A Novel Therapeutic Strategy of ADPKD

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A Novel Therapeutic Strategy of ADPKD

EPIDEMIOLOGY OF ADPKD

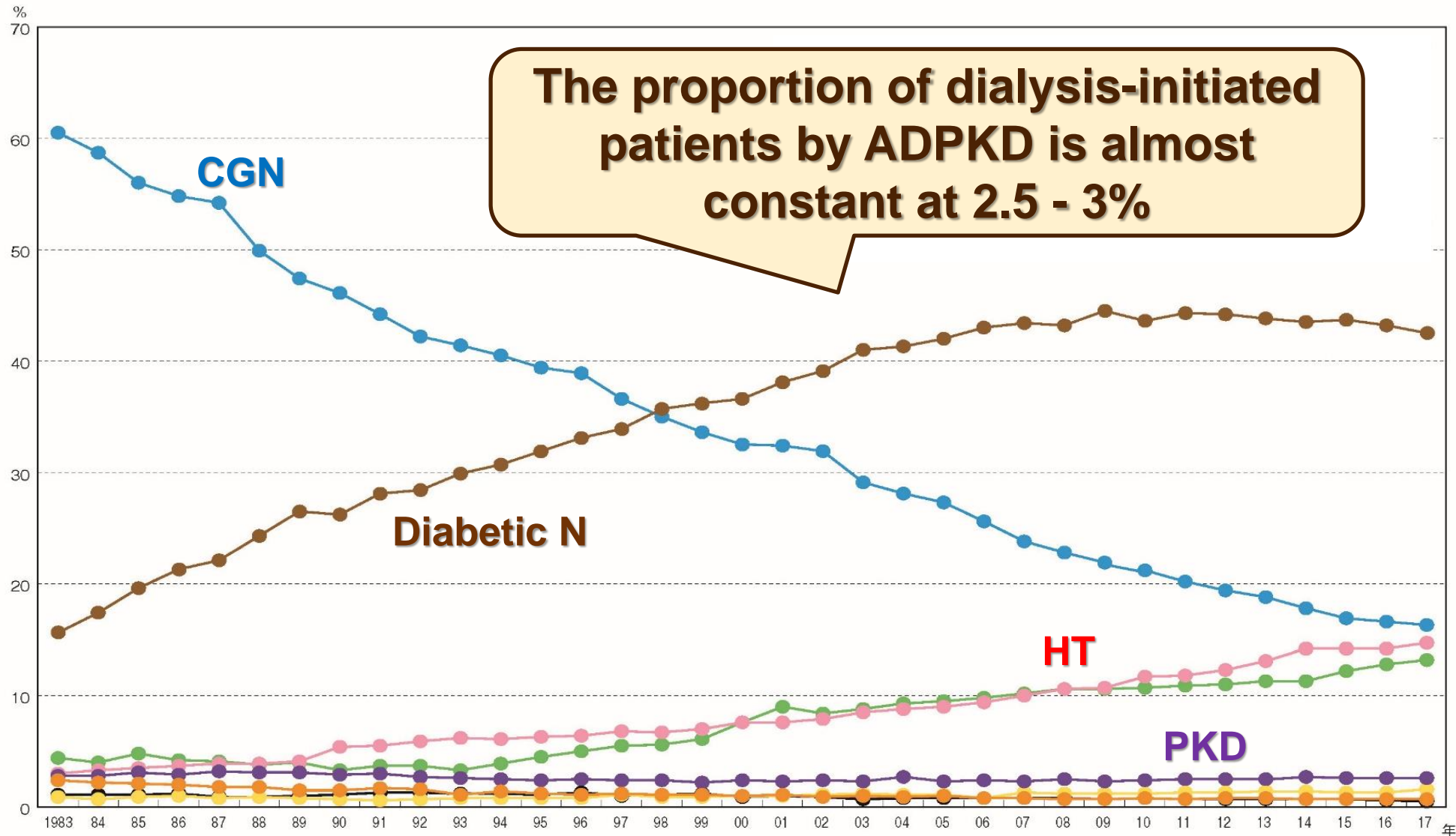# Autosomal Dominant Polycystic Kidney Disease : ADPKD

ADPKD is the most common hereditary renal disorder. Under ADPKD, multiple renal cysts are progressively developed and enlarged in both kidneys. As the cysts increase and enlarge, the renal function progressively deteriorates.

http://www.pkdfcj.org/pkd_2-1.html
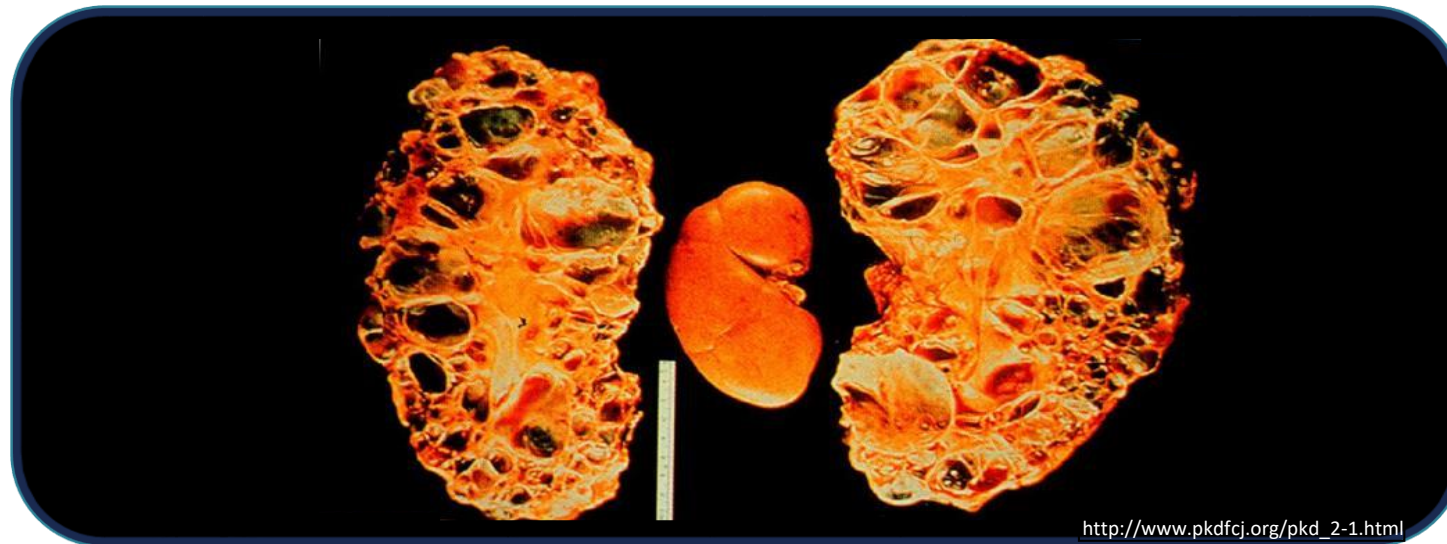
Estimated number of ADPKD patients is approximately 31,000 in Japan

85% of patients have abnormality in *PKD1* gene (code for polycystin 1),

and 15% of patients have abnormality in *PKD2* gene (code for polycystin 2)
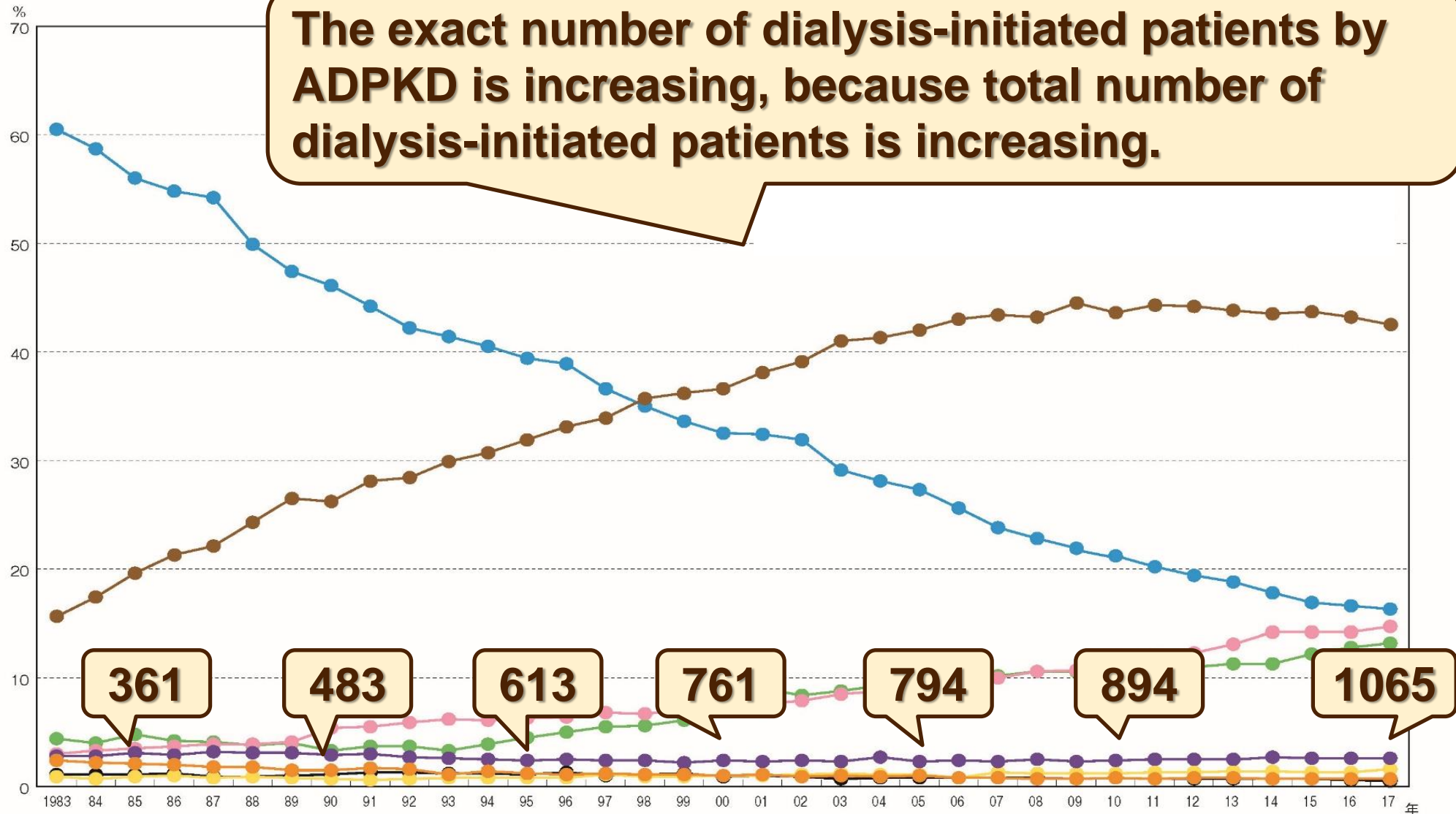
Primary disease in dialysis-initiated patients
-Source: The Japanese Society for Dialysis Therapy Website-

The proportion of dialysis-initiated patients by ADPKD is almost constant at 2.5 - 3%

CGN

Diabetic N

HT

PKD

Primary disease in dialysis-initiated patients

The exact number of dialysis-initiated patients by ADPKD is increasing, because total number of dialysis-initiated patients is increasing.
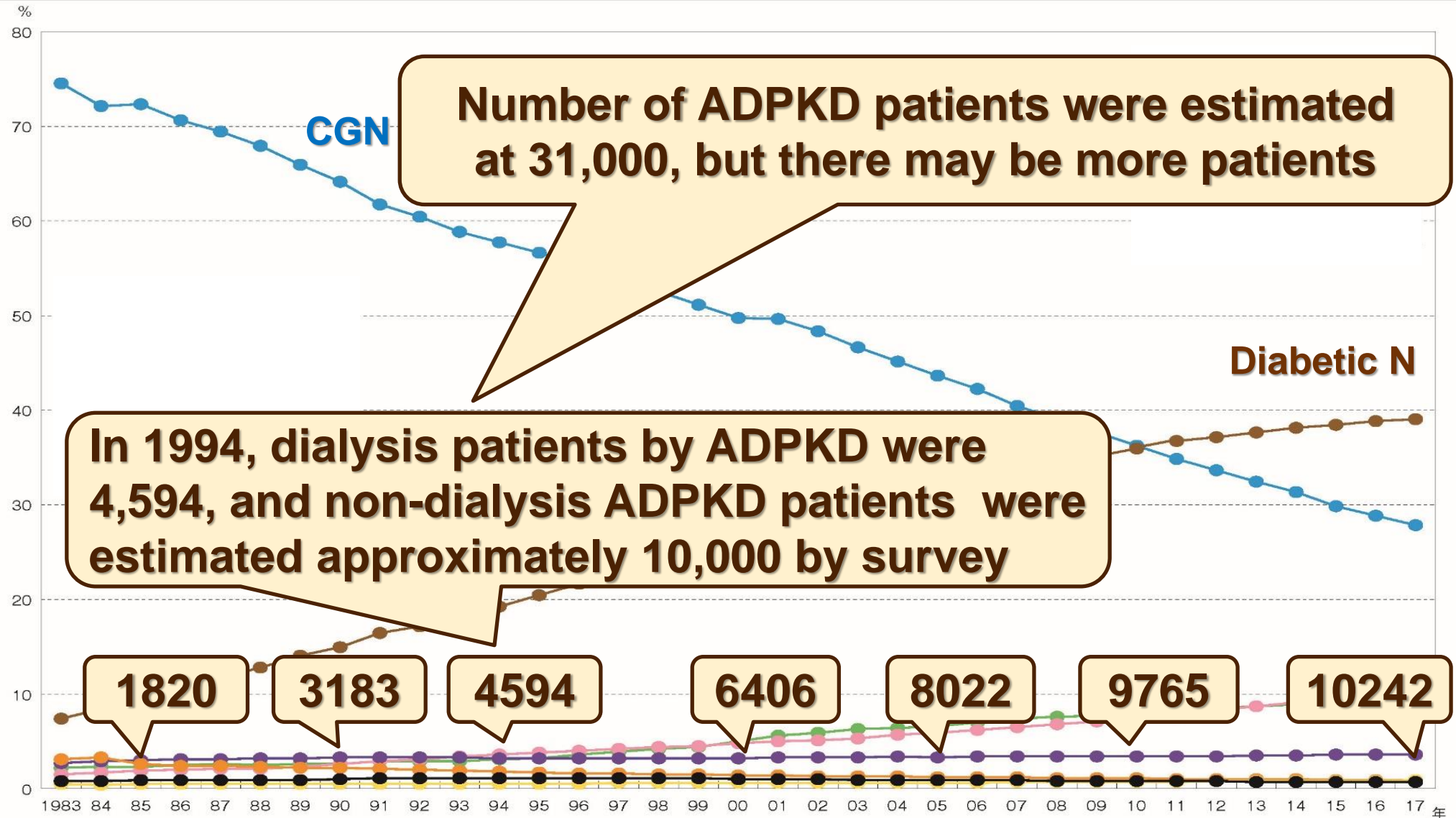
Primary diseases of total dialysis patients
-Source: The Japanese Society for Dialysis Therapy Website-

# Primary diseases of total dialysis patients are similar in Korea

| Causes	199_														2017
Chronic Glomerulonephritis	25._														7.5
Not Histologically confirmed	19._														3.7
Histologically confirmed	5.6														3.8
Diabetic nephropathy	19.5	26.1	30.8	38.9	4_._		43.4	42.3	41.9	45.2	50.6	48.0	48.4	50.2	48.9
Hypertensive nephrosclerosis	15.4	20.8	18.3	17.8	16.6	16	16.2	16.9	18.7	19.2	18.5	21.2	20.2	20.3	21.4
Cystic kidney disease	2.1	2.2	1.8	1.7	2.2	1.6	1.4	1.7	1.7	1.7	1.8	1.8	1.9	1.5	1.7
Renal tuberculosis	1.1	1.5	1.2	0.5	0.4	0.5	0.3	0.3	0.2	0.2	0.0	0.1	0.1	0.1	0.0
Pyelo/interstitial nephritis	1.3	1.1	0.7	1.0	0.8	0.6	0.6	0.6	0.5	0.4	0.5	0.8	0.3	0.4	0.5
Drugs or nephrotoxic agents	1.3	0.1	0.6	0.3	0.3	0.4	0.2	0.3	0.3	0.3	0.4	0.2	0.6	0.3	0.3
Lupus nephritis	0.8	0.7	1.0	0.5	0.9	0.8	0.6	0.6	0.6	0.5	0.6	0.5	0.3	0.5	0.5
Gouty nephropathy	0.7	0.7	0.6	0.5	0.7	0.4	0.5	0.3	0.3	0.4	0.3	0.3	0.4	0.3	0.2
Hereditary nephropathy	0.3	0.7	0.4	0.2	0.1	0.2	0.3	0.3	0.3	0.2	0.5	0.5	0.4	0.5	0.4
Kidney tumor	0.1	0.1	0.2	0.2	0.2	0.3	0.3	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.5
Other	4.1	2.7	2.8	3.9	3.0	5.6	5.9	6.0	5.8	5.1	6.8	6.1	6.3	5.5	5.9
Uncertain	28.6	17.8	15.9	16.6	20.2	19	17.8	17.5	17.6	15.3	11.4	12.1	12.3	11.7	12.1

Total number of new dialysis patients is also increasing in Korea.
The number of new dialysis patients by ADPKD is increasing.

Is ADPKD patients increasing?
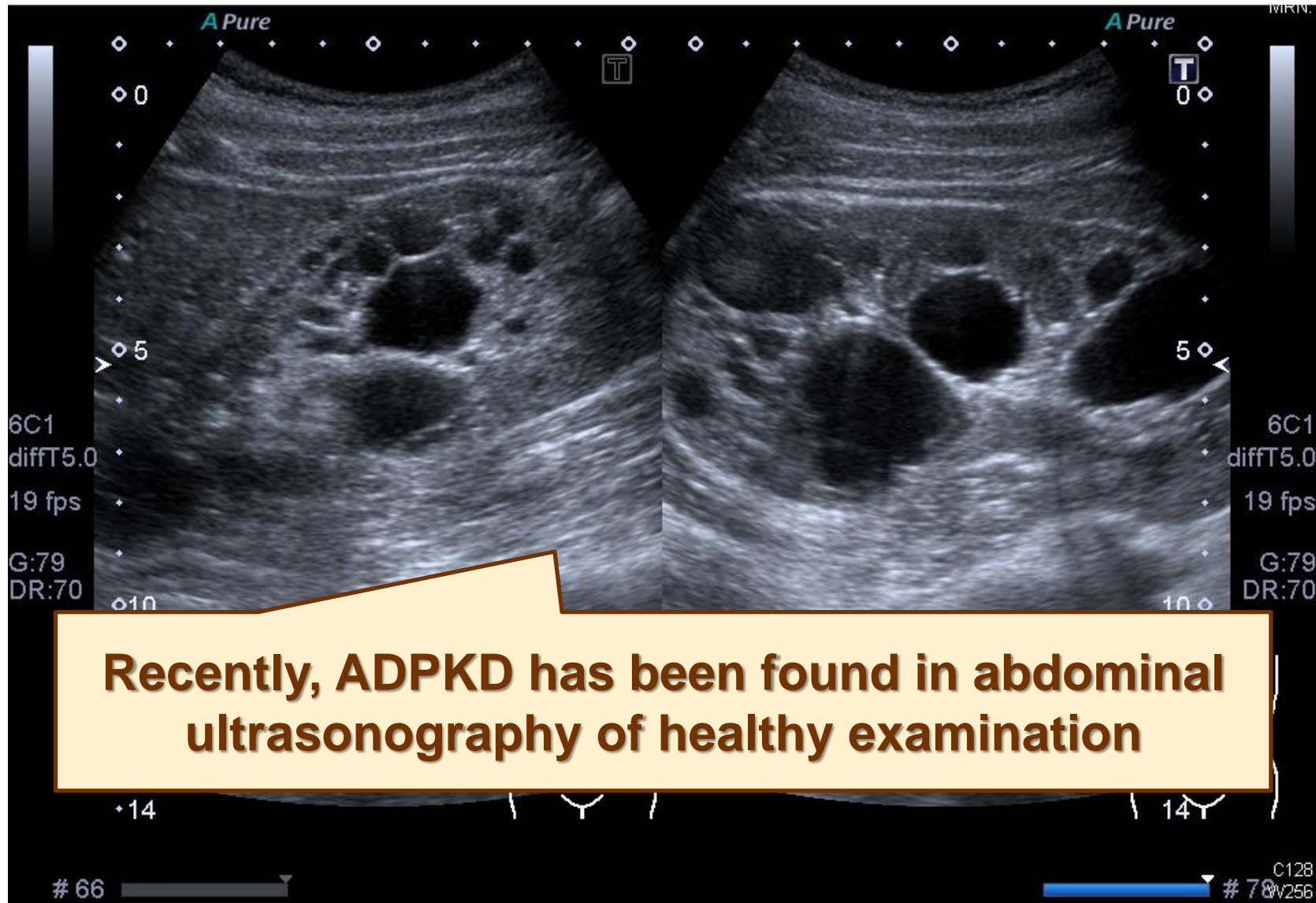
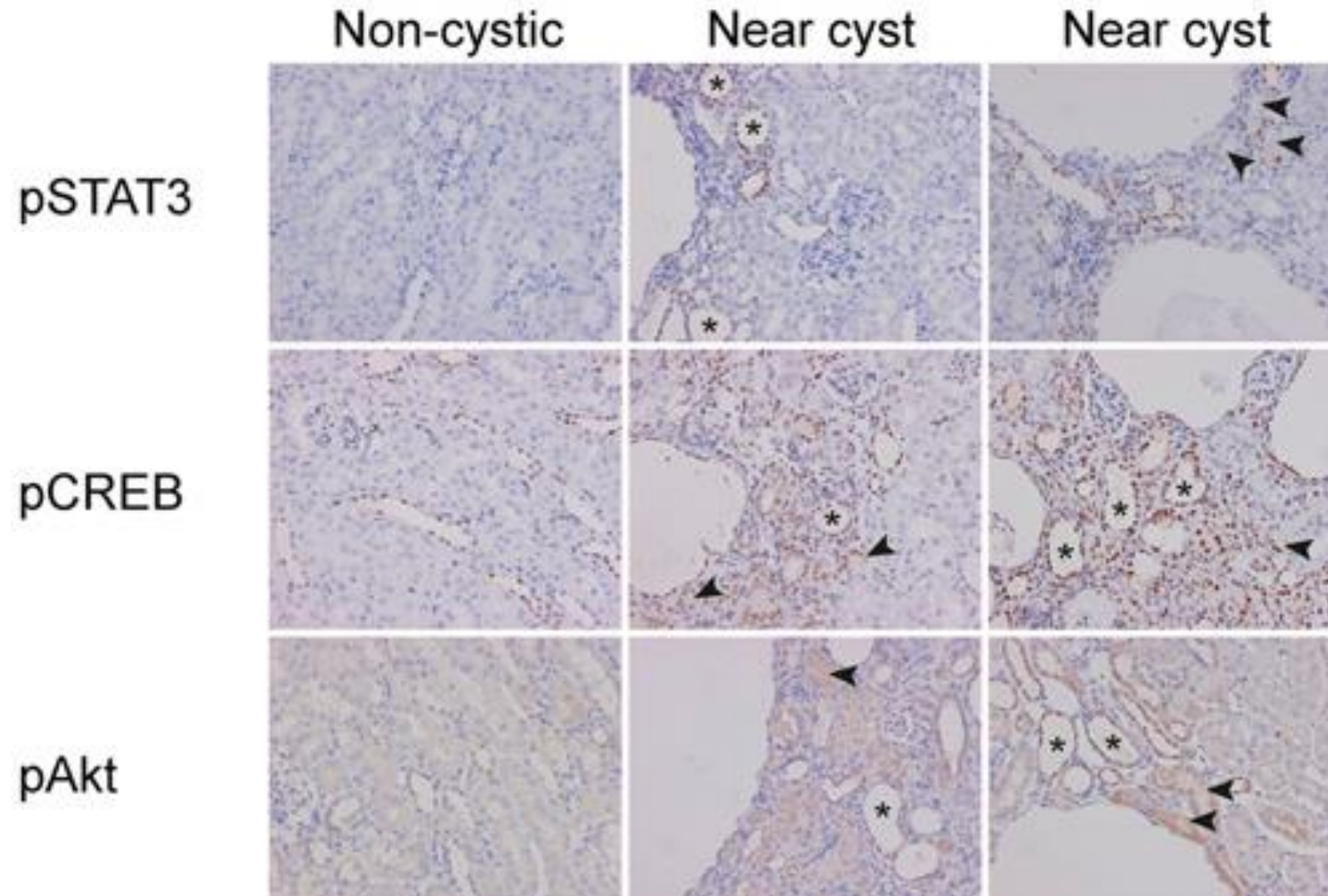
Recently, ADPKD has been found in abdominal ultrasonography of healthy examination

CT or MRI is preferable for the diagnosis of ADPKD

Cluster-shaped cysts are frequently observed
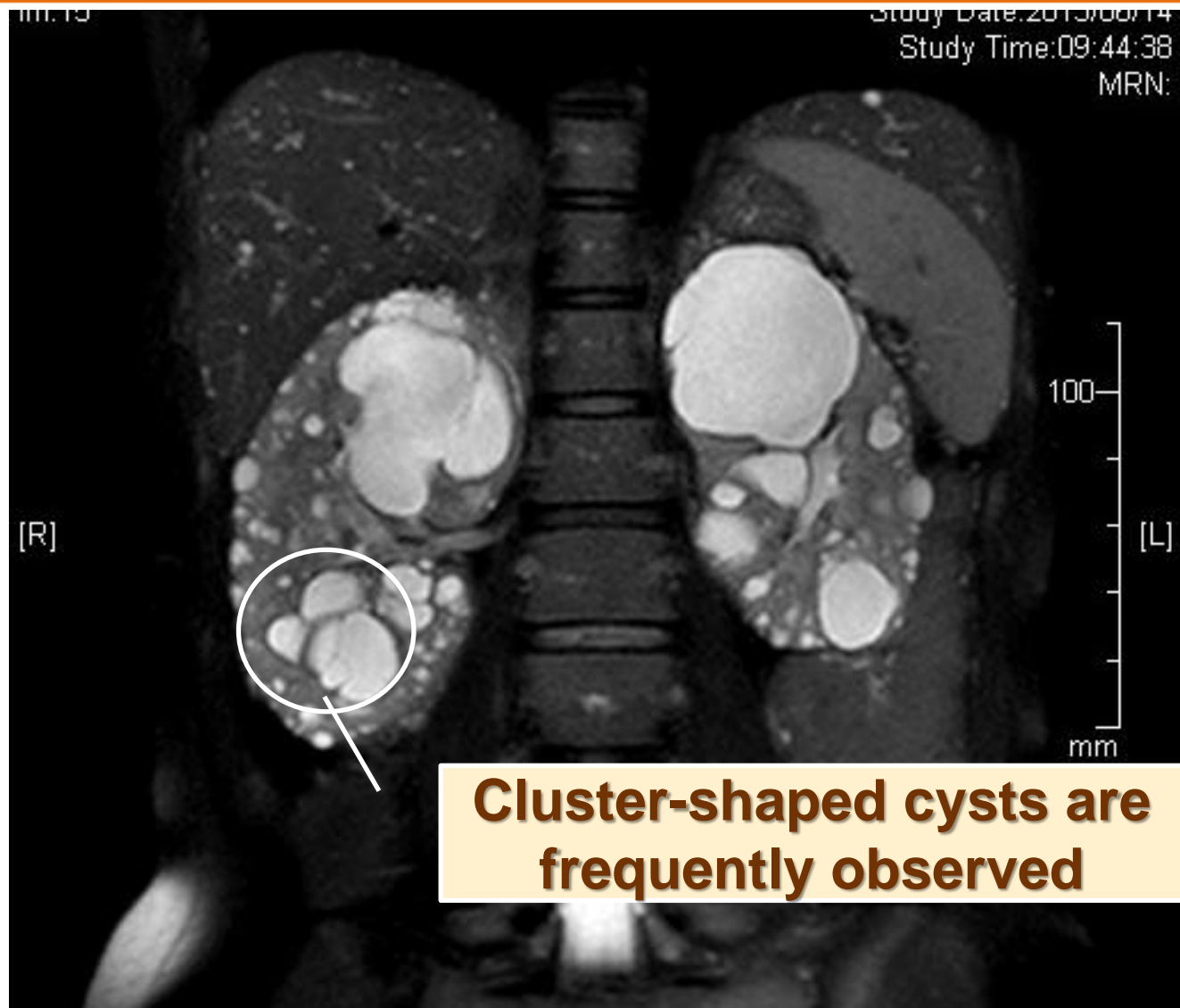
Cell transformation takes place around the cysts in ADPKD.
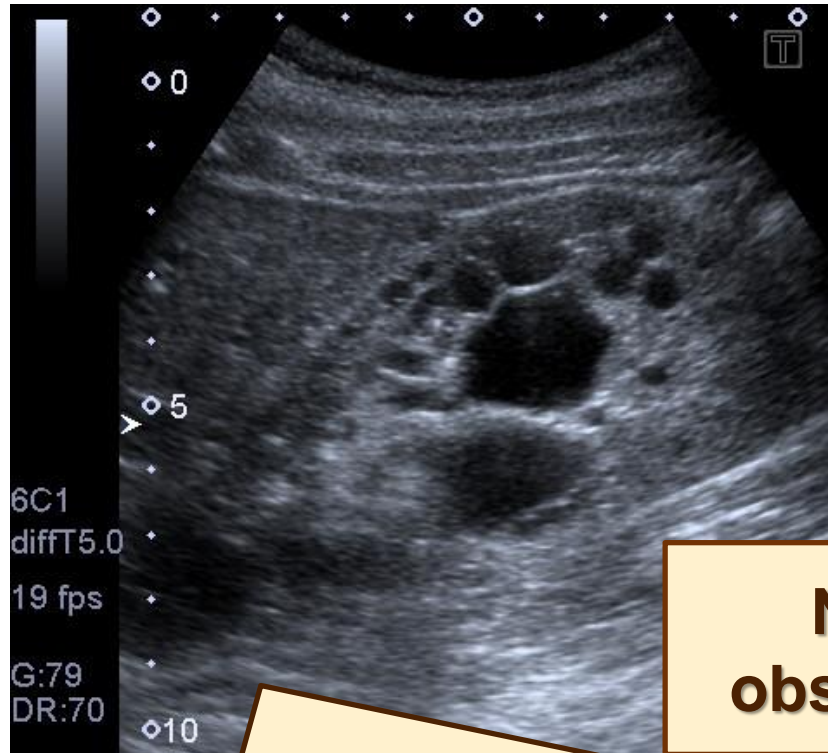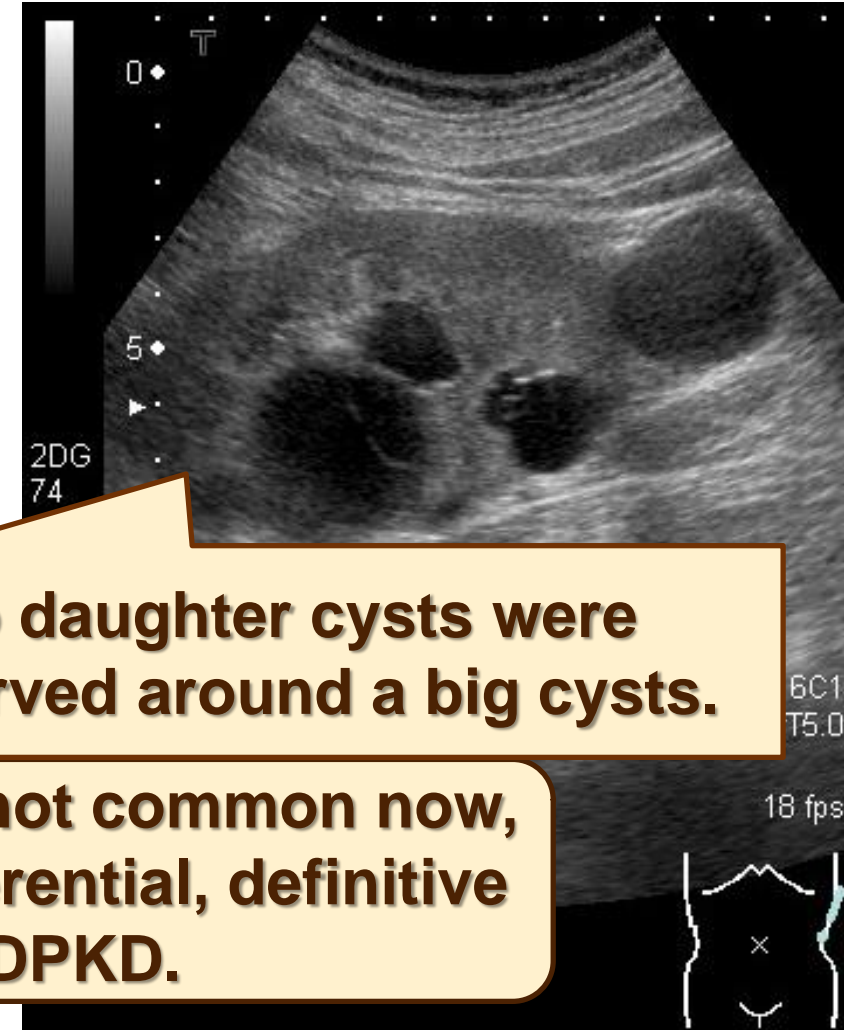
Differential diagnosis between ADPKD and multiple simple cysts is not easy

ADPKD

Multiple simple cysts

No daughter cysts were observed around a big cysts.

Although genetic testing is not common now, it may be necessary for differential, definitive diagnosis or prognosis of ADPKD.

Tips in the treatment of ADPKD patients

ENLARGEMENT OF KIDNEY IN ADPKD PATIENTS

Age and renal function in ADPKD patients

Renal function is stable until the kidney volume has increased up to 4 to 6 times normal size

After significant and irreversible damage occurs, GFR declines

Without compensation

With compensation

(mL/min)

Glomerular Filtration Rate（GFR)

140
120
100
80
60
40
20
0

0   20   30   40   50   60

Age
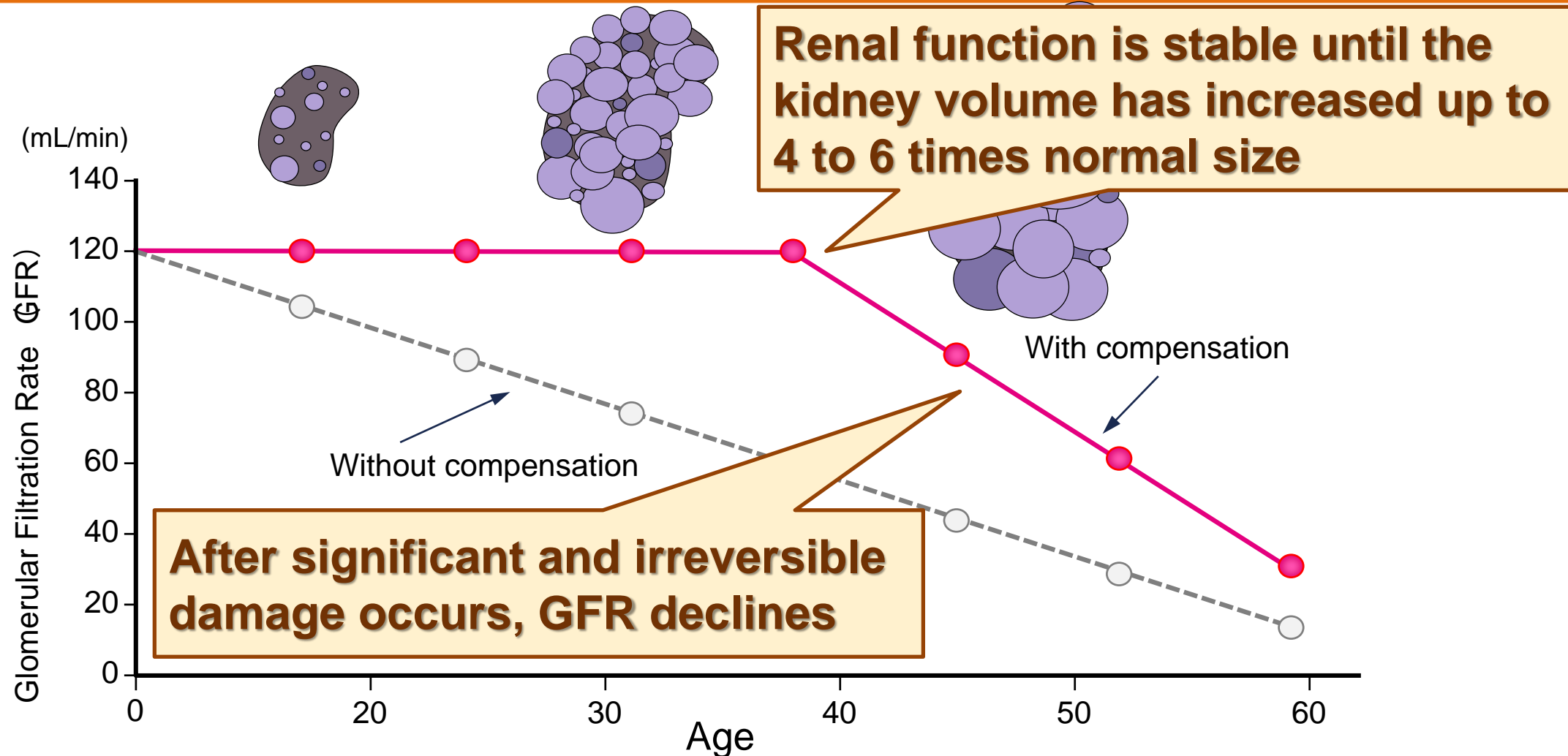
Quoted/re-edited from〔3）Grantham JJ. *et al.*: *Clin J Am Soc Nephrol* 2006: **1**: 148-157〕

Renal size gradually increased, but GFR significantly decreased after 6 years

GFR is maintained for several decades by compensatory glomerular hyperfiltration and tubule hypertrophy.

Existing treatments mainly focused on renal function, urinalysis findings or blood pressure control, but kidney size needs to be checked

htTKV

GFR

55%

-22.3%

htTKV: height adjusted total kidney volume
p<0.05（vs baseline）; # p<0.05（vs baseline）

Chapman A B et al. CJASN 2012;7:479-486

Rate of renal function decline assumed by kidney volume and age

Increase in kidney volume at constant rate per patient (Deterioration of renal function)

Renal function declines at a constant rate
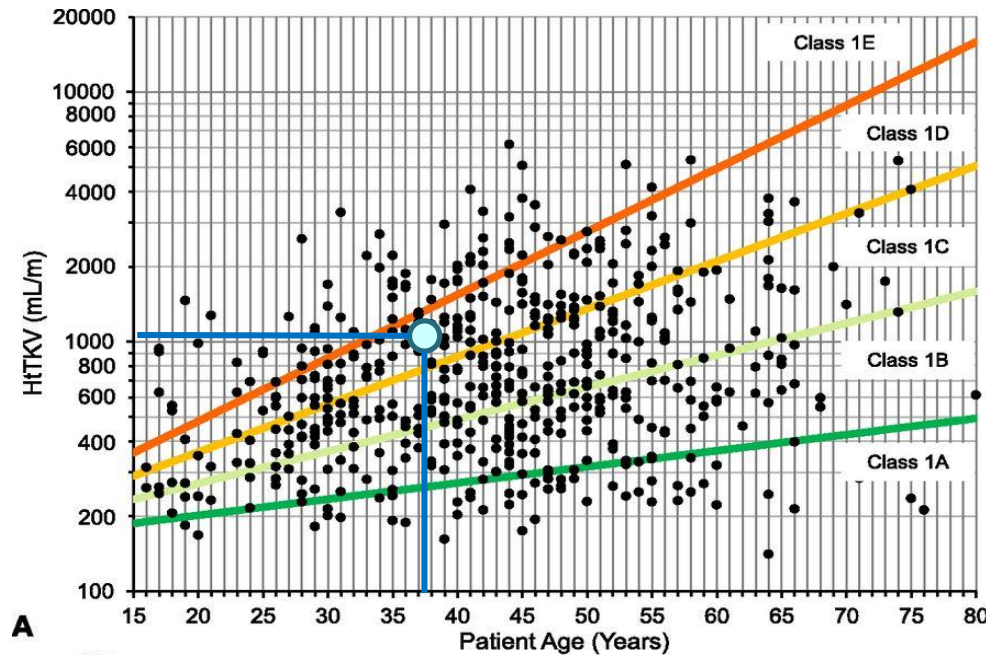
Growth rate of htTKV
<1.5% (class1A)
1.5-3% (class1B)
3-4.5% (class1C)
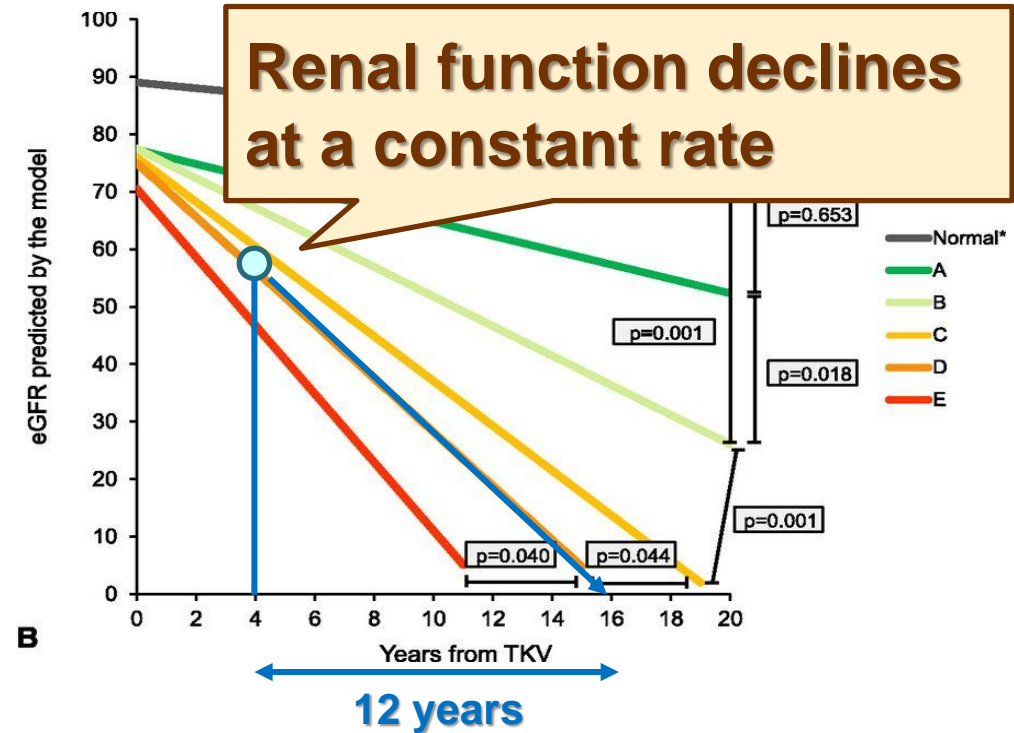4.5-6% (class1D)
≥ 6% (class1E)

12 years

Kidney volume increases at a constant rate for each patient

Irazabal M V et al. JASN 2015;26:160-172

How to Measure Kidney Volume: This is a big deal!!

Integral Calculus
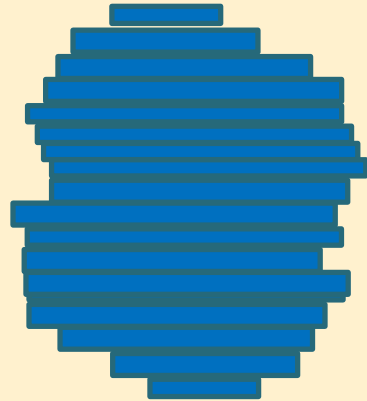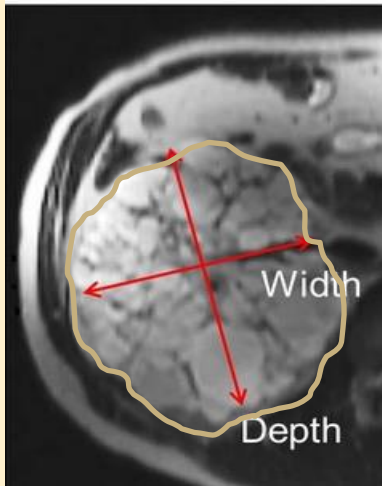
Width

Depth

- Actual calculation method
- ● Require specific software (It costs a lot)

Ellipsoid Method

- ● Calculation is cumbersome
- ● Measurement error is easy to occur
- ● Anyone can calculate

h

V c

a b

Kidney volume=π/6×length×width×depth
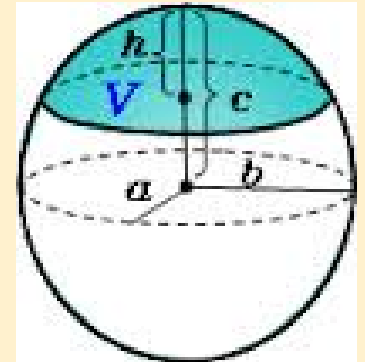
Coronal Length

Width

Depth
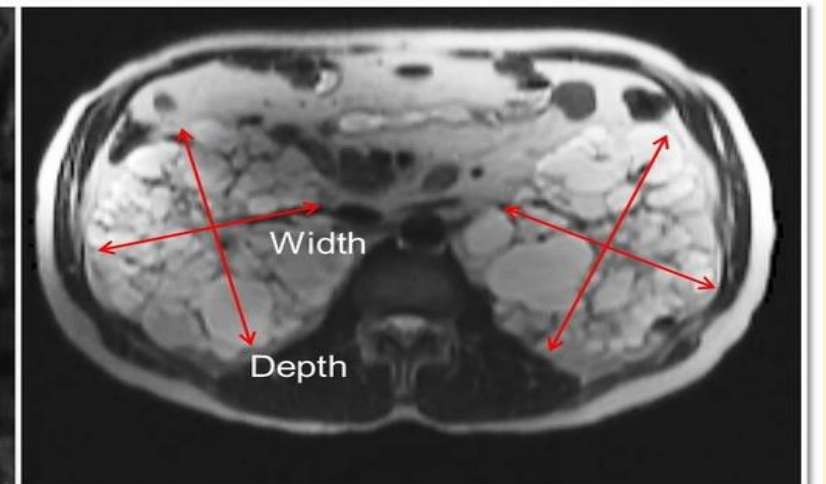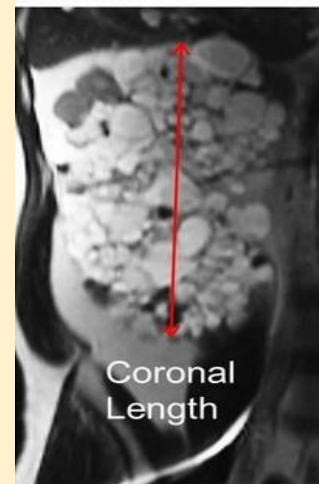
SYNAPSE VINCENT
FujiFilm's 3D Image Analysis Workstation

Extract left and right kidneys automatically from **CT image** to calculate volume.
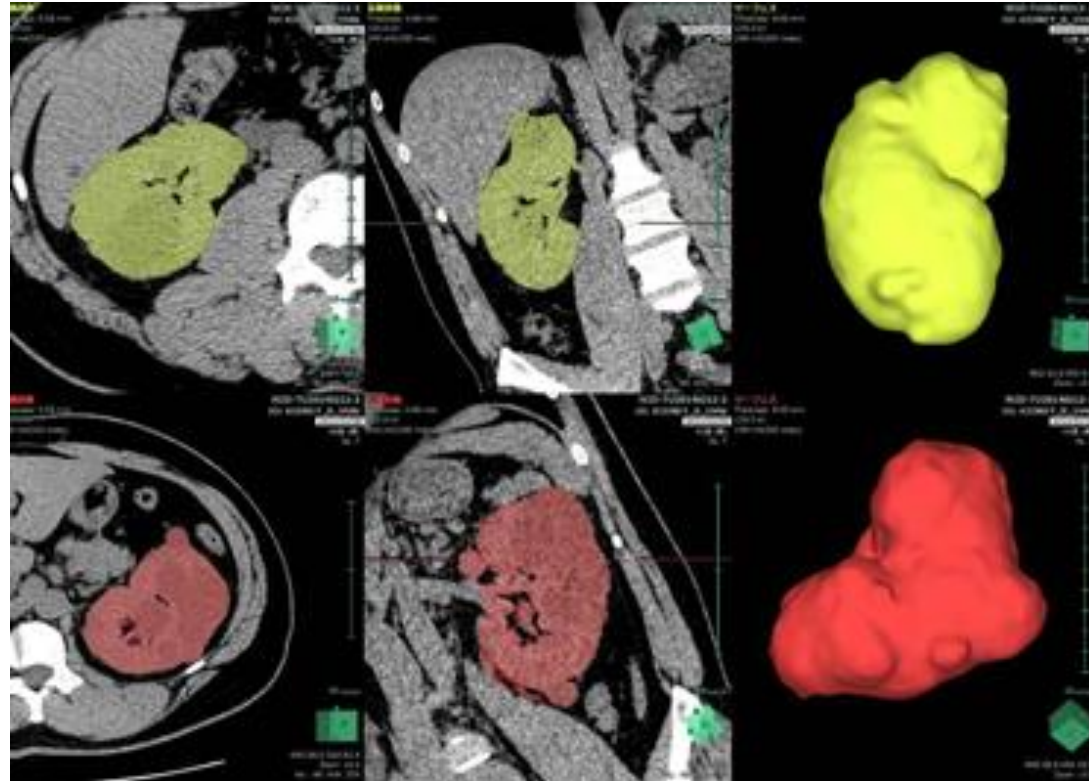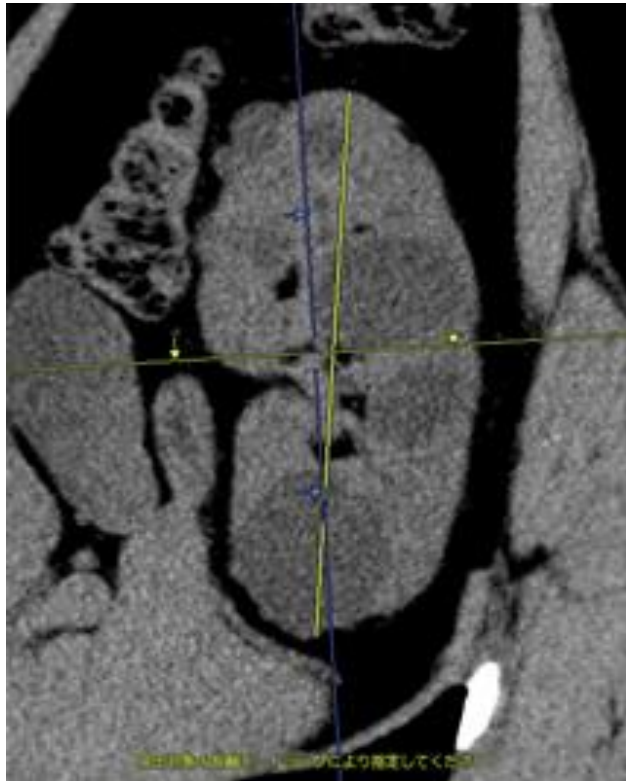
A Novel Therapeutic Strategy of ADPKD

ADH INVOLVEMENT IN ADPKD PATIENTS

Change in Mean age at dialysis-initiation
-Source: The Japanese Society for Dialysis Therapy Website-

total : 68.7 ys
PKD : 62.3 ys

ADPKD

糖尿病性腎症
慢性糸球体腎炎
腎硬化症
多発性囊胞
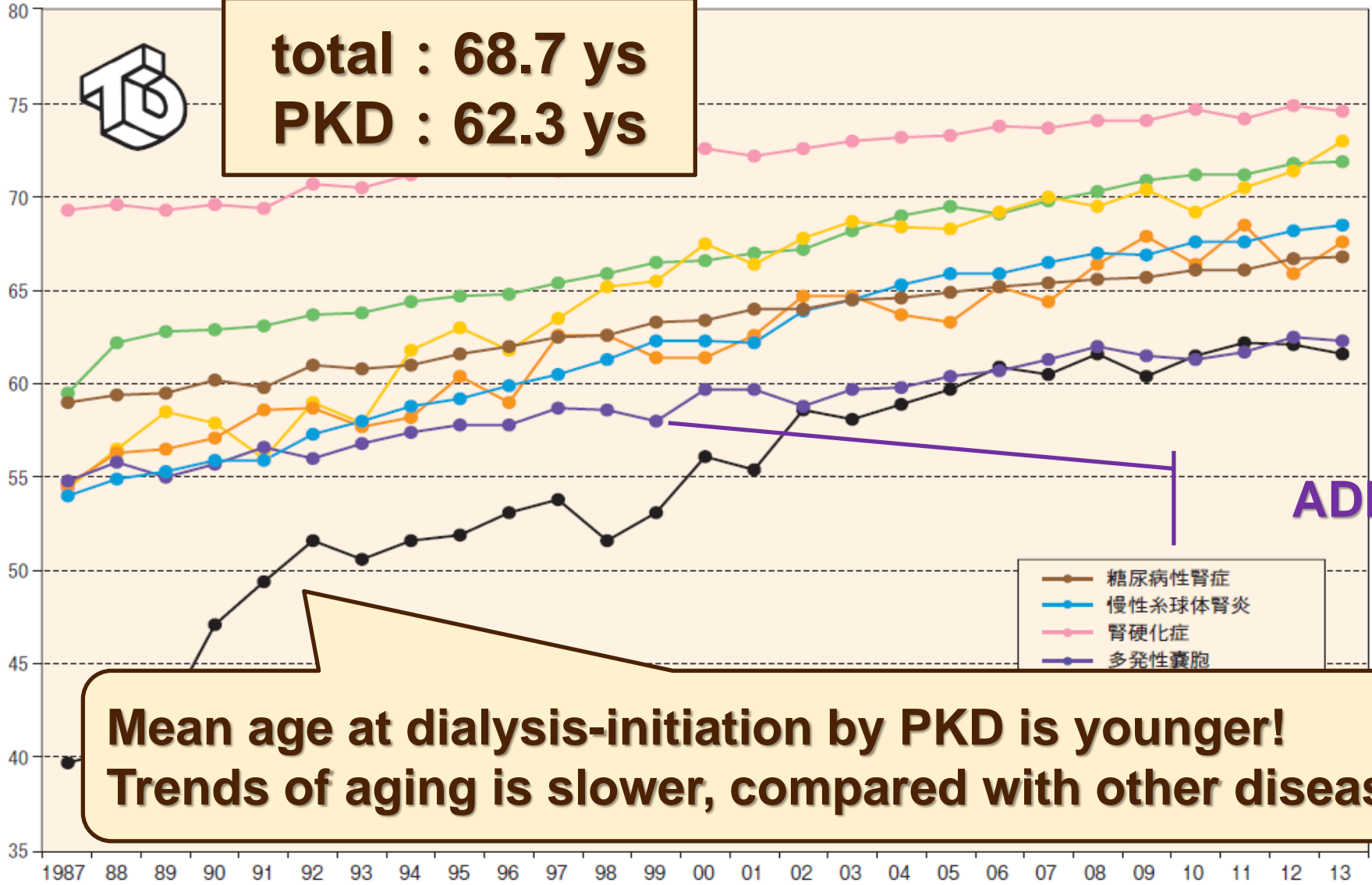
Mean age at dialysis-initiation by PKD is younger!
Trends of aging is slower, compared with other diseases!

Conventional therapy did not delay the start of RRT in ADPKD patients over time in Europe

Incidence of RRT for ADPKD from the ERA-EDTA Registry

Legend:
- 1991–1995
- 1996–2000
- 2001–2005
- 2006–2010

Y-axis: Incidence RRT for ADPKD (p.m.a.r.p.)
X-axis: Age groups (years): 0–4, 5–9, 10–14, 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, ≥85
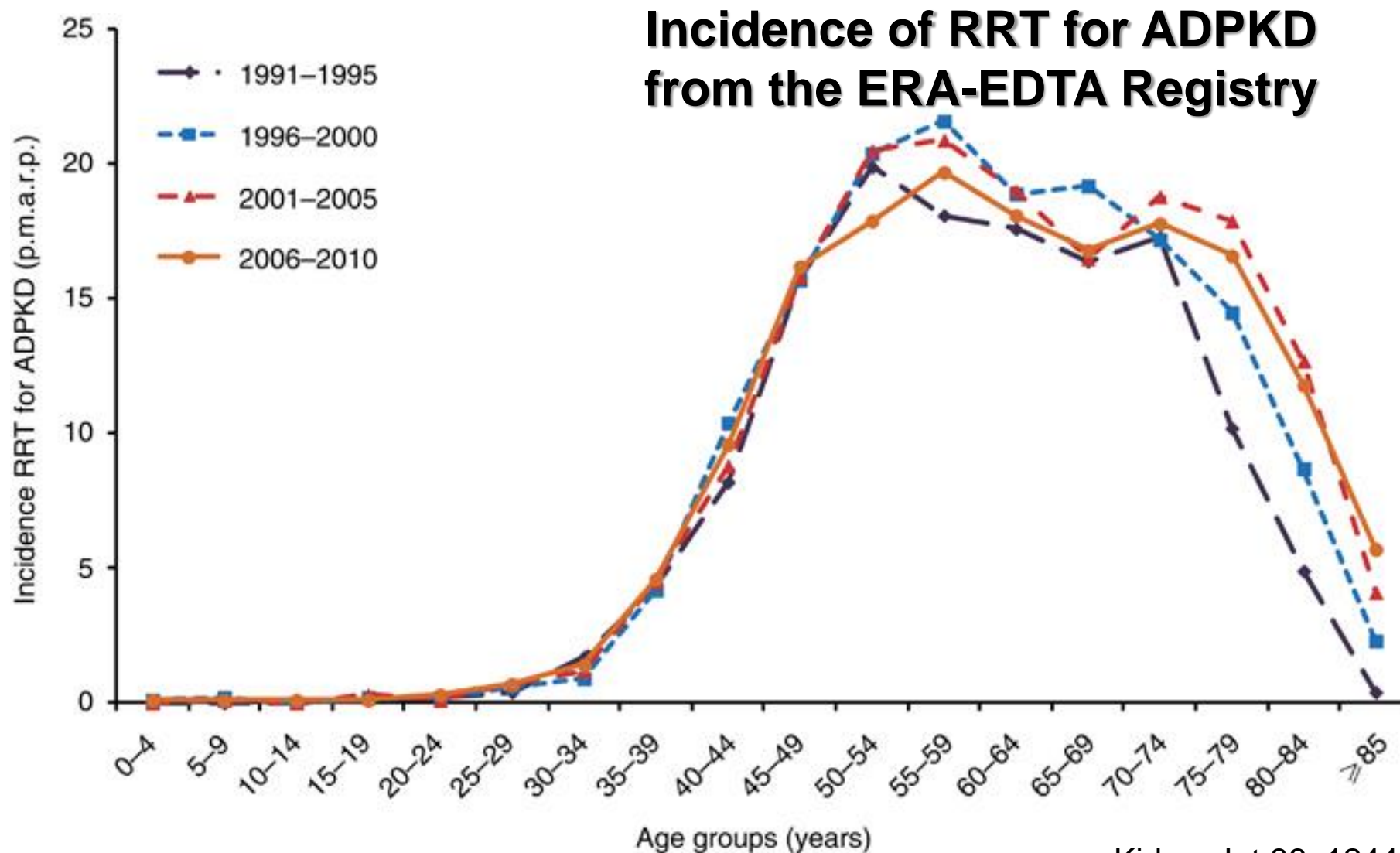
Age-distribution of dialysis-initiated patients in Japan
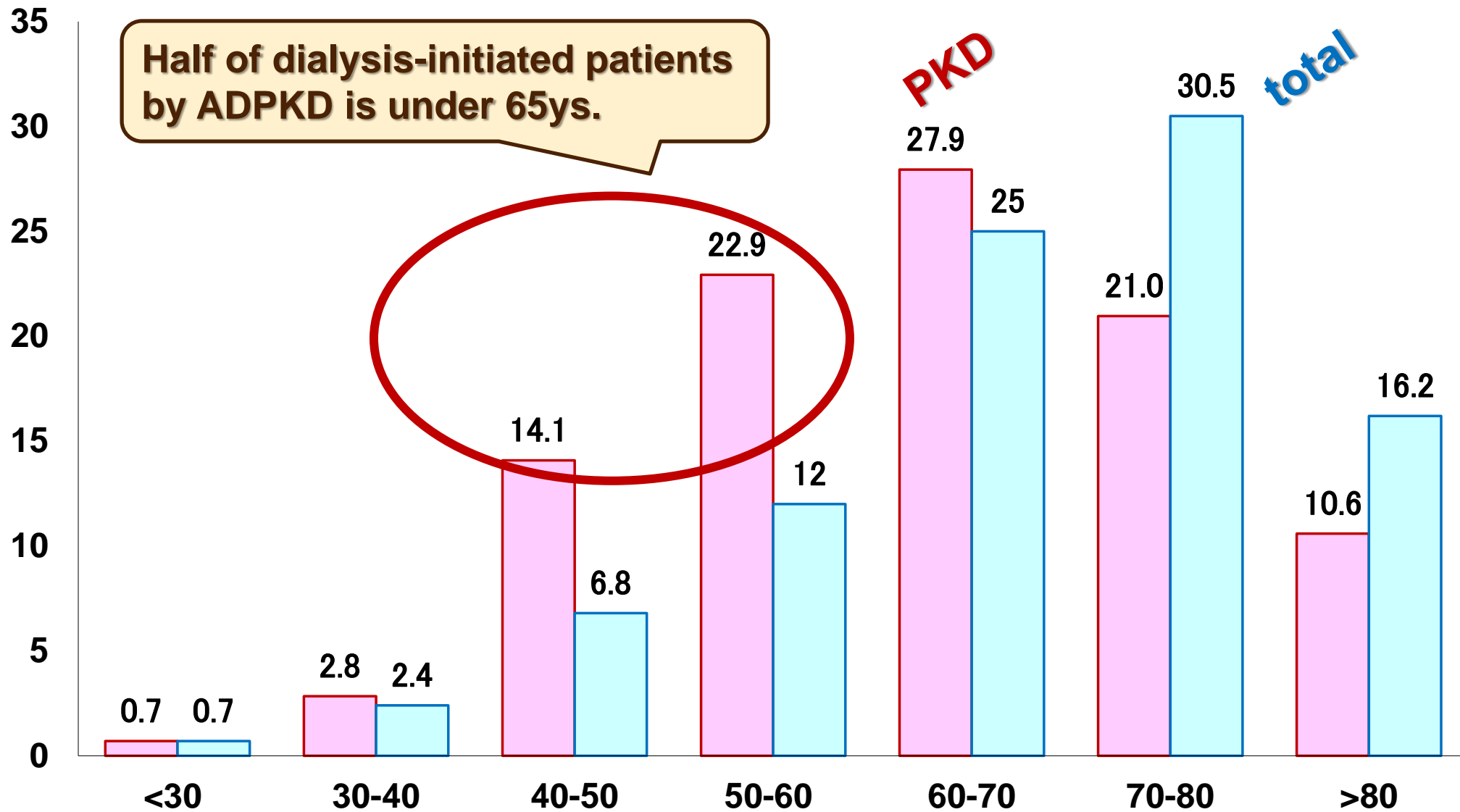
Potential benefit of tolvaptan treatment in delaying RRT

Based on TEMPO 3:4

Based on REPRISE
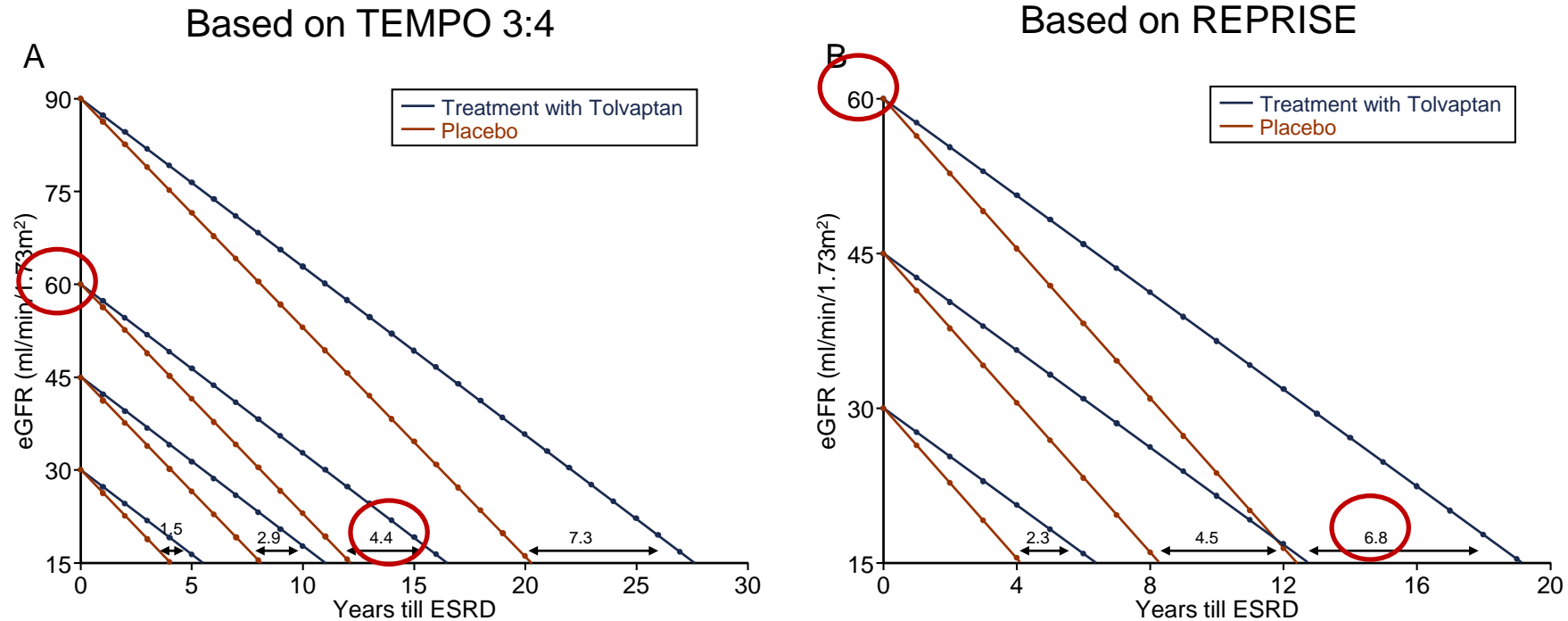
If tolvaptan can delay the start of RRT by 5-10 yrs , it will be a benefit for patients as well as for society, because they can continue to work. In case of progressive patients, early treatment may be effective.

Fouad T, Chebib. et al.: J Am Soc Nephrol., **29**, 1-7, 2018

Role of cAMP in ADPKD

Fluid secretion

PC1 or PC2 on the primary cilia senses the urinary flow and signals. If PC1 or PC2 is abnormal, intracellular Ca2+ level decreases. When Ca^{2+} level drops, intracellular cAMP concentration increases.

Cl^-

H_2O

PC1
PC2

AQP2

CFTR

PC1
PC2

K^+

$2Cl^-$

Na^+

PKA

MAPK

mTOR

Wnt

CREB

Ca^{2+}

PDE
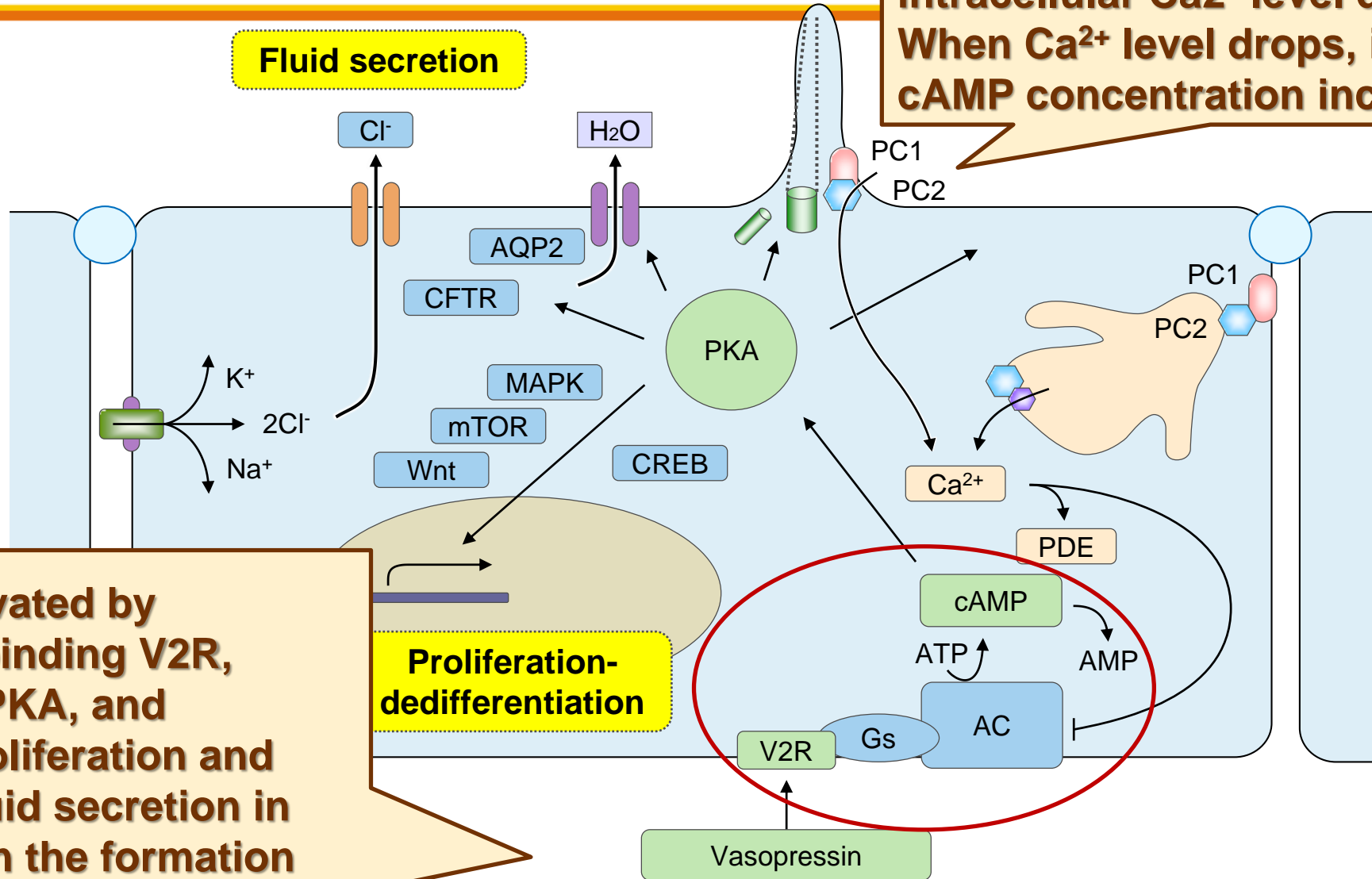
cAMP is also elevated by vasopressin by binding V2R, which activates PKA, and promotes cell proliferation and transepithelial fluid secretion in cysts, resulting in the formation and enlargement of cysts

Proliferation-dedifferentiation

cAMP

ATP

AMP

Gs

AC

V2R

Vasopressin

Devuyst O, Torres VE. *Curr Opin Nephrol Hypertens*. 2013;22 (4):459-470.

V2R antagonist, OPC31260, inhibited the progression in PKD model

Control   OPC31260   Control   OPC31260

3–10 weeks

10–18 weeks

PCK rat
（**ARPKD model rat**）

4–30 weeks

15–30 weeks

pcy **mice**
（nephronophthisis model mice）
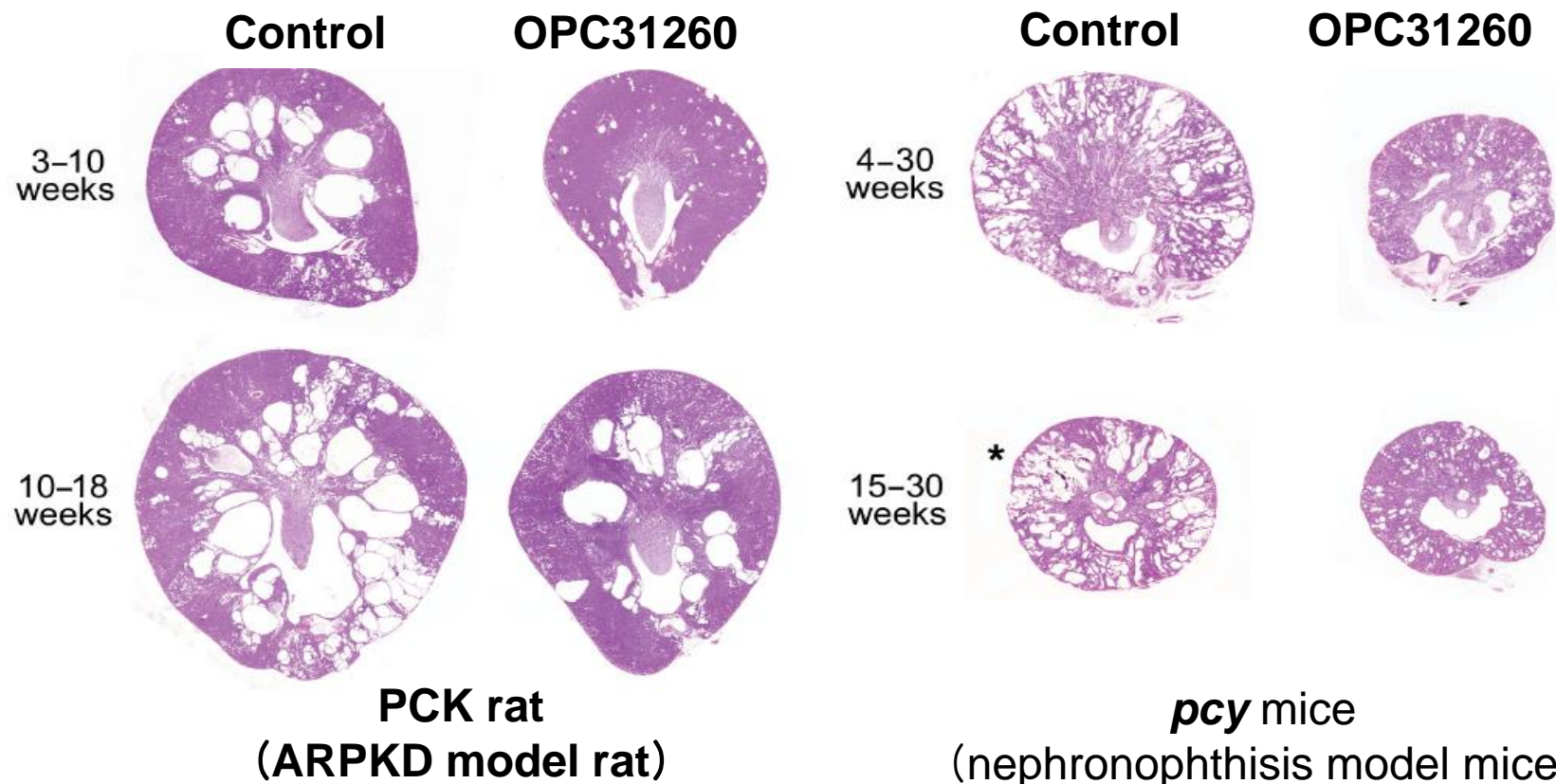
（**a**) Kidney sections from PCK rats treated with OPC32160 between 3–10 or 10–18 weeks of age, compared with untreated controls.

（**b**) Kidney sections from CD1/*pcy* mice treated with OPC32160 between 4–30 weeks or 15–30 weeks of age, compared with untreated controls. *, untreated control rat killed at 15 weeks of age.

TEMPO 3:4 Trial :
Tolvaptan Efficacy and Safety in Management of Polycystic Kidney Disease and its Outcomes

Belgium
Denmark
France
Germany
Italy
Netherlands
Poland
Romania
United Kingdom
Canada
United States
Russia
Japan
Australia
Argentina

15 countries, 129 hospital 1445 Pts
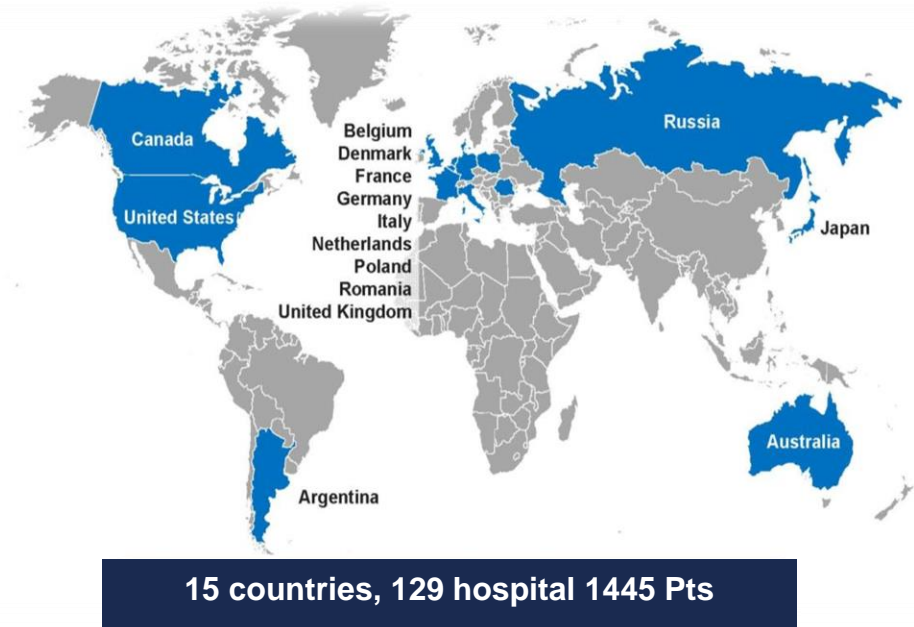
phase 3, multicenter, double-blind, placebo-controlled, 3-year trial.

ADPKD patients. 18-50 ys, with Ccr>60ml/min, TKV>750 ml, were randomly assigned to receive tolvaptan or placebo.

Primary outcome; change in TKV (%)

TEMPO 3:4 Trial
Effect of Tolvaptan on the Annual Slopes of Total Kidney Volume.

Tolvaptan : 2.80%/year

P<0.0001

Placebo : 5.51%/year

Torres, VE. et al.: N Engl J Med. 367 （25), 2407-18, 2012.
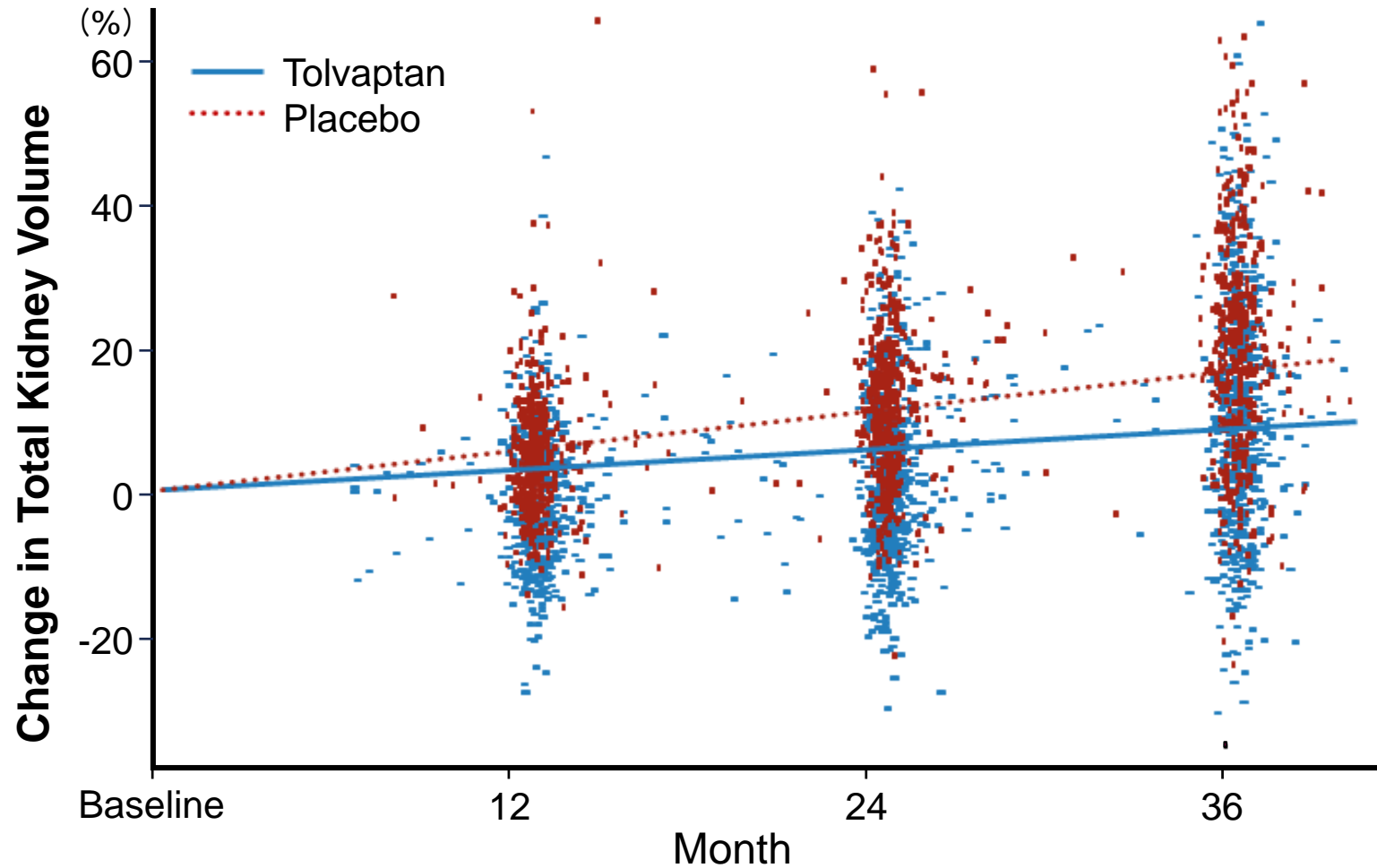
Effect of Tolvaptan on the Annual Slopes of Kidney Function (eGFR)
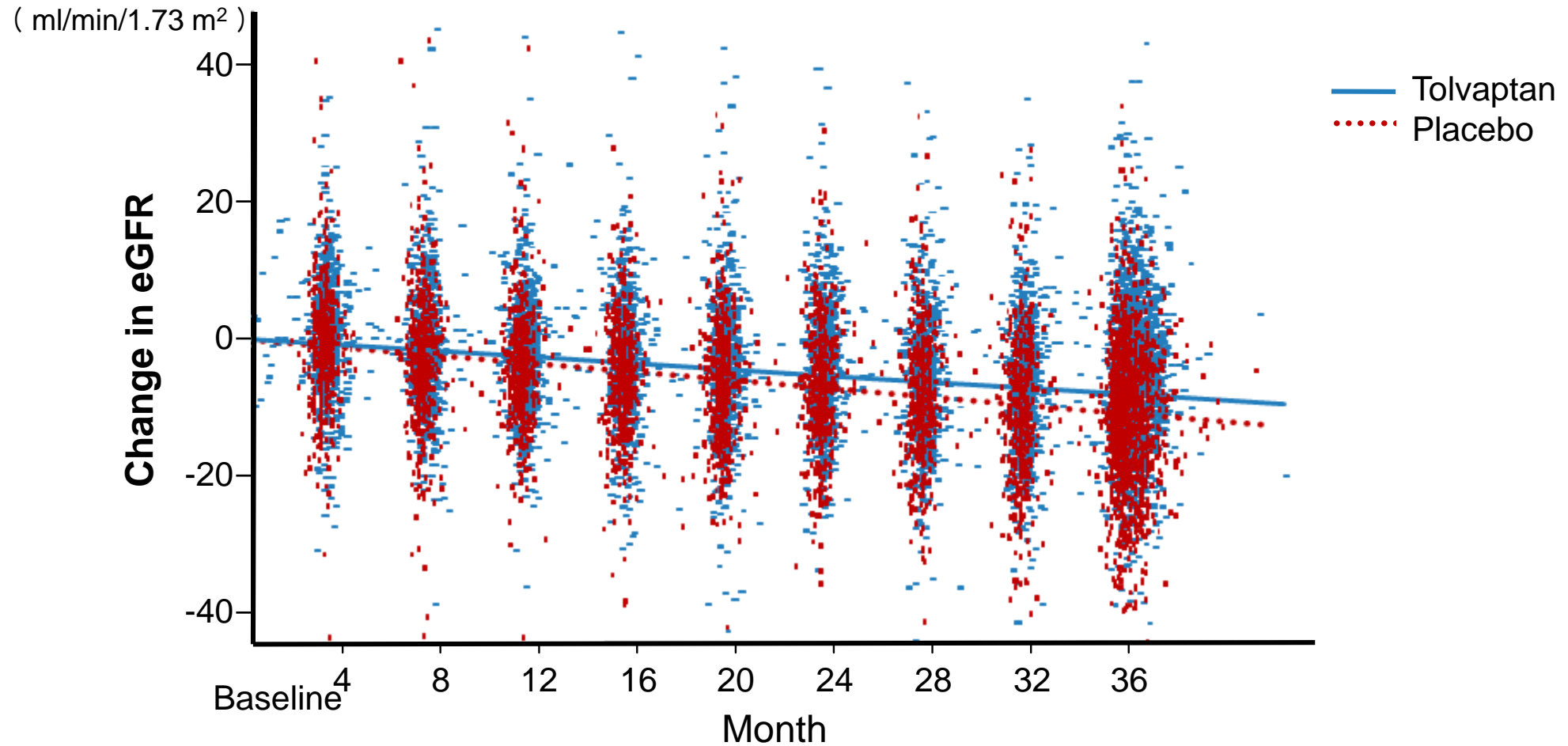
Tolvaptan : -2.61 （mg/dL）$^{-1}$

Placebo : -3.81 （mg/dL）$^{-1}$

P<0.0001

Torres, VE. et al.: N Engl J Med. 367 （25）, 2407-18, 2012.

Percentage change in TKV from baseline at 36 months
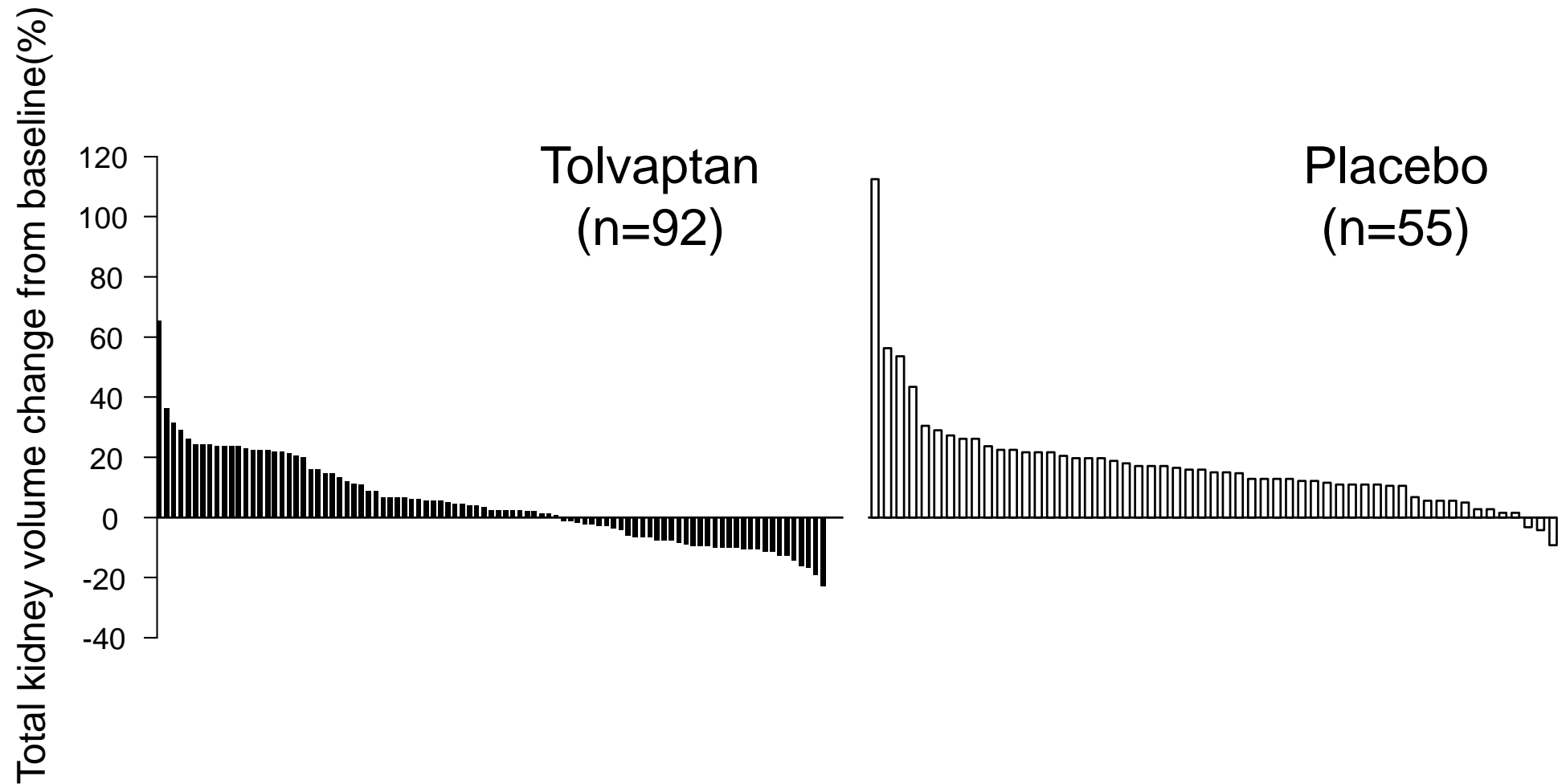
Change in eGFR from steady-state postdose baseline at 36 months in Japan

Tolvaptan (n=92)

Placebo (n=55)

40%

64%

y-axis: eGFR change from steady-state postdose baseline (mL/min/1.73m²)
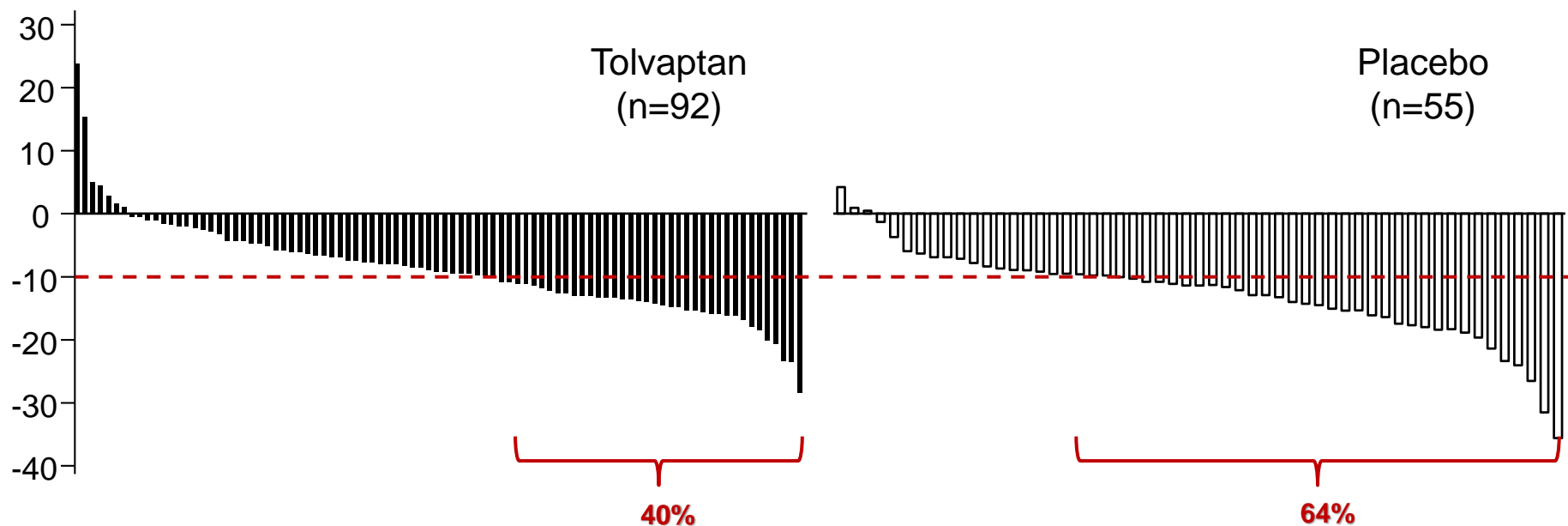
* : eGFR （mL/min/1.73 m²） $= 194 \times Cr^{-1.094} \times Age^{-0.287}$ （female: $\times 0.739$）

Muto S et al., Clin Exp Nephrol., 19(5), 867-877, 2015

- The objective was to assess the disease-modifying effects of tolvaptan on TKV and eGFR from baseline over the combined duration of TEMPO 3:4 and TEMPO 4:4,
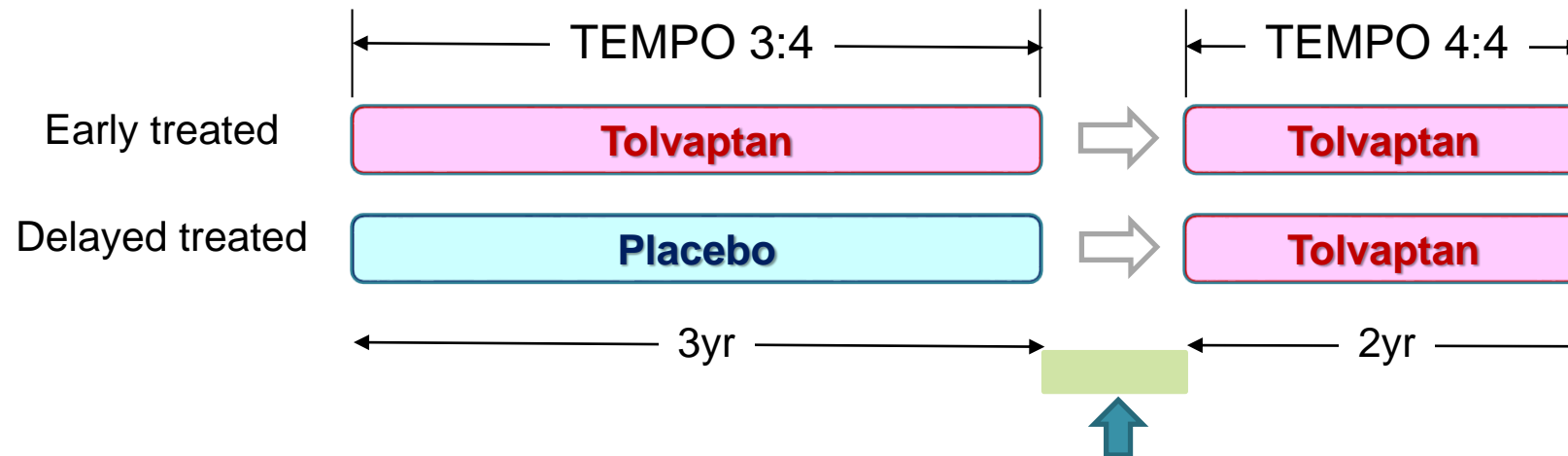
Off-treatment; 13-829 days（mean 81days, median 37days）

Disease modification effect

○ **Start of disease modifying drug**

No treatment

Late treatment start

Early treatment start

Progression

Ideal situation

First symptoms

Start of follow-up

Review
The need for prognosticators in rheumatoid arthritis.
Biological and clinical markers: where are we now?
Smolen JS et.al., Arthritis Research & Therapy ,10(3), 208, 2008
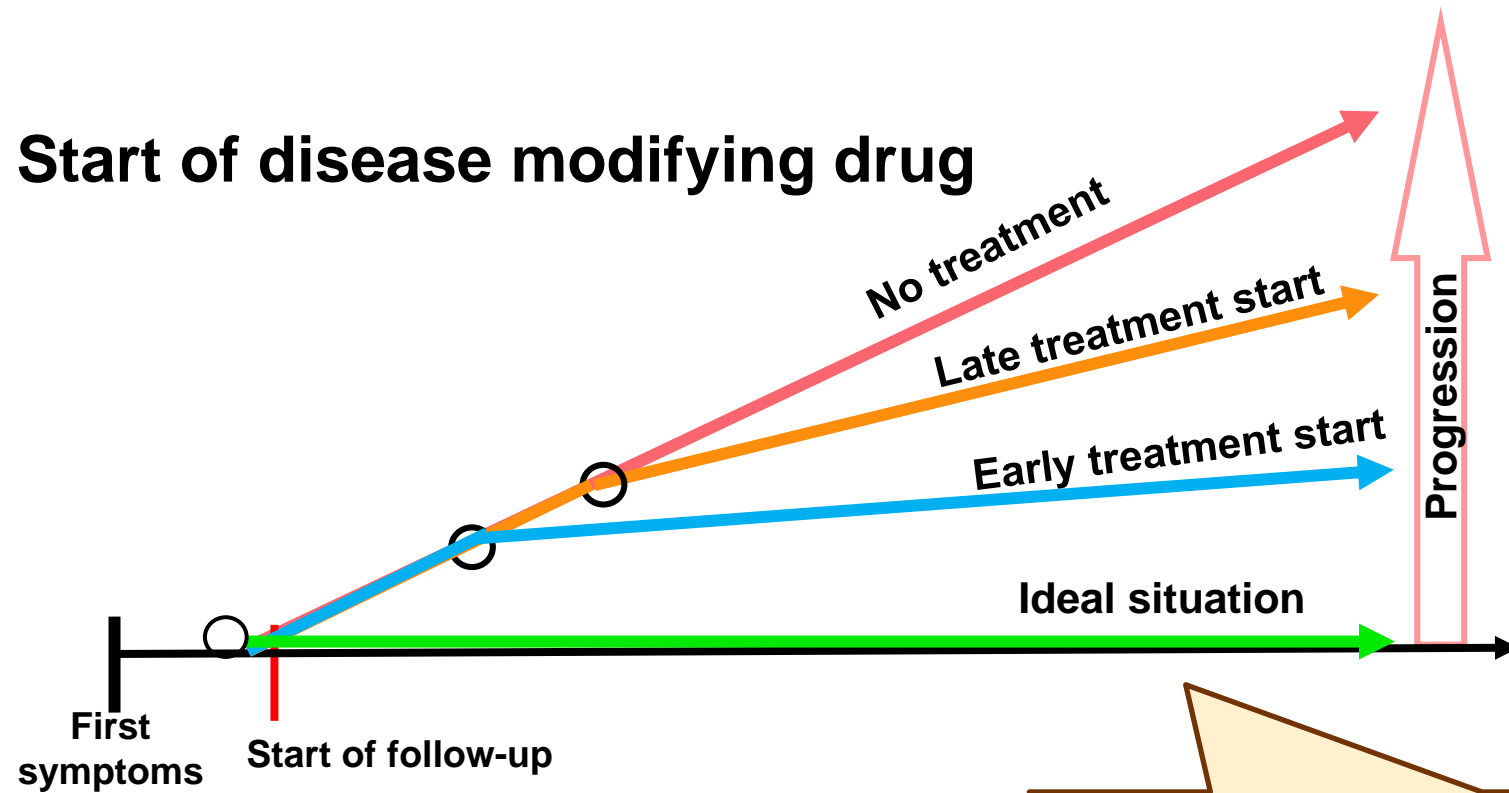
Tolvaptan is not a fundamental treatment for ADPKD, but may slow the progression of ADPKD.

Percentage change in TKV from TEMPO 3:4 baseline to TEMPO 4:4 at 24 months

Percentage change from baseline in TKV when adjusted for covariates

Total Kidney Volume Growth (% of baseline)

Legend:
- Early Tolvaptan (covariate correction)
- Early Tolvaptan
- Delayed Tolvaptan (covariate correction)
- Delayed Tolvaptan

** $p < 0.01$

Covariates;
age, gender, gender visit interaction, eGFR, eGFR visit interaction and urine ACR

p=0.04
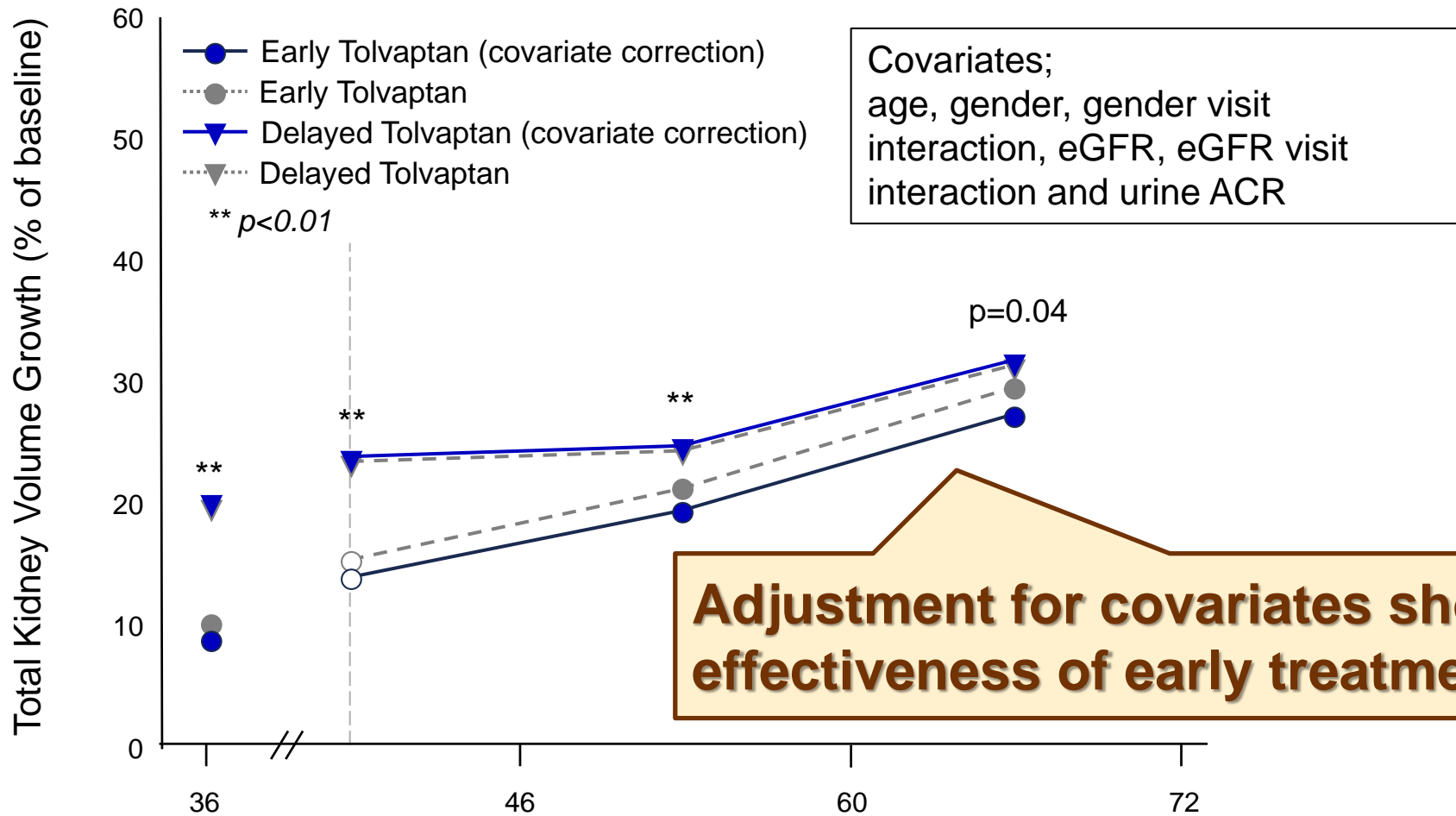
Adjustment for covariates showed the effectiveness of early treatment on TKV

Treatment duration (month)

	36		46	60	72
Early Tolvaptan N	552	499	535	505	
Delayed Tolvaptan N	312	289	287	267	

Change in eGFR from the TEMPO 3:4 baseline to TEMPO 4:4 at 24 months.

Treatment duration (month)

Tolvaptan induces initial decline in eGFR.

Discontinuation of tolvaptan induces increase of eGFR.

eGFR is higher in early G

No inferiority

Change in eGFR (mL/min/1.73m²)

- ● Tolvaptan
- ▽ Placebo
- ▼ Delayed Tolvaptan
- ○ Early Tolvaptan - Follow-up
- ▽ Placebo - Follow-up

*p<0.05
**p<0.01

Off treatment
13-829 days

TEMPO 3:4   TEMPO 4:4

Early Tolvaptan N	555	553	551	550	398	528	503
Delayed Tolvaptan N	331	308	310	309	231	276	264

	n	eGFR Slope (/year)	Treatment Difference	95% CI	p-value	NI margin
Early-Treated*	548	-3.26	-0.11	-0.75, 0.52	0.73	0.65
Delayed-Treated*	304	-3.14				

Change from baseline in TKV and eGFR by gender
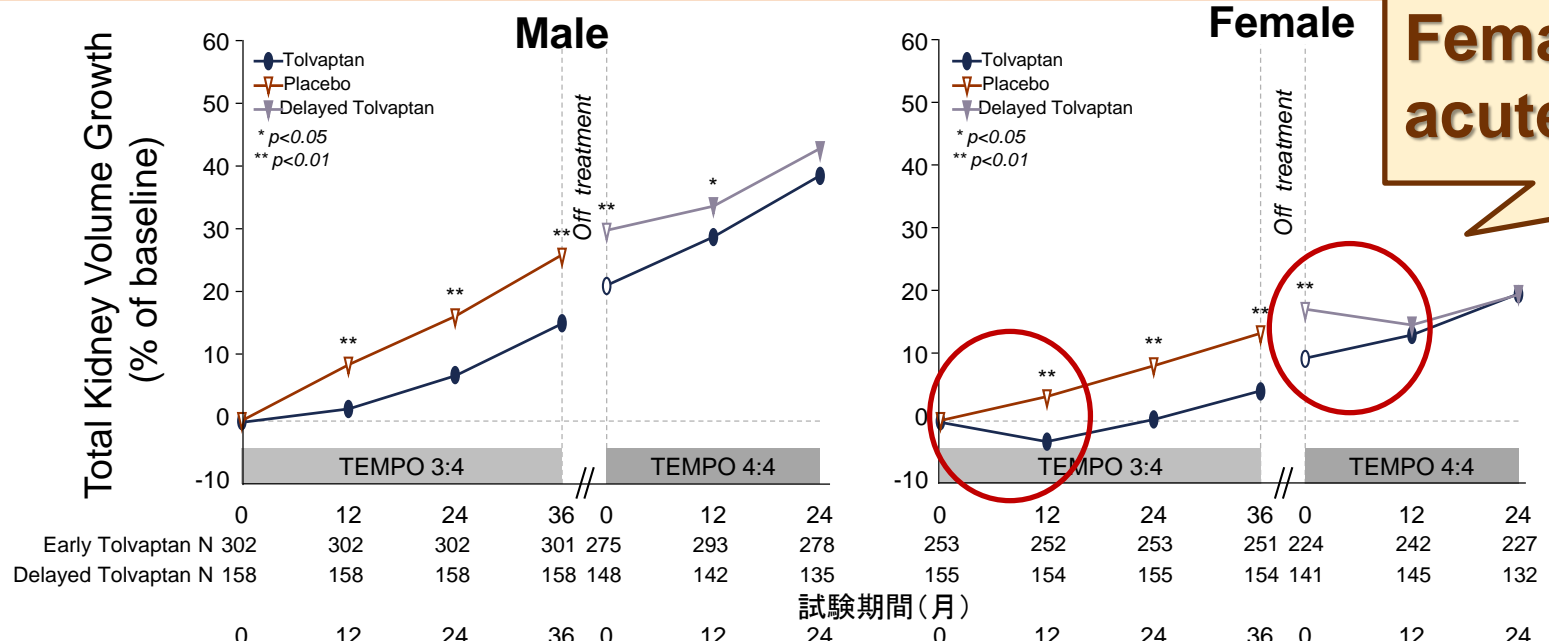
Female shows the larger acute response to tolvaptan
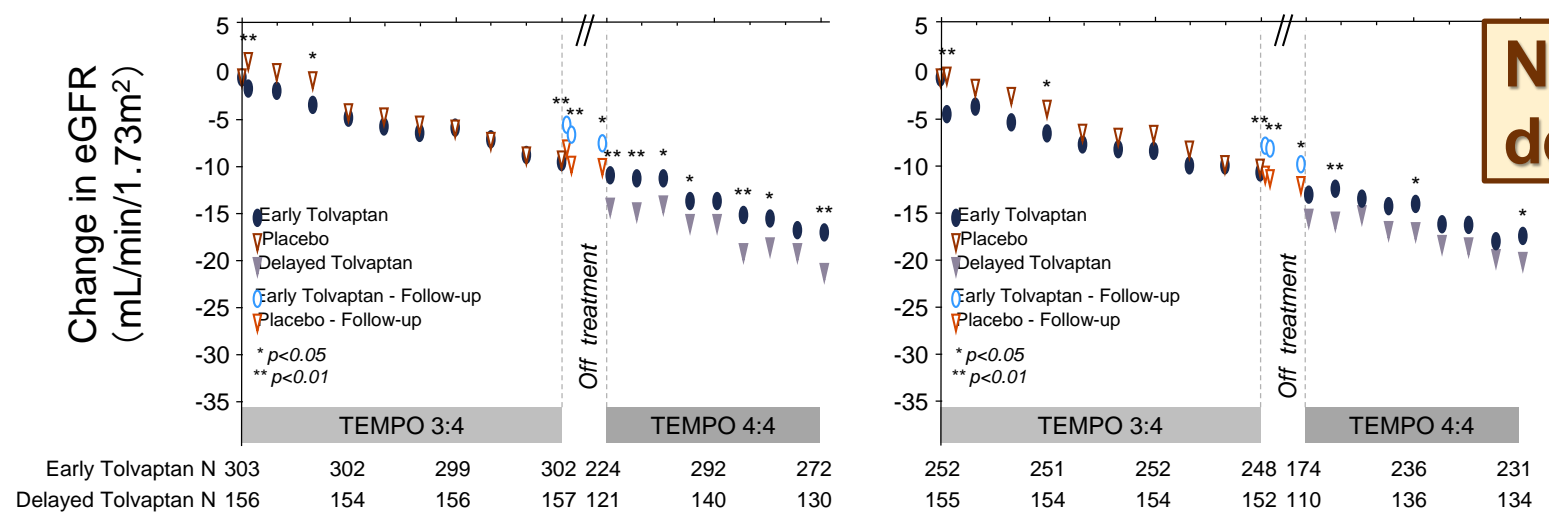
No difference in eGFR decline by gender

Change from baseline in TKV and eGFR by CKD stage

Effects of tolvaptan on TKV and eGFR were prominent in more severe groups

Change from baseline in TKV and eGFR by genotype

Effects of tolvaptan on TKV and eGFR were prominent in more severe groups
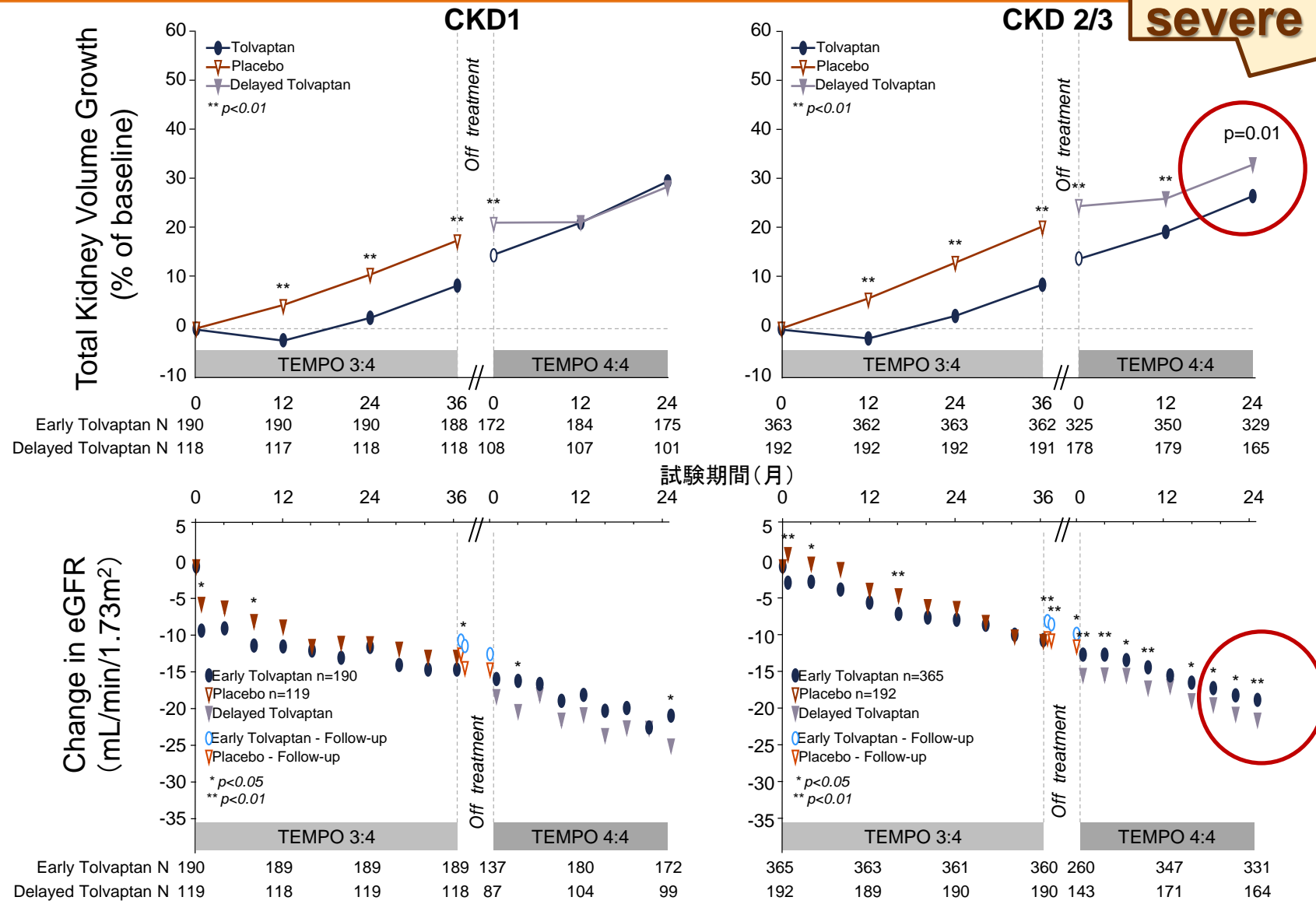
Change from baseline in TKV and eGFR by imaging classification

Effects of tolvaptan on TKV and eGFR were prominent in more severe groups
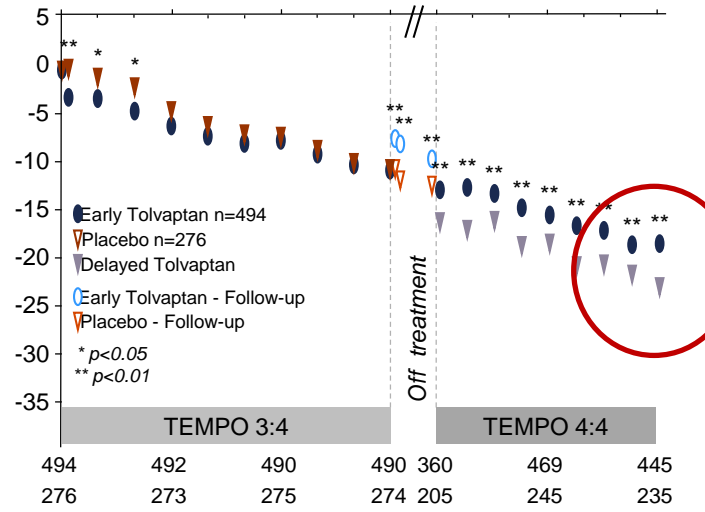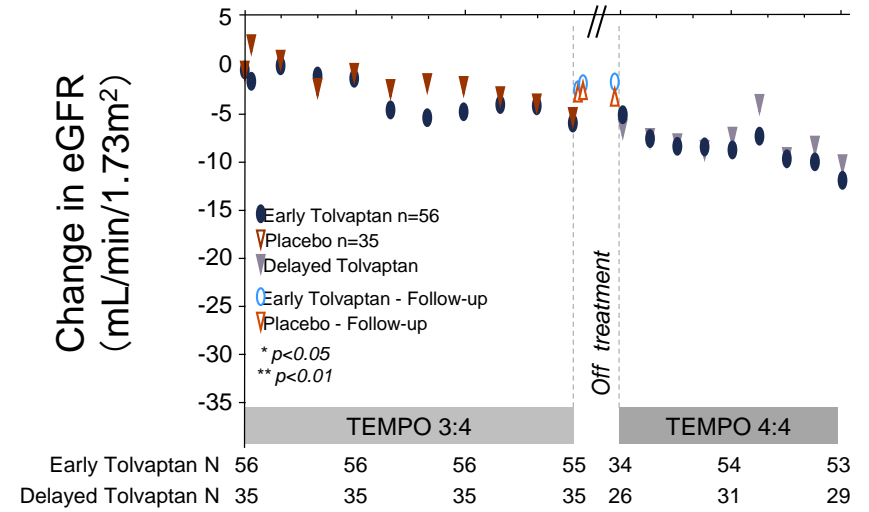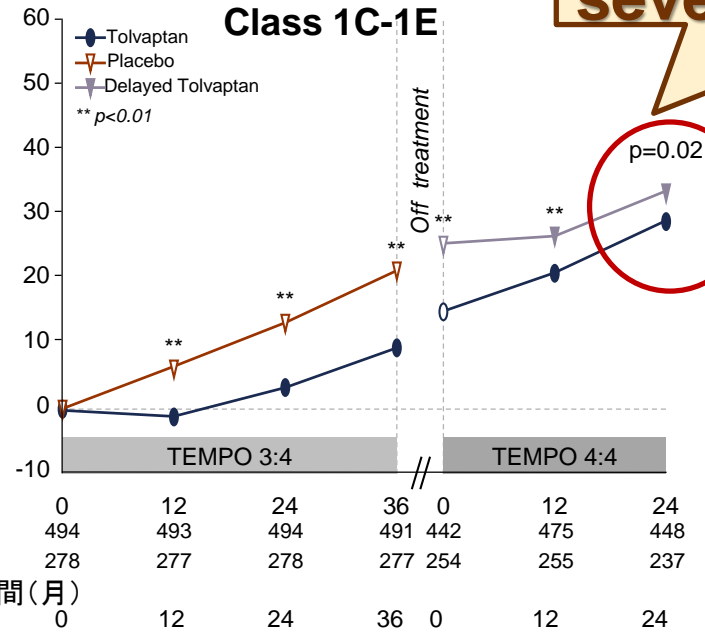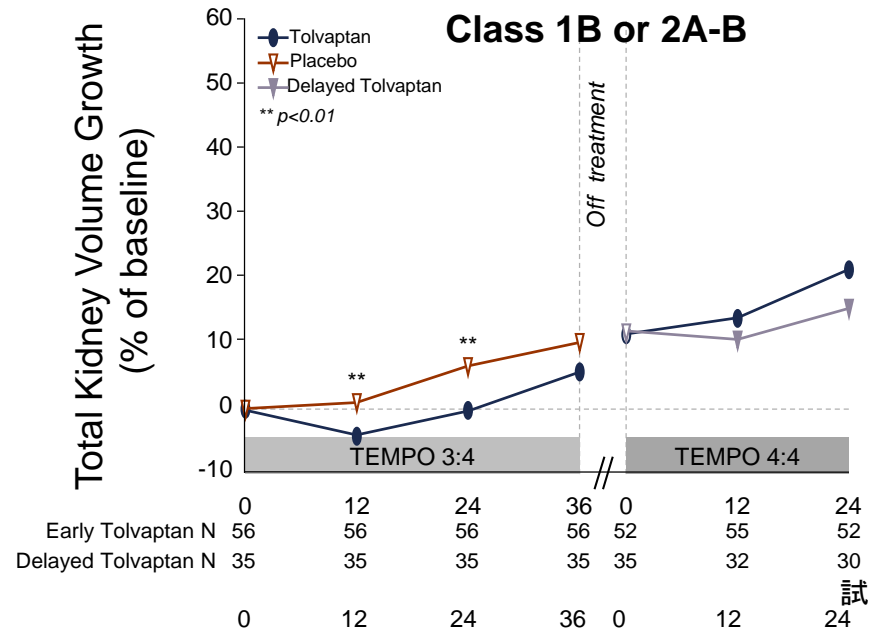
Schematic design of the REPRISE clinical trial

Screening	Placebo Run-in	Tolvaptan Titration	Tolvaptan Run-in	Double-blind Treatment	Follow-Up
1-2 Weeks	1 weeks	2 weeks	3 weeks	12 months	2 weeks (7-21 days post-treatment)

Tolvaptan Titration arrows:
- 90/30 mg
- 60/30 mg
- 45/15 mg
- 30/15 mg

Tolvaptan Run-in:
- 90/30 mg
- 60/30 mg

Double-blind Treatment:
- Tolvaptan / Placebo — 90/30 mg
- Tolvaptan / Placebo — 60/30 mg
- Tolvaptan / Placebo — 45/15 mg

1st Endpoint
Pre-treatment Off-Drug Baseline
(Mean of 3 sCr)

Randomization Day (-1)

1st Endpoint
Post-treatment Off-Drug Baseline
(Mean of 3 sCr)

Key 2nd Endpoint
Pre-treatment slope from placebo run-in to post treatment follow-up

*SAP allowed for serum creatinine to be collected up to 40 days follow-up to complete the requirement for 3 samples

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

Clinical Characteristics at Baseline

Characteristic	Tolvaptan Group (N=683)	Placebo Group (N=687)
Age — yr	47.3 ±8.2	47.2 ±8.2
Male sex — no. (%)	347 (50.8)	333 (48.5)
Height — cm	174 ±10	173 ±10
Weight — kg	84.6 ±19.9	81.6 ±19.3
Body-mass index	28.0 ±5.8	27.7 ±5.6
Race — no. (%)†		
White	626 (91.7)	632 (92.0)
Asian	22 (3.2)	19 (2.8)
Black	25 (3.7)	23 (3.3)
Other	10 (1.5)	13 (1.9)
Family history of polycystic kidney disease — no./total no. (%)	514/679 (75.7)	529/687 (77.0)
Blood pressure — mm Hg		
Systolic	129.3 ±13.8	129.9 ±14.5
Diastolic	82.1 ±9.6	82.6 ±9.7
Estimated GFR — ml/min/1.73 m^2‡	40.7 ±10.9	41.4 ±11.2
Chronic kidney disease stage — no./total no. (%)		
2	32/683 (4.7)	39/684 (5.7)
3a	209/683 (30.6)	202/684 (29.5)
3b	303/683 (44.4)	315/684 (46.1)
4	139/683 (20.4)	128/684 (18.7)
Hypertension — no. (%)§	634 (92.8)	640 (93.2)
Current use of RAAS inhibitor — no. (%)	595 (87.1)	581 (84.6)
History of kidney pain — no. (%)	338/675 (50.1)	344/679 (50.7)
Dose at end of single-blind tolvaptan period — no. (%)		
60 mg in morning and 30 mg in afternoon	118 (17.3)	124 (18.0)
90 mg in morning and 30 mg in afternoon	565 (82.7)	563 (82.0)

Torres VE et al., Am J Nephrol., 45(3), 257-266, 2017

Primary Endpoints : Change in eGFR

Torres VE, et al.: N Engl J Med. 377 (20), 1930-1942, 2017
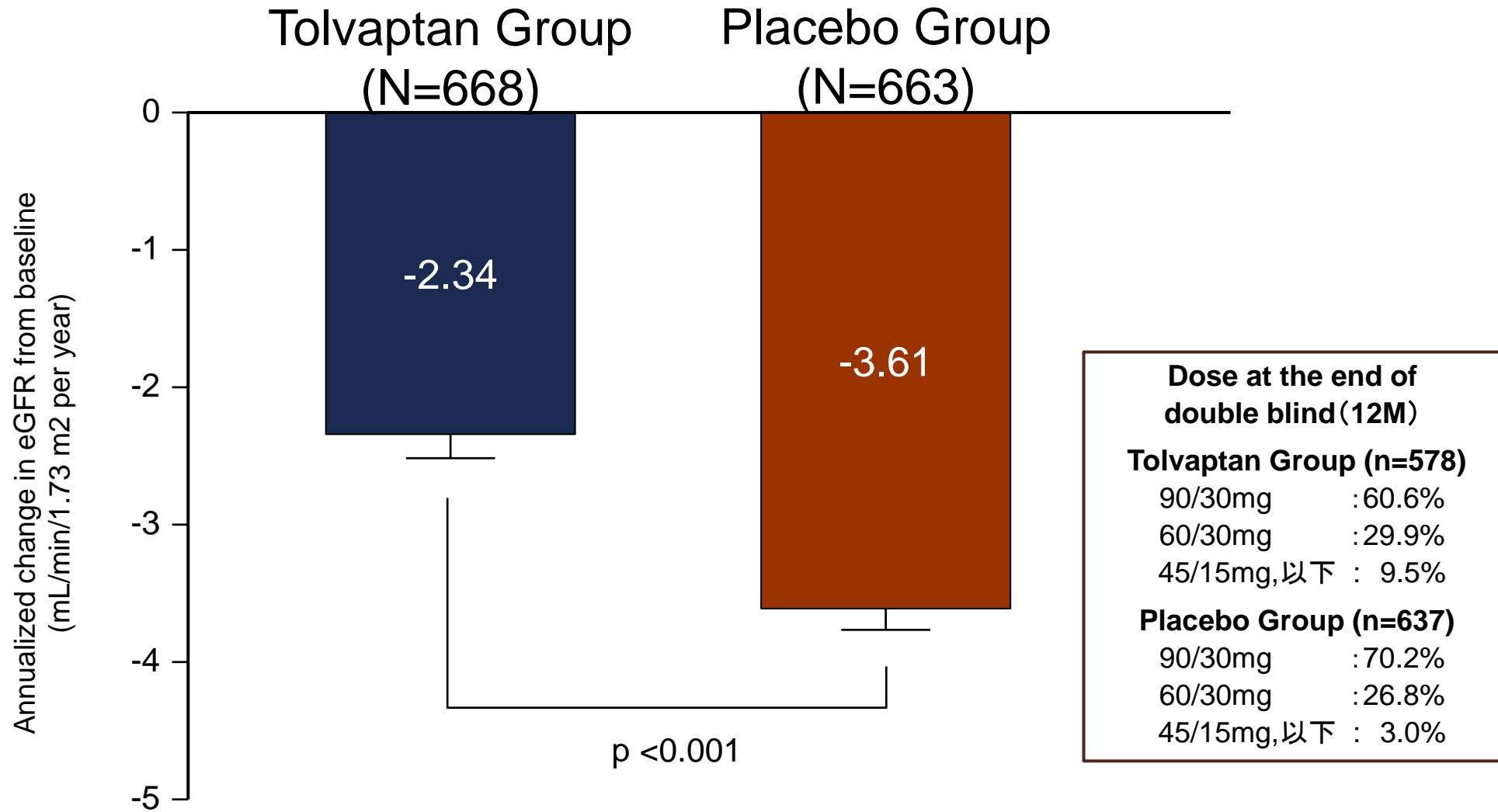
Sub-group analysis of the primary endpoint

Subgroup	no. of patients Tolvaptan	Placebo	Mean eGFR Change (95%CI)	Tolvaptan	Placebo	Difference	P value
All patients	668	663		−2.34	−3.61	1.27	<0.001
Age							
≤55 yr	572	569		−3.07	−4.60	1.54	<0.001
>55 yr	96	94		−2.54	−2.34	−0.20	0.65
Sex							
Female	327	341		−2.89	−4.13	1.23	<0.001
Male	341	322		−3.09	−4.43	1.34	<0.001
Race							
White	614	610		−2.97	−4.34	1.37	<0.001
Nonwhite	54	53		−3.29	−3.54	0.25	0.79
Baseline eGFR							
≤45 mL/分/1.73 m^2	432	423		−3.45	−4.35	0.90	<0.001
>45 mL/分/1.73 m^2	236	240		−2.20	−4.11	1.91	<0.001
CKD stage							
2	31	38		−2.81	−4.65	1.84	0.14
3a	206	196		−2.13	−4.49	2.36	<0.001
3b	294	304		−3.20	−3.99	0.78	0.008
4	137	125		−3.80	−4.60	0.81	0.02
Geographic region							
United States	286	282		−2.88	−4.14	1.26	<0.001
Other	382	381		−3.09	−4.38	1.29	<0.001

−6   −4   −2   0   2   4   6

← Placebo Better   Tolvaptan Better →

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

Change in eGFR over Course of the Trial

During the tolvaptan run-in phase, GFR drop was observed.

Discontinuation increased GFR.

Torres VE, et al.: N Engl J Med. 377 (20), 1930-1942, 2017
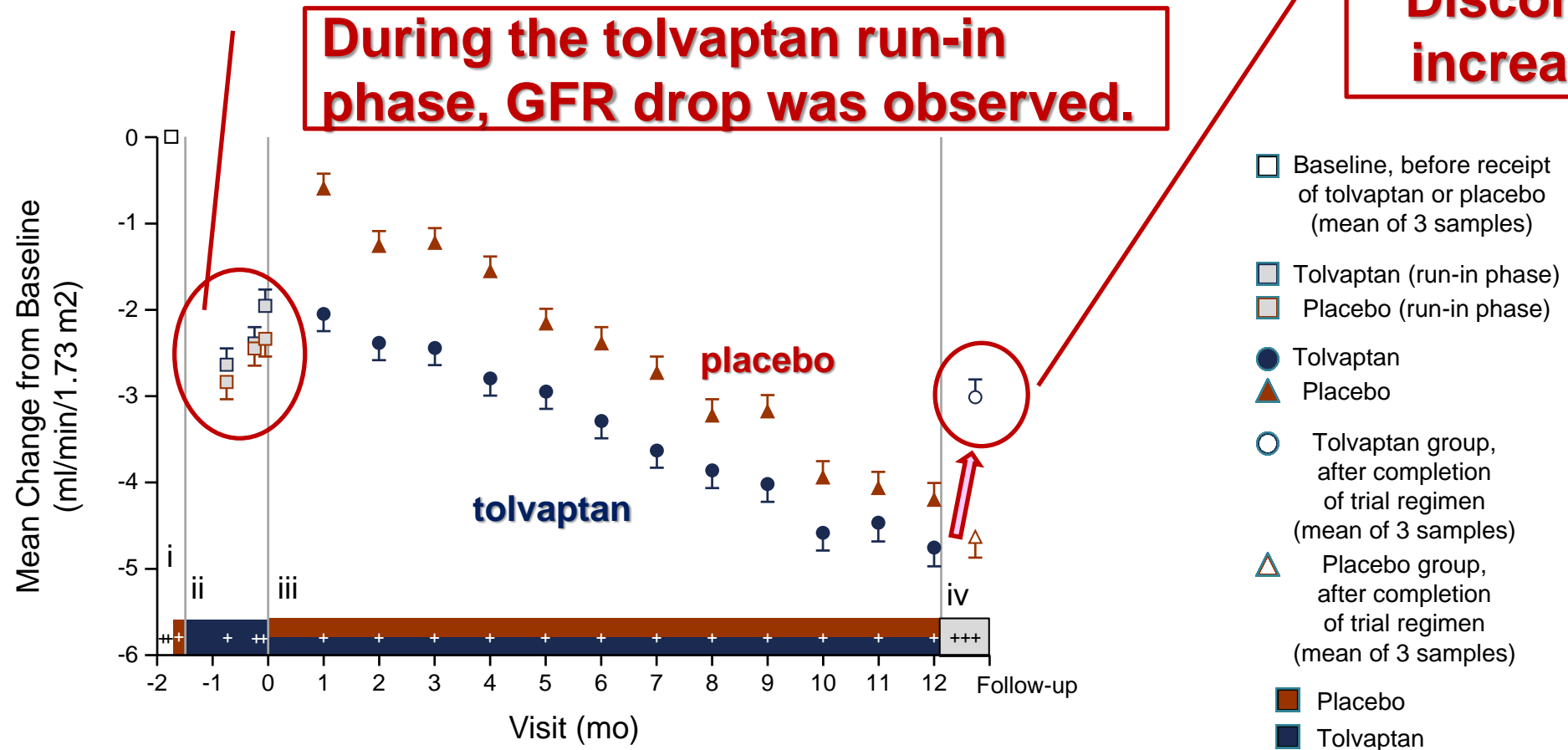
Second Endpoints : Slope of eGFR

Tolvaptan（n=680） Placebo（n=682）

-3.16

-4.17

eGFR(CKD-EPI) slope （mL/min/1.73m^2/yr）

Difference in eGFR slope：1.01 mL/min/1.73 m^2
p<0.001

Torres VE, et al.: N Engl J Med. 377 (20), 1930-1942, 2017より作成
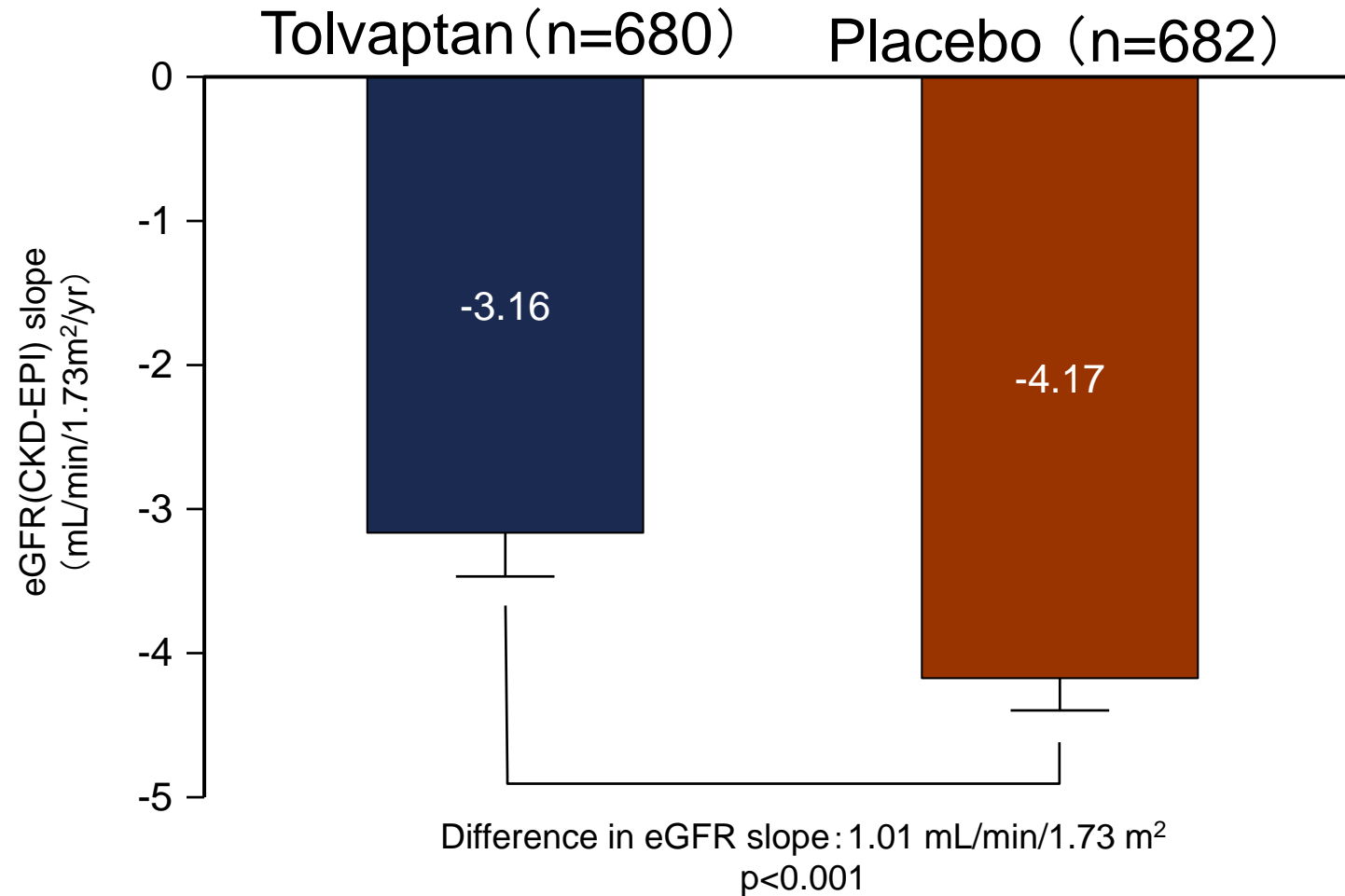
Tolvaptan slows the rate of eGFR decline and its effect is sustained

Annualized eGFR vs Follow-up Duration

slope=-0.11
95% CI=[-0.32, 0.09]
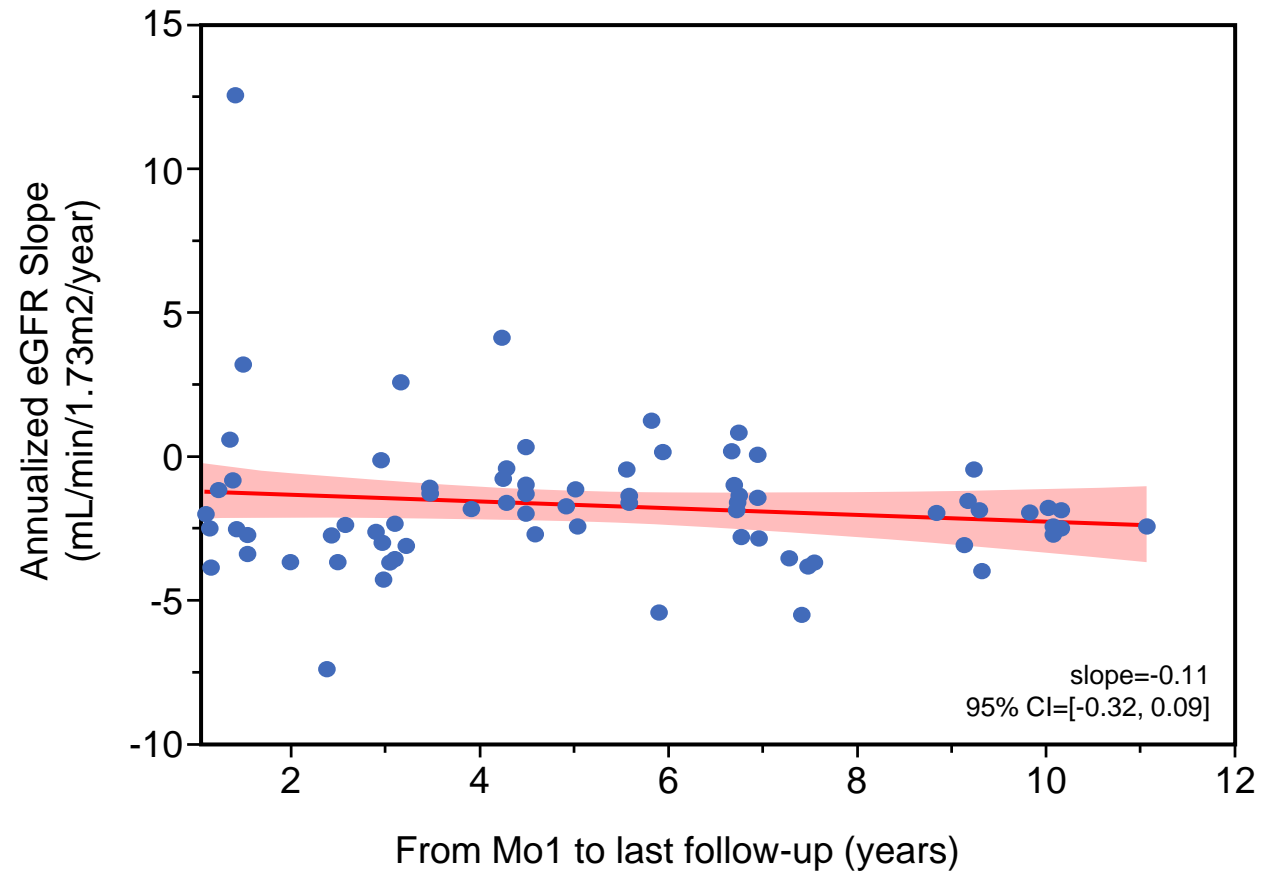
Algorithm of tolvaptan treatment in ADPKD

Renal cysts
↓
Confirm ADPKD diagnosis

Typical ADPKD (Bilateral/diffuse cyst distribution)

Atypical ADPKD (focal disease or parenchymal atrophy)

Measure total kidney volume by CT/MRI

Monitoring

Mayo Class 1C, 1D or 1E

Mayo Class 1A or 1B

Rapidly progressive ADPKD

Reassurance/ Confirm rate of progression in 2-3 years

eGFR ≥ 25 ml/min Age: 18-55

Recommend starting tolvaptan

General management of ADPKD
- Blood pressure control
- Moderate sodium restriction
- Increased hydration
- Maintain normal BMI
- Cholesterol: LDL < 100, HDL > 50 mg/dL

Moderate protein and phosphorus restriction
- Maintain serum bicarbonate ≥ 22 mEq/L

Fouad T, Chebib. et al.: J Am Soc Nephrol., **29**, 1-7, 2018

Time to First Elevation of ALT Level
(3 times>normal range)

Hazard ratio, 4.91 (95% CI, 2.29-10.53)

Proportion of Patients with Alanine Aminotransferase Level >3 × ULN

Tolvaptan

Placebo

Days since Randomization
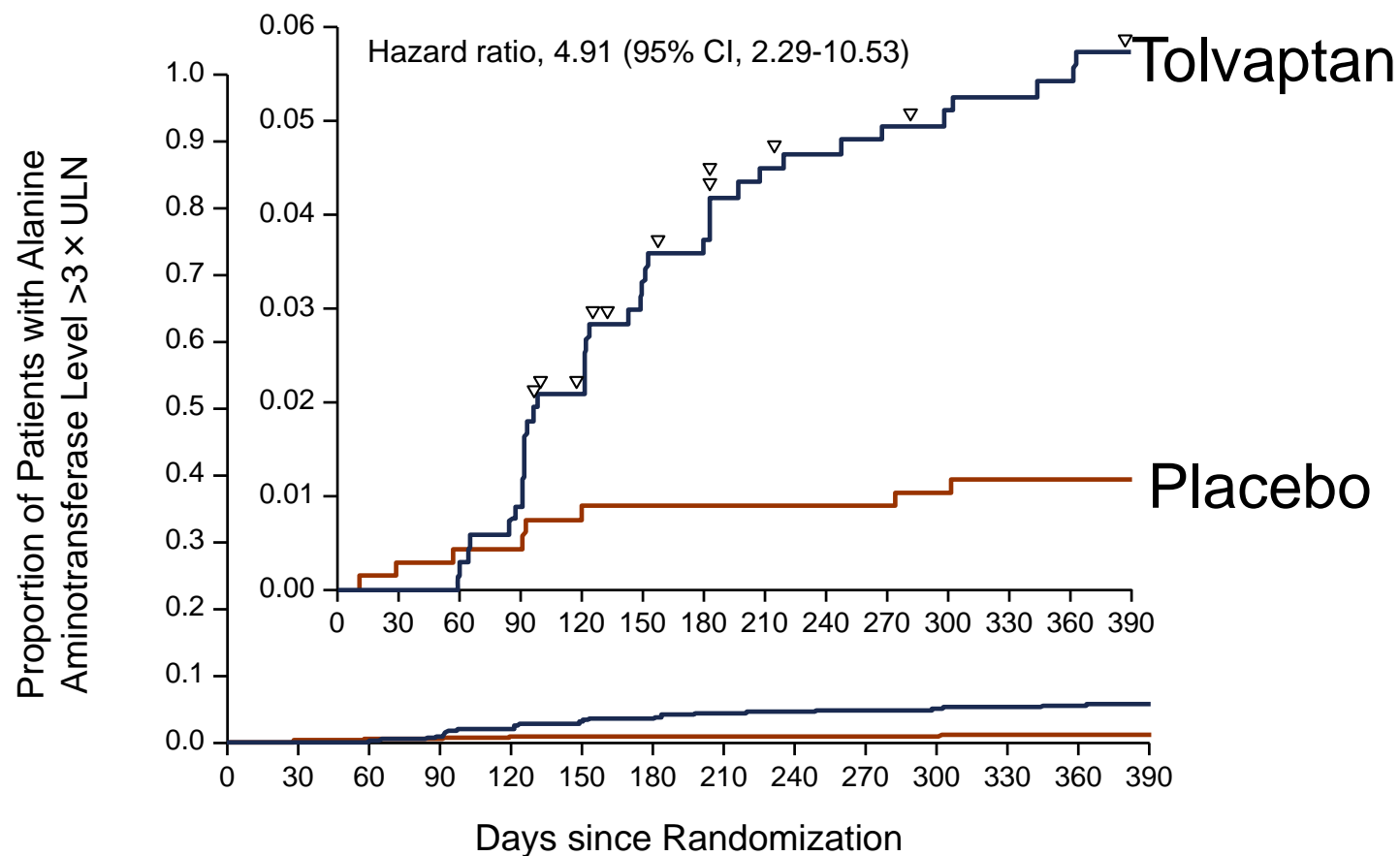
No.at Risk

Tolvaptan	680	677	671	666	657	649	639	632	629	625	620	616	595	36
Placebo	684	680	678	675	673	672	671	668	665	661	660	656	645	40

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

Algorithm of potential drug-induced liver injury

| AST, ALT, bilirubin Increased to ≥ 3 X | AST, ALT, bilirubin Increased to > 2 X Or > 2 X baseline | Multiple signs and symptoms highly suggestive of liver injury |

Hold tolvaptan

Repeat LFTs within 48-72 hr

Assess for other etiologies (other disease, drugs, exposures)

Increased to ≥ 3 X

Stable or improved

Additional work-up and expert consultation if needed

Permanently discontinue tolvaptan unless other explanation for liver injury and injury resolved

Reinitiate tolvaptan with frequent monitoring

LFT, liver function tests.