Tolvaptan Protocols In ADPKD

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Introduction

- Autosomal dominant polycystic kidney disease (ADPKD), the fourth leading cause of end stage kidney disease in adults, is caused by mutations in either of two genes:
- PKD1 (encoding polycystin-1)
- PKD2 (encoding polycystin-2).

Introduction

- Autosomal recessive polycystic kidney disease (ARPKD), an important cause of ESRD and mortality in infants and children, is caused by mutations in PKHD1 (encoding fibrocystin).

Introduction

- In both diseases, disruption of mechanisms controlling tubular diameter, excessive cell proliferation and fluid secretion, and pathogenic interactions of mutated epithelial cells with an abnormal extracellular matrix and alternatively activated interstitial macrophages contribute to cyst formation.

Introduction

- Numerous therapies targeting diverse, seemingly unconnected pathophysiologic mechanisms have been successful in animal models of polycystic kidney disease (PKD).

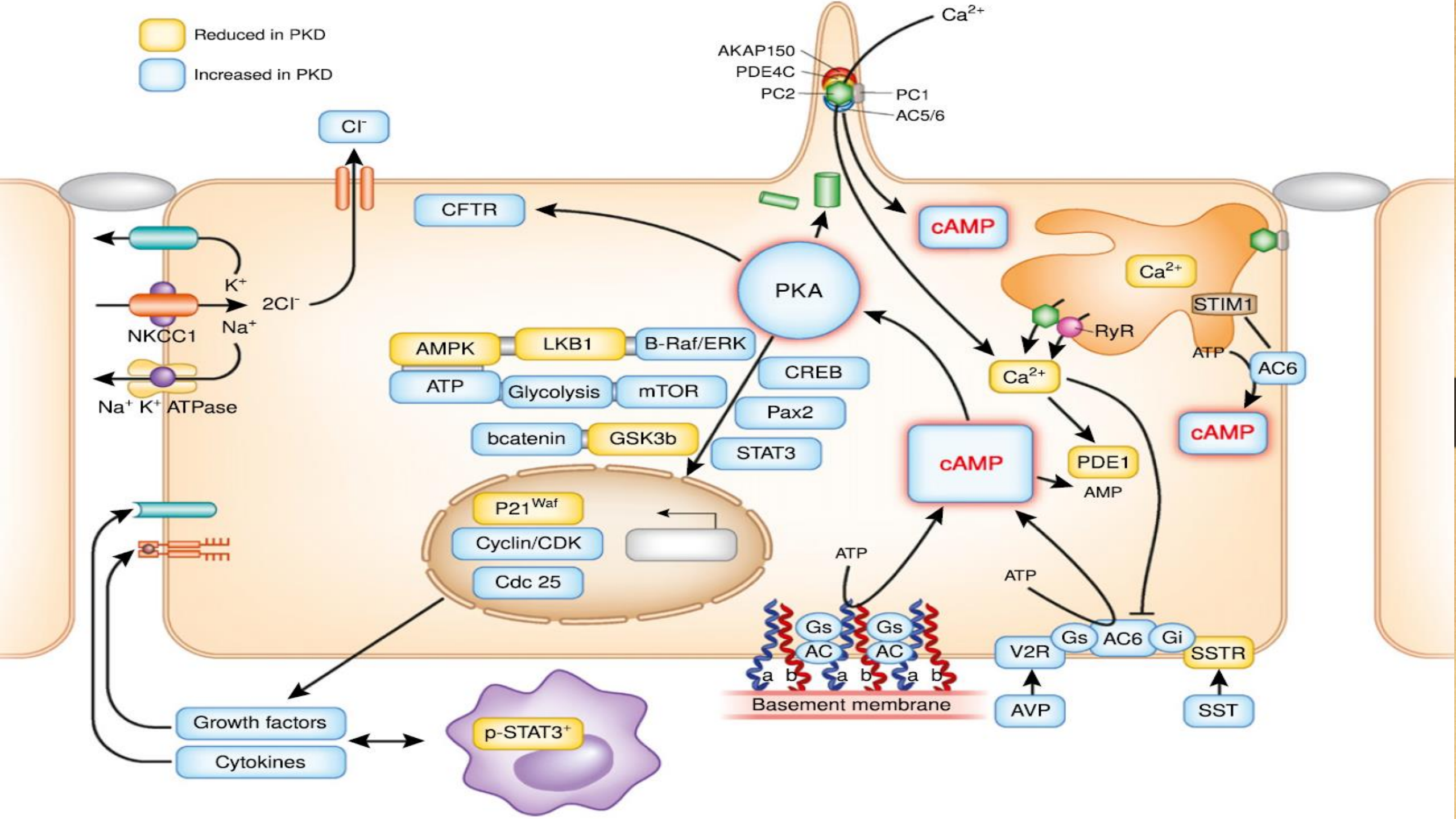

Reduced in PKD
Increased in PKD
Ca2+
AKAP150
PDE4C
PC2
PC1
AC5/6
Cl-
CFTR
cAMP
PKA
Ca2+
STIM1
RyR
ATP
AC6
K+
2Cl-
NKCC1
Na+
Na+ K+ ATPase
AMPK
LKB1
B-Raf/ERK
ATP
Glycolysis
mTOR
CREB
Pax2
bcatenin
GSK3b
STAT3
Ca2+
cAMP
PDE1
AMP
P21 Waf
Cyclin/CDK
Cdc 25
ATP
ATP
Gs
Gs
AC
AC
a b a b a b
Basement membrane
Gs
AC6
Gi
V2R
SSTR
AVP
SST
Growth factors
Cytokines
p-STAT3+

Figure 1. Diagram depicting putative pathways up- or downregulated in PKD. Dysregulation of [Ca2+]i and increased concentrations of cAMP play a central role. Increased accumulation of cAMP in polycystic kidneys may be explained the following hypotheses. (*1*) Reduced calcium activates calcium-inhibitable AC6, directly inhibits calcium/calmodulin-dependent PDE1 (by also increasing the levels of cGMP), and indirectly inhibits cGMP-inhibitable PDE3. (*2*) Dysfunction occurs in a ciliary protein complex (comprising A-kinase anchoring protein 150, AC5/6, polycystin-2, PDE4C, and PKA), which normally restrains cAMP signaling through inhibition of AC5/6 activity by polycystin-2–mediated calcium entry and degradation of cAMP by PDE4C transcriptionally controlled by HNF1β. (*3*) Depletion of the endoplasmic reticulum calcium stores trigger oligomerization and translocation of STIM1 to the plasma membrane, where it recruits and activates AC6. (*4*) Other contributory factors include disruption of PC1 binding to heterotrimeric G proteins, upregulation of the vasopressin V2 receptor, and increased levels of circulating vasopressin or accumulation of forskolin, lisophosphatidic acid, ATP, or other adenylyl cyclase agonists in the cyst fluid. Increased cAMP levels disrupt tubulogenesis, stimulate chloride and fluid secretion, and activate proproliferative signaling pathways, including mitogen-activated protein kinase/extracellularly-regulated kinase (in an Src- and Ras-dependent manner), mTOR, and β-catenin signaling. Activated mTOR transcriptionally stimulates aerobic glycolysis, increasing ATP synthesis and lowering AMP levels, which together with B-Raf–dependent activation of LKB1, inhibits AMPK, further enhancing mTOR activity and CFTR-driven chloride and fluid secretion. PKA signaling also activates a number of transcription factors, including STAT3. Activated STAT3 induces the transcription of cytokines, chemokines, and growth factors that, in turn, activates STAT3 on interstitial alternatively activated (M2) macrophages, which results in a feedforward loop between cyst-lining cells and M2 macrophages. Aberrant integrin–extracellular membrane interaction and cAMP signaling within focal adhesion complexes may contribute to the increased adhesion of cyst-derived cells to laminin-322 and collagen. AC-VI, adenylate cyclase 6; AMPK, AMP kinase; AVP, arginine vasopressin; B-Raf, B rapidly accelerated fibrosarcoma kinase; CDK, cyclin-dependent kinase; cGMP, cyclic guanosine monophosphate; CREB, cAMP response element binding transcription factor; ER, endoplasmic reticulum; GSK3β, glycogen synthase kinase 3β; LKB1, liver kinase B1; MAPK, mitogen-activated protein kinase; Pax2, paired box gene 2; PC1, polycystin-1; PC2, polycystin-2; SST, somatostatin; SSTR, somatostatin receptor; STIM1, stromal interaction molecule 1.

cAMP agonists accelerate cyst growth

1. cAMP agonist: **Vasopressin** (AVP)
2. **V2** receptors on collecting ducts and distal nephron, sites for cyst formation in ADPKD and ARPKD.
3. AVP stimulating both mural epithelial cell proliferation and transepithelial Cl^- secretion coupled to osmotic water flow.

Biochim Biophys Acta 1812: 1291–1300, 2011.

- Reduction in intracellular Ca2 levels contribute to the phenotypic difference in the proliferative response to cAMP between PKD and normal renal Cells.

J Biol Chem 279: 40419–40430, 2004.

Tolvaptan inhibits ERK-dependent cell proliferation, Cl^- secretion, and in vitro cyst growth of human ADPKD cells

- Tolvaptan (OPC-41061) , a derivative of OPC-31260 (nonpeptide V2R antagonist) : higher affinity for V2R
- Cell line : primary culture of human ADPKD cyst epithelial cells and normal human kidney cells

- Exam the effects of tolvaptan on

(1) AVP-induced cAMP production

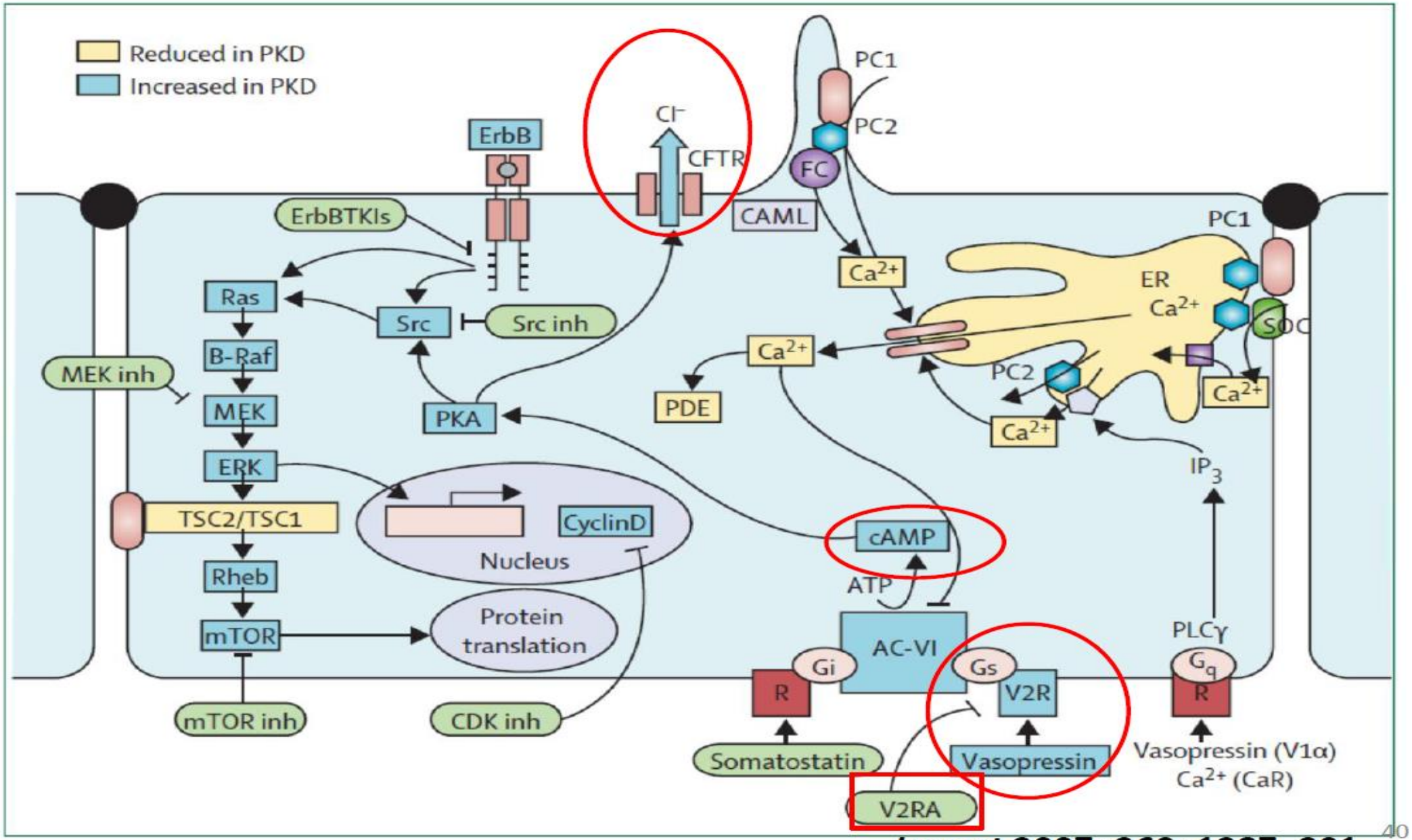
(2) ERK-mediated cell proliferation

(3) Cl^- secretion

(4) In vitro cyst growth

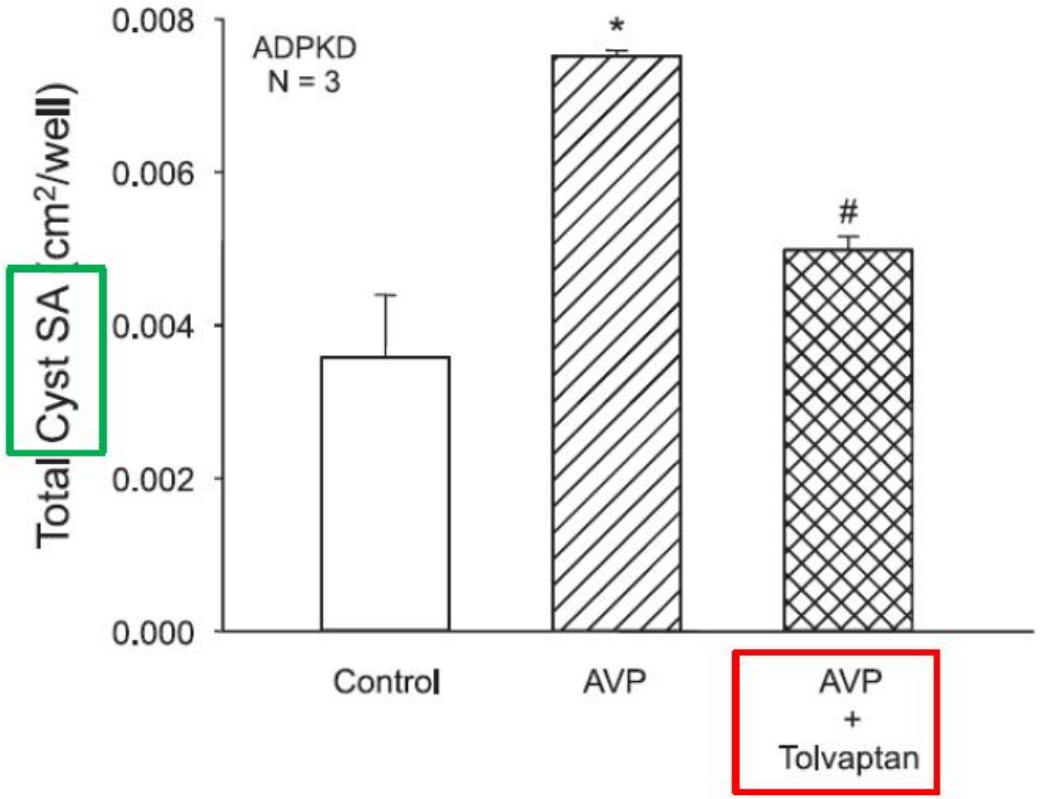
Am J Physiol Renal Physiol **301:F1005-F1013, 2011**

cAMP-dependent transcellular Cl^- secretion by apical CFTR Cl^- channels



Lancet 2007; 369: 1287–301

V2 receptor antagonism inhibits cell proliferation



Tolvaptan (10^{-10} to 10^{-8} M)

1. Inhibit AVP-induced activation of the B-Raf/MEK/ERK pathway and cell proliferation
2. Decrease AVP-stimulated Cl^- secretion
3. Decrease in vitro cyst growth of ADPKD cells

Am J Physiol Renal Physiol **301:F1005-F1013, 2011**

Table 3. Therapeutic targets for PKD supported by preclinical trials

Calcium signaling
Polycystin-2 channel activator
TRPV4 channel activator
Calcium-sensing receptor activator
cAMP signaling
Vasopressin V2 receptor antagonist
Somatostatin receptor agonist
PGE2 receptor (EP2 or EP4) antagonist
Catechol-*O*-methyl transferase
Phosphodiesterase activator
Cell proliferation
Receptor tyrosine kinase inhibitor (ErbB1, ErbB2, IGF1, VEGF, cMET)
Nonreceptor tyrosine kinase inhibitor (Src)
Serine-threonine kinase inhibitor (B-Raf, MEK1/2, p38MAPK, mTOR) or activator (AMPK)
Transcription factor agonists (PPARγ) or inhibitors (STAT3, STAT6)
Histone deacetylase (HDAC1, HDAC5, HDAC6) inhibitors
Cyclin-dependent kinase and Cdc25 phosphatase inhibitors
Apoptosis
Caspase inhibitors
Fluid secretion
CFTR channel blocker
KCa3.1 channel blocker
Other mechanisms
Proteasome inhibitors
Glycosyl ceramide synthase inhibitors
Lovastatin
ACE inhibitors
20-HETE synthase inhibitors
Protein restriction
Soy, flax diets
Citrate

References available on request. VEGF, vascular endothelial growth factor; B-Raf, B rapidly accelerated

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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

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Rational

- Until recently, no interventions were shown to slow the rate of disease progression in ADPKD.
- The treatment of ADPKD has therefore been symptomatic, with the aim of reducing morbidity and mortality associated with disease manifestations.
- This changed with the publication of the TEMPO 3:4 trial, which tested the efficacy of the vasopressin V2 receptor antagonist tolvaptan.

TEMPO 3:4 trial

- In this trial, 1445 patients with ADPKD were randomized to receive either placebo or tolvaptan in a split-dose regimen of 45 mg in the morning and 15 mg in the afternoon, uptitrated to 90/30 mg when tolerated.
- The trial duration was 3 years, which is typical for trials investigating renoprotective effects of medical interventions.

TEMPO 3:4 trial

- Per protocol, all patients were advised to increase fluid intake.
- Inclusion criteria were age 18–50 years,
- Estimated creatinine clearance (eCrCl) (Cockroft-Gault) ≥60 mL/min
- Total kidney volume (TKV) ≥750 mL.

TEMPO 3:4 trial

- Study medication was discontinued in 23% of tolvaptan- and 14% of placebo-treated patients.
- The intention-to-treat analysis of this study showed that tolvaptan slowed the rate of TKV growth by 49%from 5.5 to 2.8% per year,
- The rate of eGFR loss on treatment by 26% from 3.70 to 2.72 mL/min/1.73 m2 per year during the median observation period of 3 years.

TEMPO 3:4 trial

- Provided that this effect was maintained, it would translate into every 4 years of treatment delaying the incidence of ESRD by approximately one additional year.
- When studying the incidence of a 25% reduction in eGFR [a priori defined in the TEMPO 3:4 trial and accepted by the European Medicines Agency (EMA)], there was a significant 61% relative risk reduction with tolvaptan (number needed to treat to prevent one event was ~11)

GUIDANCE

- According to the EMA label, tolvaptan ‘is indicated to slow the progression of cyst development and renal insufficiency of ADPKD in adults with CKD stages 1–3 at initiation of treatment with evidence of rapidly progressing disease’.
- This indication incorporates two issues that need clarification:

CKD STAGE AND AGE AT THE INITIATION OF TREATMENT

- The EMA label for tolvaptan allows the treatment of patients with CKD stages 1–3, i.e. with an eGFR of >30 mL/min/1.73 m2.
- One of the inclusion criteria for the pivotal TEMPO3:4 trial was a creatinine clearance as estimated with the Cockroft-Gault equation ≥60 mL/min/1.73 m2. Due to tubular creatinine secretion, creatinine clearance overestimates GFR by ~20%

CKD STAGE AND AGE AT THE INITIATION OF TREATMENT

- Consequently, the TEMPO 3:4 trial included a considerable number of ADPKD patients (n = 247; 17%) with an eGFR, as determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, of <60 mL/min/1.73 m2.
- A post hoc analysis indicated that in these patients, treatment efficacy was similar or even slightly better than in those with higher eGFR

Recommendation 1.1: *We suggest that tolvaptan can be prescribed to adult ADPKD patients aged <50 years with CKD stages 1–3a (eGFR >45 mL/min/1.73 m²) who have demonstrated or who are likely to have rapidly progressing disease, but that CKD stage must be interpreted in conjunction with age.*

Recommendation 1.2: *We recommend not starting tolvaptan in patients aged 30–40 years with CKD stage 1 (eGFR >90 mL/min/1.73 m²).*

Recommendation 1.3: *We recommend not starting tolvaptan in patients aged 40–50 years with CKD stages 1 or 2 (eGFR >60 mL/min/1.73 m²).*

EVIDENCE OF RAPID DISEASE PROGRESSION

- While the EMA does not state why the indication for tolvaptan use focuses on patients with rapidly progressing disease, it is plausible that the benefit-to-risk ratio is highest in such patients.
- In contrast, patients who are slowly progressive would receive long drug exposure for little or no benefit.
- However, no official recommendations are provided as to who qualifies as having ‘rapid disease progression’.

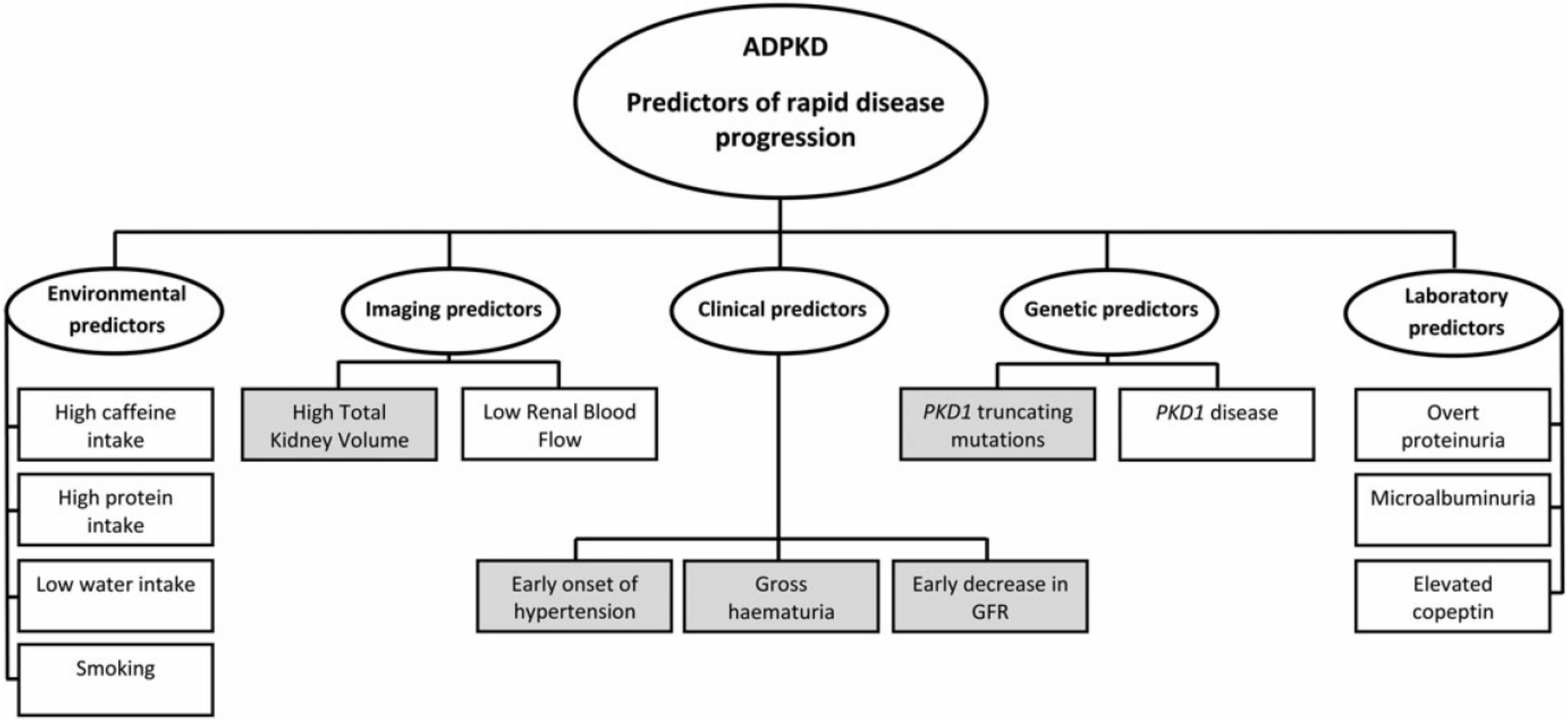

FIGURE 1: Markers used to assess prognosis in ADPKD. Shaded rectangles represent the best-validated markers (adapted from ref. [24]).

Recommendation 2: *A confirmed annual eGFR decline ≥5 mL/min/1.73 m^2 in 1 year, and/or ≥2.5 mL/min/1.73 m^2 per year over a period of 5 years, defines rapid progression.*

Recommendation 3: *A TKV increase of >5% per year by repeated measurements (preferably three or more, each at least 6 months apart and by MRI), defines rapid progression.*

JASN

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PMID: 24904092

Imaging Classification of Autosomal Dominant Polycystic Kidney Disease: A Simple Model for Selecting Patients for Clinical Trials

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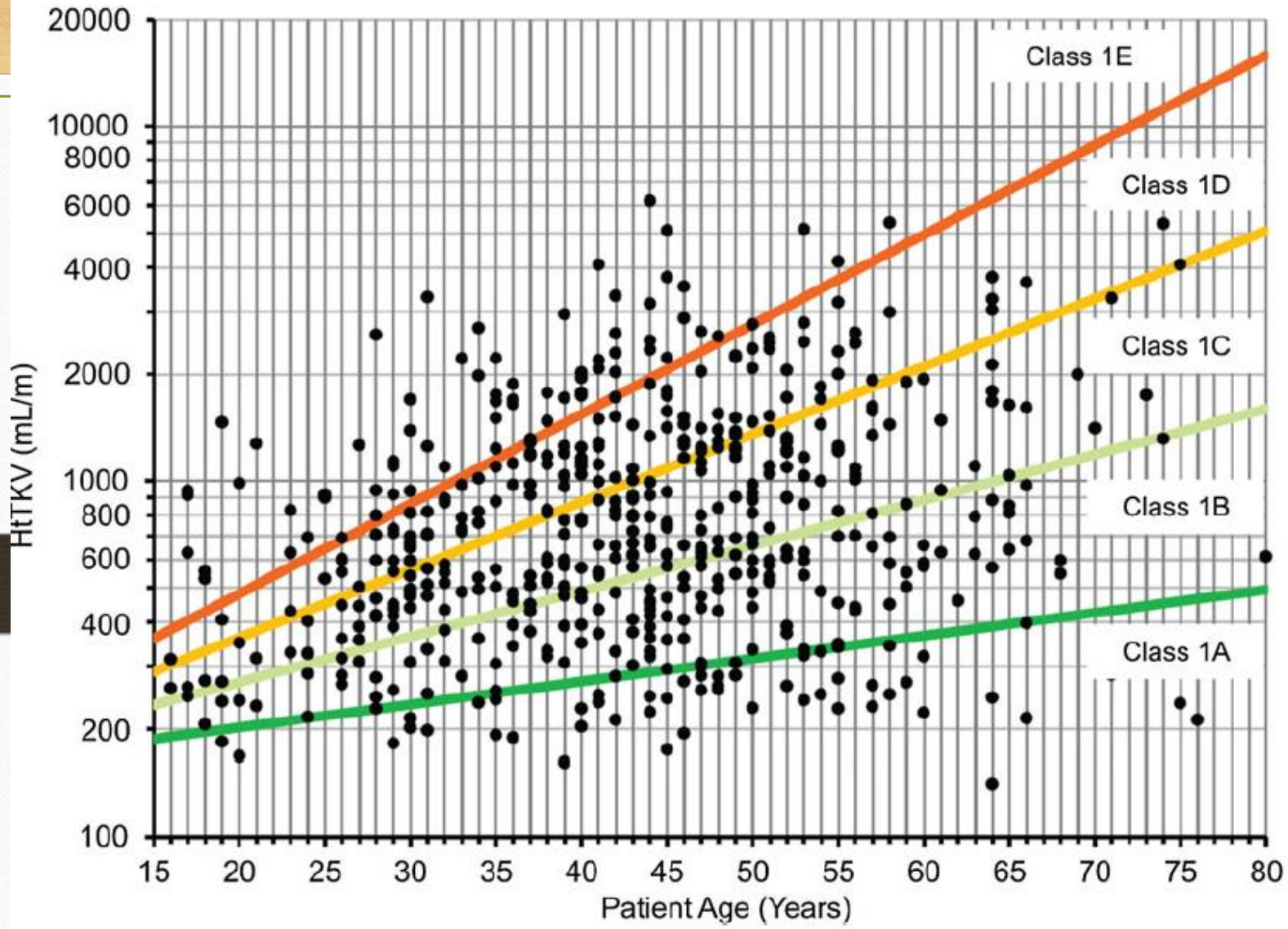
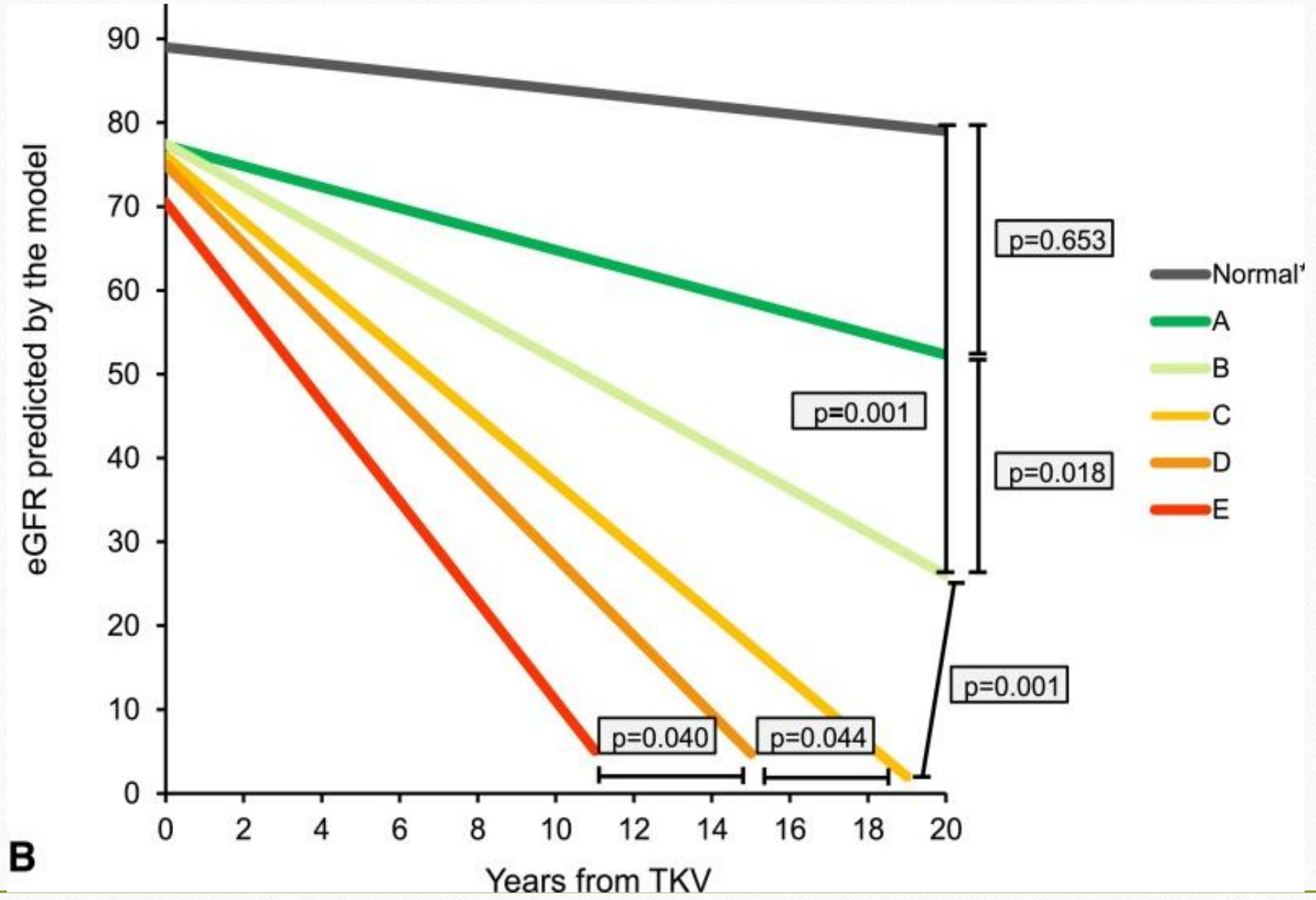


FIGURE 2: The Mayo classification for prediction of disease progression in ADPKD by htTKV and age. In general, class 1C, 1D and 1E patients will have rapid disease progression and qualify for treatment (derived from ref. [27]). Limits are defined based on estimated TKV growth rates of 1.5, 3.0, 4.5 and 6.0% per year. Estimated slopes of eGFR loss by subclass (1A–1E) are −0.1, −1.2, −2.5, −3.4 and −4.6 mL/min/1.73 m^2 per year, respectively, with no significant differences between men and women. The incidence of ESRD at 10 years increased by subclass (1A–1E), being 2.4, 11.0, 37.8, 47.1 and 66.9%, respectively [30].


90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
eGFR predicted by the model
Years from TKV
B
p=0.653
p=0.001
p=0.018
p=0.001
p=0.040
p=0.044
Normal
A
B
C
D
E

Imaging classification of ADPKD:
A simple model for selecting patients for clinical trials

FOR RESEARCH USE ONLY
This classification is intended to optimize the selection of patients for clinical trials.

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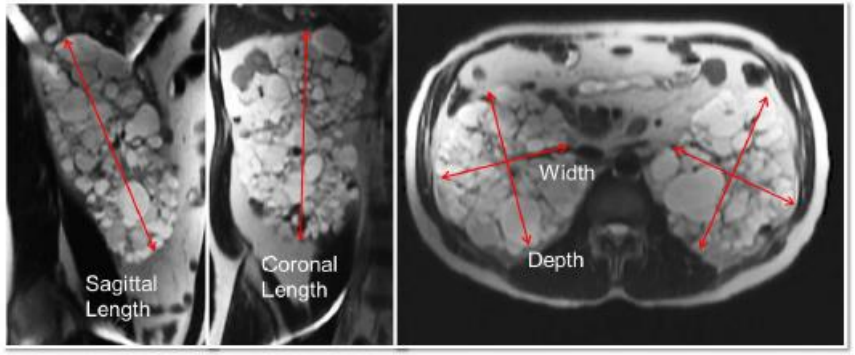
This application is compatible with Internet Explorer 9, Firefox, Chrome and Safari. Using a different browser will not display the graph correctly.

This classification should be applied only to patients previously classified as Typical* ADPKD, ages 15-80.
The classification is based on patient's height adjusted Total Kidney Volume (TKV) and Age.
The Kidney Volume Calculator (box 1) can be used to estimate patient's TKV using simple measurements from MRI or CT images.
If TKV has been previously calculated by Stereology technique, please skip box 1 and 2 and go straight to box 3.



1 Kidney Volume Calculator based on Ellipsoid equation (π/6xLxWxD) from MRI or CT image

Required Data Entry

Right Kidney		Left Kidney	
Sagittal Length (mm)		Sagittal Length (mm)	
Coronal Length (mm)		Coronal Length (mm)	
Width (mm)		Width (mm)	
Depth (mm)		Depth (mm)	

Calculated Results

Right Kidney Volume (mL) | Left Kidney Volume (mL) | Total Kidney Volume (mL)

Clear All | Calculate Volumes

2 ADPKD Classification using Kidney Volume Calculator

Required Data Entry		Calculated Results	
Patient Height (m)		Height Adjusted TKV (mL/m)	
Patient Age (years)		ADPKD Classification	

Clear All | Calculate Classification

3 ADPKD Classification if Kidney Volume previously calculated by Stereology

Required Data Entry		Calculated Results	
Kidney Volume (mL)		Height Adjusted TKV (mL/m)	

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

Recommendation 4.1: *We recommend the use of the Mayo classification of ADPKD that makes a distinction between '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).*

Recommendation 4.2: *We suggest that in ADPKD patients with Mayo classes 1C–1E disease (corresponding to a predicted eGFR decrease ≥2.5 mL/min/1.73 m^2 per year), rapid disease progression is likely.*

Recommendation 4.3: *We suggest that in patients with atypical morphology of ADPKD, as described in the Mayo classification, rapid disease progression is unlikely.*

Recommendation 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.*

Risk prediction using genetic and clinical factors

Table 1. The PRO-PKD score to assess prognosis in ADPKD (derived from ref. [42])

Being male: 1 point

Hypertension before 35 years of age: 2 points

First urological event (macroscopic haematuria, flank pain or cyst infection) before 35 years of age: 2 points

PKD2 mutation: 0 points

Non-truncating *PKD1* mutation: 2 points

Truncating *PKD1* mutation: 4 points

A score of ≤3 excludes progression to ESRD before the age of 60 years with a negative predictive value of 81.4%.

A score of >6 predicts rapid disease progression with ESRD onset before the age of 60 years with a positive predictive value of 90.9%.

For those with an intermediate score (4–6 points), the prognosis is unclear.

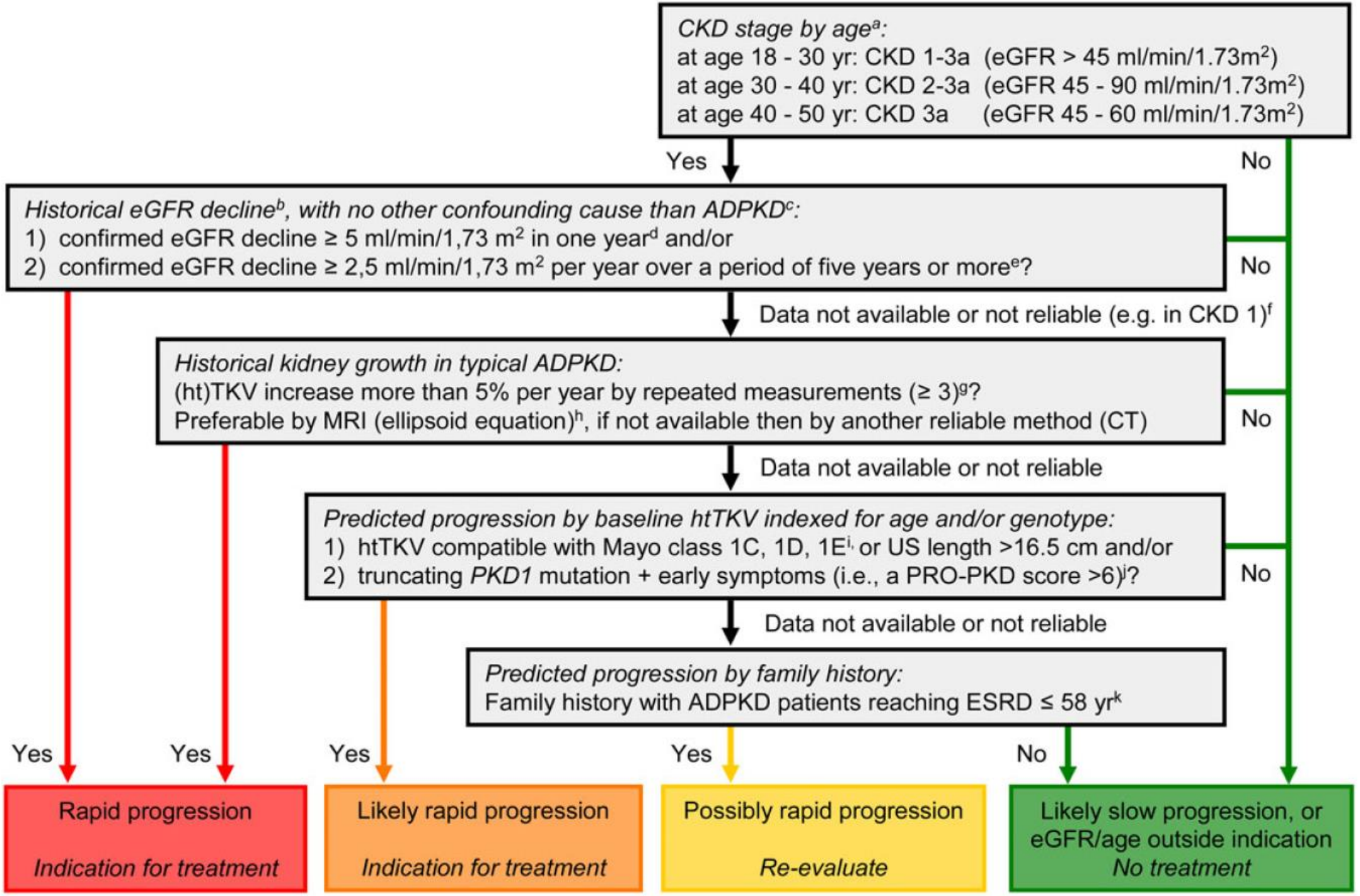

CKD stage by age[a]:
at age 18 - 30 yr: CKD 1-3a (eGFR > 45 ml/min/1.73m²)
at age 30 - 40 yr: CKD 2-3a (eGFR 45 - 90 ml/min/1.73m²)
at age 40 - 50 yr: CKD 3a (eGFR 45 - 60 ml/min/1.73m²)
Yes
No
Historical eGFR decline[b], with no other confounding cause than ADPKD[c]:
1) confirmed eGFR decline ≥ 5 ml/min/1,73 m² in one year[d] and/or
2) confirmed eGFR decline ≥ 2,5 ml/min/1,73 m² per year over a period of five years or more[e]?
No
Data not available or not reliable (e.g. in CKD 1)[f]
Historical kidney growth in typical ADPKD:
(ht)TKV increase more than 5% per year by repeated measurements (≥ 3)[g]?
Preferable by MRI (ellipsoid equation)[h], if not available then by another reliable method (CT)
No
Data not available or not reliable
Predicted progression by baseline htTKV indexed for age and/or genotype:
1) htTKV compatible with Mayo class 1C, 1D, 1E[i], or US length >16.5 cm and/or
2) truncating PKD1 mutation + early symptoms (i.e., a PRO-PKD score >6)[j]?
No
Data not available or not reliable
Predicted progression by family history:
Family history with ADPKD patients reaching ESRD ≤ 58 yr[k]
Yes
Yes
Yes
Yes
No
Rapid progression
Indication for treatment
Likely rapid progression
Indication for treatment
Possibly rapid progression
Re-evaluate
Likely slow progression, or eGFR/age outside indication
No treatment

Table 2. Contraindications, special warnings and precautions for the use of tolvaptan in ADPKD as derived from the EMA-approved label [45]

Contraindications	
• 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 that meet the requirements for permanent discontinuation of tolvaptan	
• Volume depletion	
• Hypernatraemia	
• Patients who cannot perceive or respond to thirst	
• Pregnancy	
• Breast-feeding	
Special warnings and precautions	
Idiosyncratic hepatic toxicity	Tolvaptan has been associated with idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST) with infrequent cases of concomitant elevations in bilirubin-total (BT). While these concomitant elevations were reversible with prompt discontinuation of tolvaptan, they represent a potential for significant liver injury. Guidelines to stop tolvaptan include: ALT or AST >8 times ULN ALT or AST >5 times ULN for >2 weeks ALT or AST >3 times ULN and BT >2 times ULN ALT or AST >3 times ULN with persistent symptoms of hepatic injury

cess to water	Tolvaptan induces aquaresis and may cause adverse reactions related to water loss, such as thirst, polyuria, nocturia and pollakiuria. Therefore, patients must have access to water (or other aqueous fluids) and be able to drink sufficient amounts of these fluids to avoid dehydration.
ydration	Special care must be taken in patients having diseases that impair appropriate fluid intake or who are at an increased risk of water loss, e.g. in case of vomiting or diarrhoea. Such patients should interrupt or reduce the dose of tolvaptan and increase fluid intake.
ne outflow obstruction	Urinary output must be secured. Patients with partial obstruction of urinary outflow, for example patients with prostatic hypertrophy or impairment of micturition, have an increased risk of developing acute retention.
id and electrolyte disturbances	The aquaretic effect of tolvaptan may cause dehydration and increases in serum sodium. Therefore, serum creatinine and electrolytes have to be assessed prior to and after starting tolvaptan to monitor for dehydration.
aphylaxis	Anaphylaxis has been reported very rarely following administration of tolvaptan. In case of anaphylaxis, administration of tolvaptan must be discontinued immediately and appropriate therapy initiated.
betes mellitus	It has been suggested that tolvaptan may cause hyperglycaemia. Therefore, diabetic patients treated with tolvaptan must be managed cautiously.
c acid increases	Decreased uric acid clearance by the kidney is a known effect of tolvaptan. Adverse reactions of gout were reported more frequently in tolvaptan-treated patients (2.9%) than in patients receiving placebo (1.4%).
ect on GFR	A reversible reduction in GFR has been observed at the initiation of tolvaptan treatment.

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 contraindications and adverse effects such as hepatic toxicity and other precautions as listed in Table 2 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.*

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 uptitrating the dose of tolvaptan to 60/30 and 90/30 mg when tolerated.*

Recommendation 9.3: *We suggest tolvaptan treatment to be discontinued when patients approach ESRD.*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease

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Robert D. McQuade, Ph.D., Jaime D. Blais, Ph.D., Frank S
and Olga Sergeyeva, M.D., M.P.H., for the REPRISE

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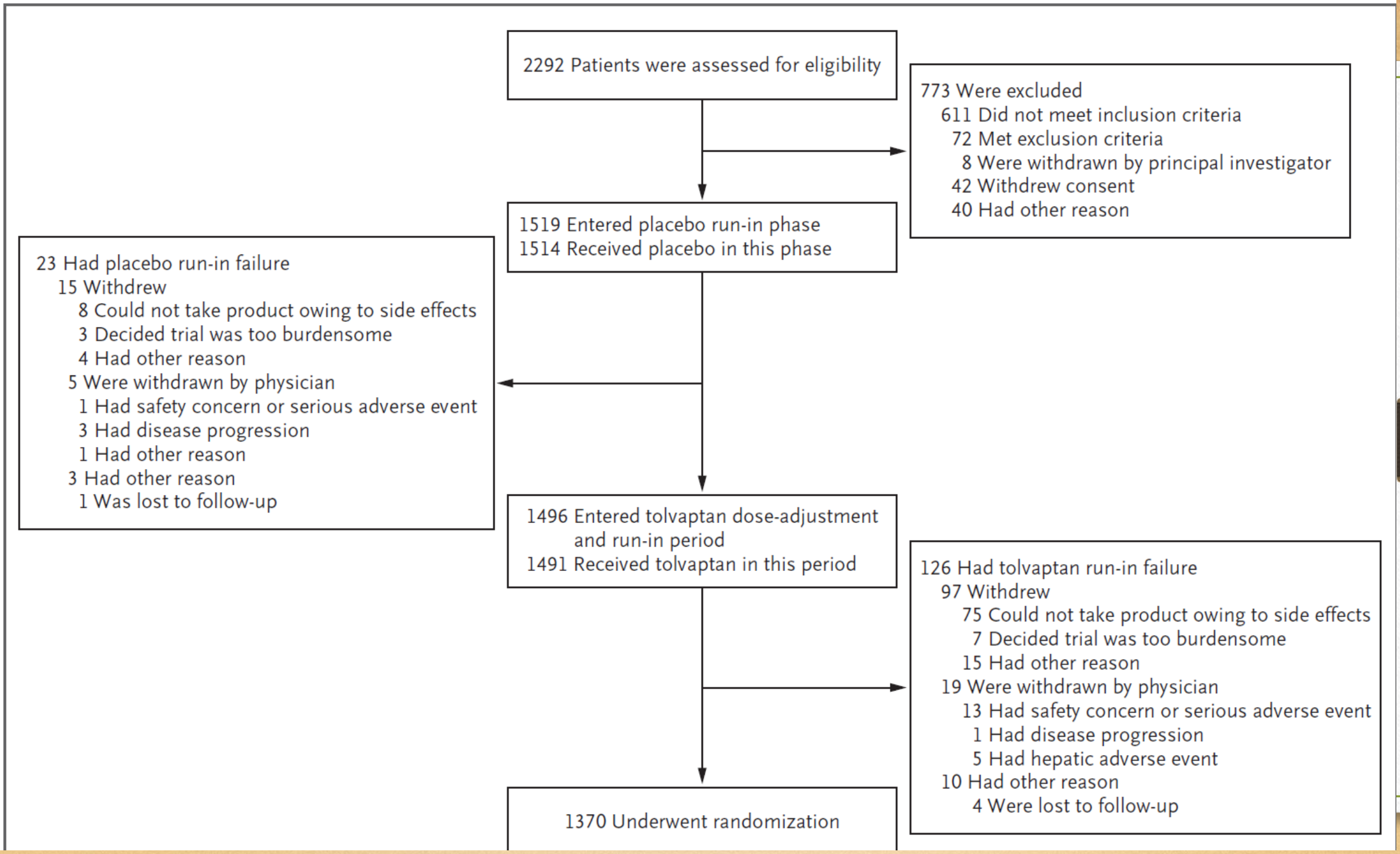
We conducted a phase 3, randomized withdrawal, multicenter, placebo-controlled, double-blind trial. After an 8-week prerandomization period that included sequential placebo and tolvaptan run-in phases, during which each patient's ability to take tolvaptan without dose-limiting side effects was assessed, 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 m^2 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 m^2 were randomly assigned in a 1:1 ratio to receive tolvaptan or placebo for 12 months. The primary end point was the change in the estimated GFR from baseline to follow-up, with adjustment for the exact duration that each patient participated (interpolated to 1 year). Safety assessments were conducted monthly.

RESULTS

The change from baseline in the estimated GFR was –2.34 ml per minute per 1.73 m^2 (95% confidence interval [CI], –2.81 to –1.87) in the tolvaptan group, as compared with –3.61 ml per minute per 1.73 m^2 (95% CI, –4.08 to –3.14) in the placebo group (difference, 1.27 ml per minute per 1.73 m^2; 95% CI, 0.86 to 1.68; P<0.001). Elevations in the alanine aminotransferase level (to >3 times the upper limit of the normal range) occurred in 38 of 681 patients (5.6%) in the tolvaptan group and in 8 of 685 (1.2%) in the placebo group. Elevations in the aminotransferase level were reversible after stopping tolvaptan. No elevations in the bilirubin level of more than twice the upper limit of the normal range were detected.

CONCLUSIONS

Tolvaptan resulted in a slower decline than placebo in the estimated GFR over a 1-year period in patients with later-stage ADPKD. (Funded by Otsuka Pharmaceuticals and Otsuka Pharmaceutical Development and Commercialization; REPRISE ClinicalTrials.gov number, NCT02160145.)


2292 Patients were assessed for eligibility
773 Were excluded
611 Did not meet inclusion criteria
72 Met exclusion criteria
8 Were withdrawn by principal investigator
42 Withdrew consent
40 Had other reason
1519 Entered placebo run-in phase
1514 Received placebo in this phase
23 Had placebo run-in failure
15 Withdrew
8 Could not take product owing to side effects
3 Decided trial was too burdensome
4 Had other reason
5 Were withdrawn by physician
1 Had safety concern or serious adverse event
3 Had disease progression
1 Had other reason
3 Had other reason
1 Was lost to follow-up
1496 Entered tolvaptan dose-adjustment and run-in period
1491 Received tolvaptan in this period
126 Had tolvaptan run-in failure
97 Withdrew
75 Could not take product owing to side effects
7 Decided trial was too burdensome
15 Had other reason
19 Were withdrawn by physician
13 Had safety concern or serious adverse event
1 Had disease progression
5 Had hepatic adverse event
10 Had other reason
4 Were lost to follow-up
1370 Underwent randomization

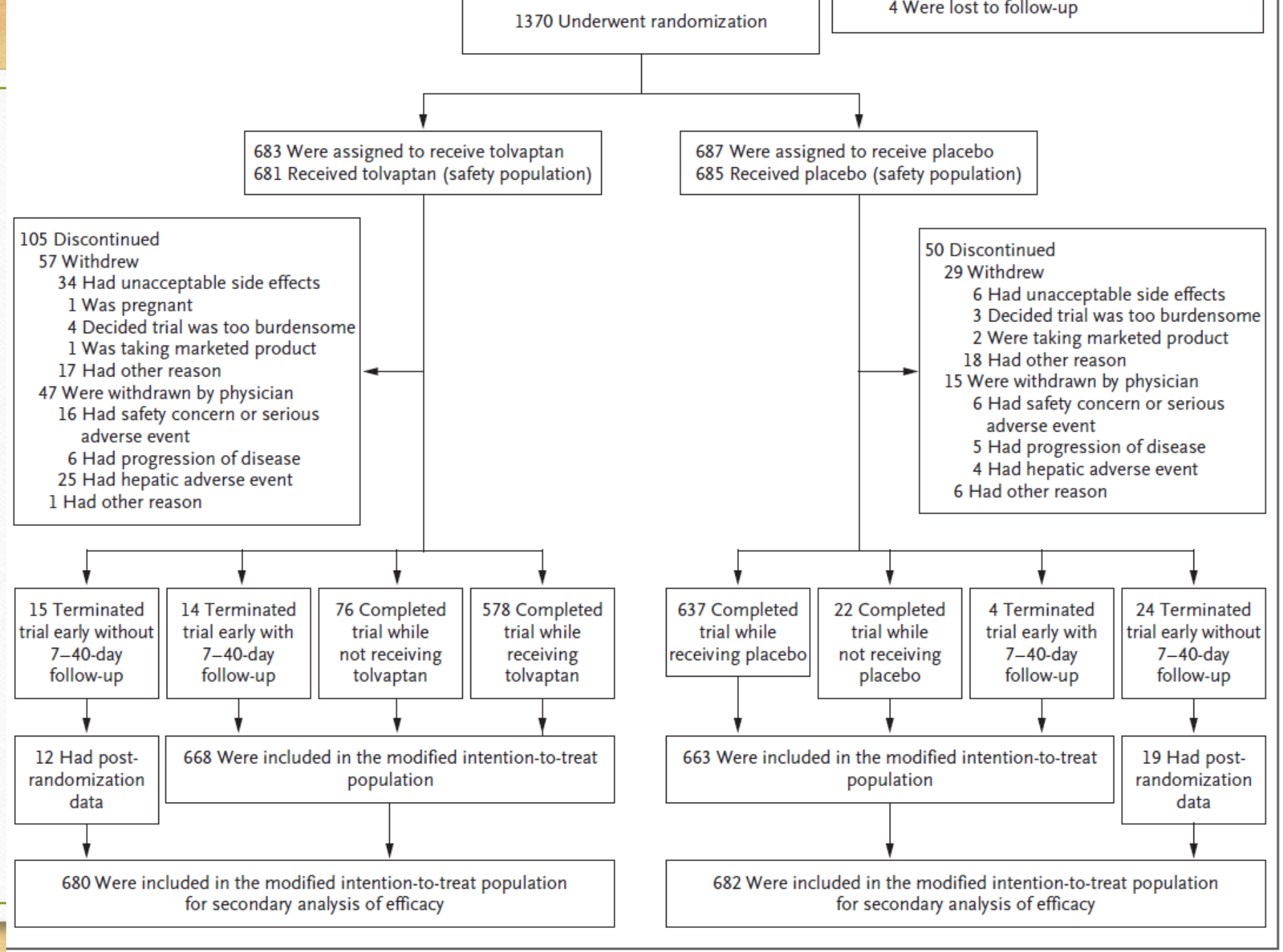

1370 Underwent randomization
4 Were lost to follow-up
683 Were assigned to receive tolvaptan
681 Received tolvaptan (safety population)
687 Were assigned to receive placebo
685 Received placebo (safety population)
105 Discontinued
57 Withdrew
34 Had unacceptable side effects
1 Was pregnant
4 Decided trial was too burdensome
1 Was taking marketed product
17 Had other reason
47 Were withdrawn by physician
16 Had safety concern or serious adverse event
6 Had progression of disease
25 Had hepatic adverse event
1 Had other reason
50 Discontinued
29 Withdrew
6 Had unacceptable side effects
3 Decided trial was too burdensome
2 Were taking marketed product
18 Had other reason
15 Were withdrawn by physician
6 Had safety concern or serious adverse event
5 Had progression of disease
4 Had hepatic adverse event
6 Had other reason
15 Terminated trial early without 7–40-day follow-up
14 Terminated trial early with 7–40-day follow-up
76 Completed trial while not receiving tolvaptan
578 Completed trial while receiving tolvaptan
637 Completed trial while receiving placebo
22 Completed trial while not receiving placebo
4 Terminated trial early with 7–40-day follow-up
24 Terminated trial early without 7–40-day follow-up
12 Had post-randomization data
668 Were included in the modified intention-to-treat population
663 Were included in the modified intention-to-treat population
19 Had post-randomization data
680 Were included in the modified intention-to-treat population for secondary analysis of efficacy
682 Were included in the modified intention-to-treat population for secondary analysis of efficacy

Table 1. Demographic and Clinical Characteristics at Baseline and Safety Profile during the Single-Blind Tolvaptan Period.*

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)

A Subgroup Analyses

Subgroup	Tolvaptan	Placebo	Mean Estimated GFR Change (95% CI) Tolvaptan	Mean Estimated GFR Change (95% CI) Placebo	Difference	P Value
	no. of patients		*ml/min/1.73 m²*			
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 estimated GFR						
≤45 ml/min/1.73 m²	432	423	−3.45	−4.35	0.90	<0.001
>45 ml/min/1.73 m²	236	240	−2.20	−4.11	1.91	<0.001
Chronic kidney disease 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