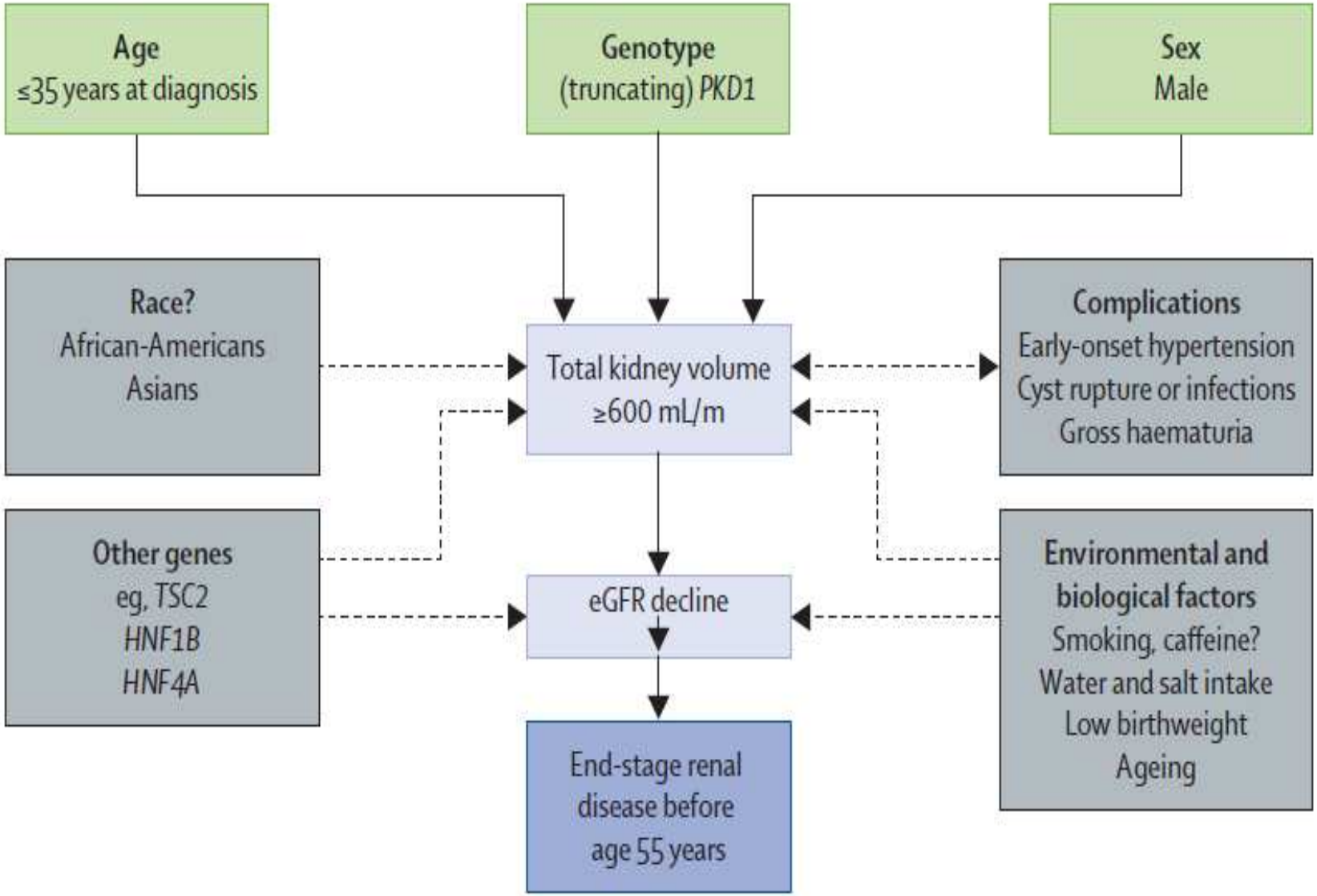
- **Età (18-50 anni)**
- **GFR (Cockroft-Gault)≥60 ml/min**
- **TKV ≥750 ml**

ADPKD - Autosomal Dominant Polycystic Kidney Disease

Genotype-Phenotype correlation in ADPKD opens new perspectives for therapy

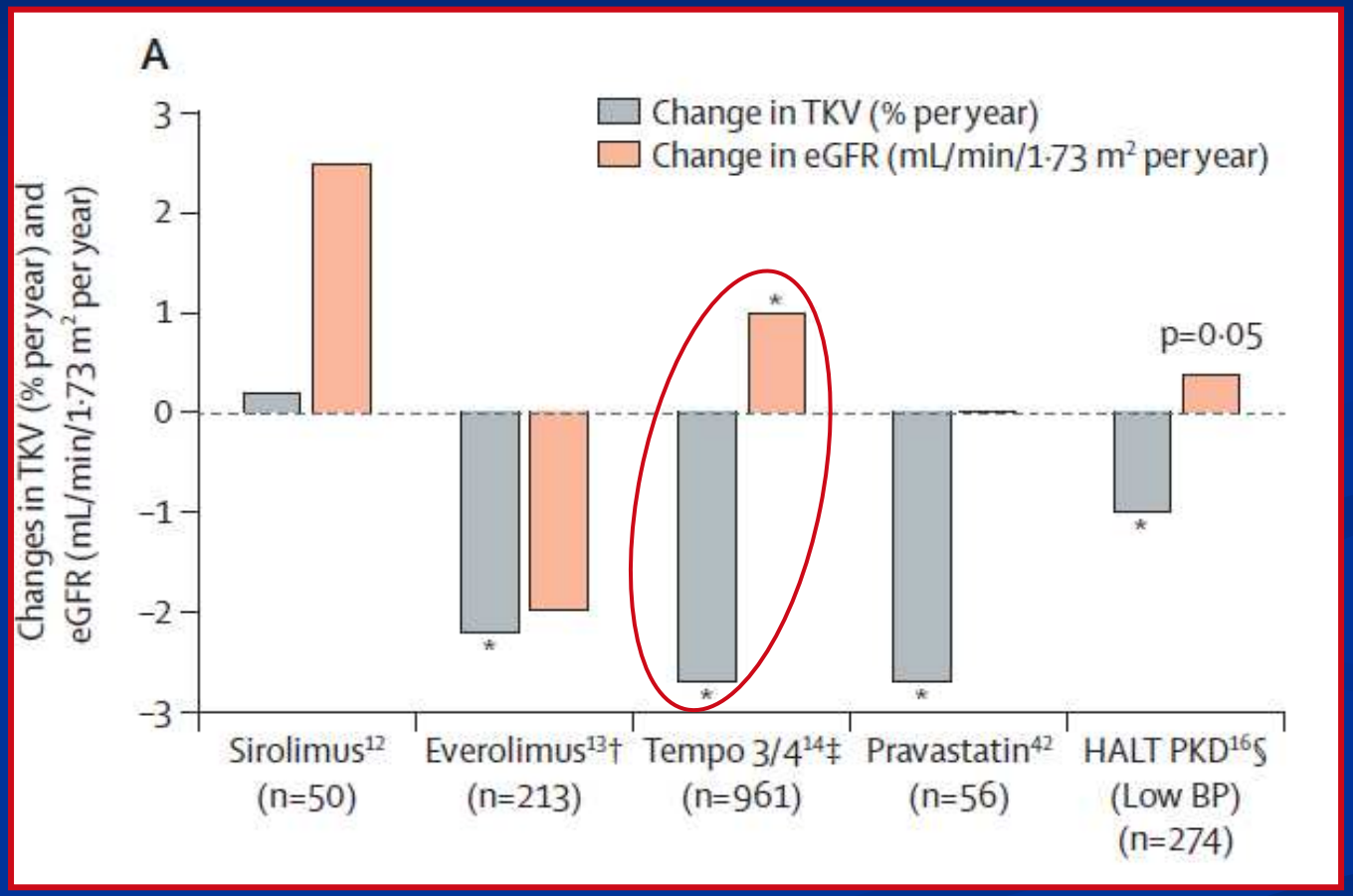


Cornec-Le Gall et al, *J Am Soc Nephrol*, 2013

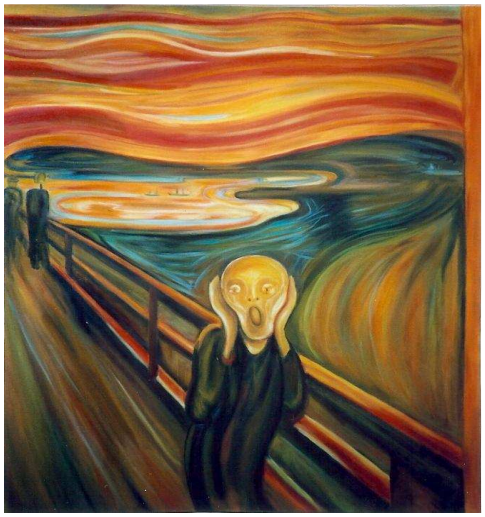


Ong A.C.M et al. The Lancet 2015

Ong A.C.M et al. The Lancet 2015



… Quanto costa?



Sirolimus **(RAPAMUNE)**

- dose di 5 mg/die
- 1 mg 100 cpr 611.41 €
- Costo annuale 11158,23 €

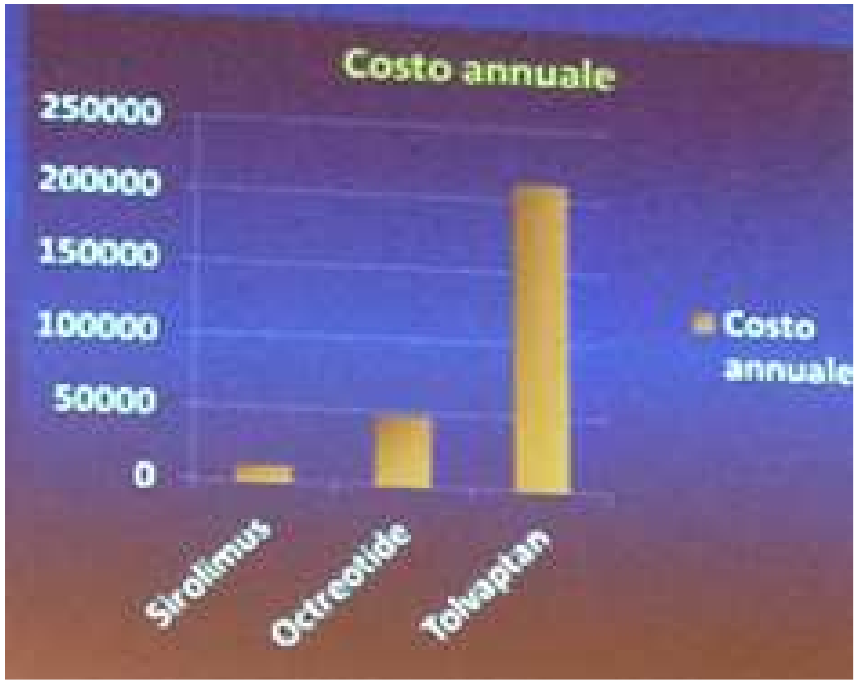
Octreotide (**SANDOSTATINA)**

- dose di 40 mg/mese
- IV sc fl 1mg 5 ml 99.96 €
- Costo annuale 47980.8 €

Tolvaptan **(SAMSCA)**

- Dose di 90 mg die
- 10 cpr 30 mg 1936 €

Costo annuale: 211992 €



… alcune domande che restano…

- Quando iniziare la terapia?
- Per quanto tempo protrarre la terapia?
- Quando sospendere la terapia?
- Dopo la sospensione permangono gli effetti del farmaco?
- L’impatto sull’ESRD?
- E sulla mortalità?

Storari A.