KCC Lunch & Learn

PKD Education

October 28, 2021

12:00pm to 1:00pm

BCRenal

Provincial Health Services Authority

Agenda

- Welcome
- Assessment and management of ADPKD
  - Patient evaluation
  - Treatment
  - Extra-renal considerations
- ADPKD Resources
- PROMIS updates
- ADPKD Evaluation
- ADPKD & Genetics

Disclosures

- I have accepted:
  - Otsuka Pharmaceuticals Canada (advisory, consultant and speaker's fees; grants)
  - Sanofi Canada (advisory fees)
  - Boehringer Ingelheim Canada (speaker's fees)
  - AstraZeneca Canada (speaker's fees)
  - Janssen Canada (advisory and speaker's fees)

Lots of credit goes to our ADPKD Network team!!

The BC ADPKD Network

Patient partners: Elyse Gawley, Phaydy Phanouvong and Paul Watson.

Healthcare providers and administrators: Judith Andrews, Caroline Babich, Lianne Berst, Micheli Bevilacqua, Alice Cabarlo, Jesse Colbeck, Fareen Din, Ognjenka Djurdjev, John Duncan, Debra Fairhurst, Myriam Farah, Kirsten Flood, Sharon Gradin, Dallas Hengstler, Robert Humphreys, Karin Jackson, Charlene Kearsley, Mercedeh Kiaii, Sanford Kong, Brenda Lee, Adeera Levin, Clifford Lo, Lisa MacKenzie, Judith Marin, Dan Martinussen, Kristin Mole, Paula Ranier-Pope, Kiyomi Renville, Alexandra Romann, Lynn Tomita, Violet Tong, Mary Van Der Hoek, Alexis Whatley, Carla Williams, Hilary Wu, Nadia Zalunardo and Jennifer Zinetti

Epidemiology

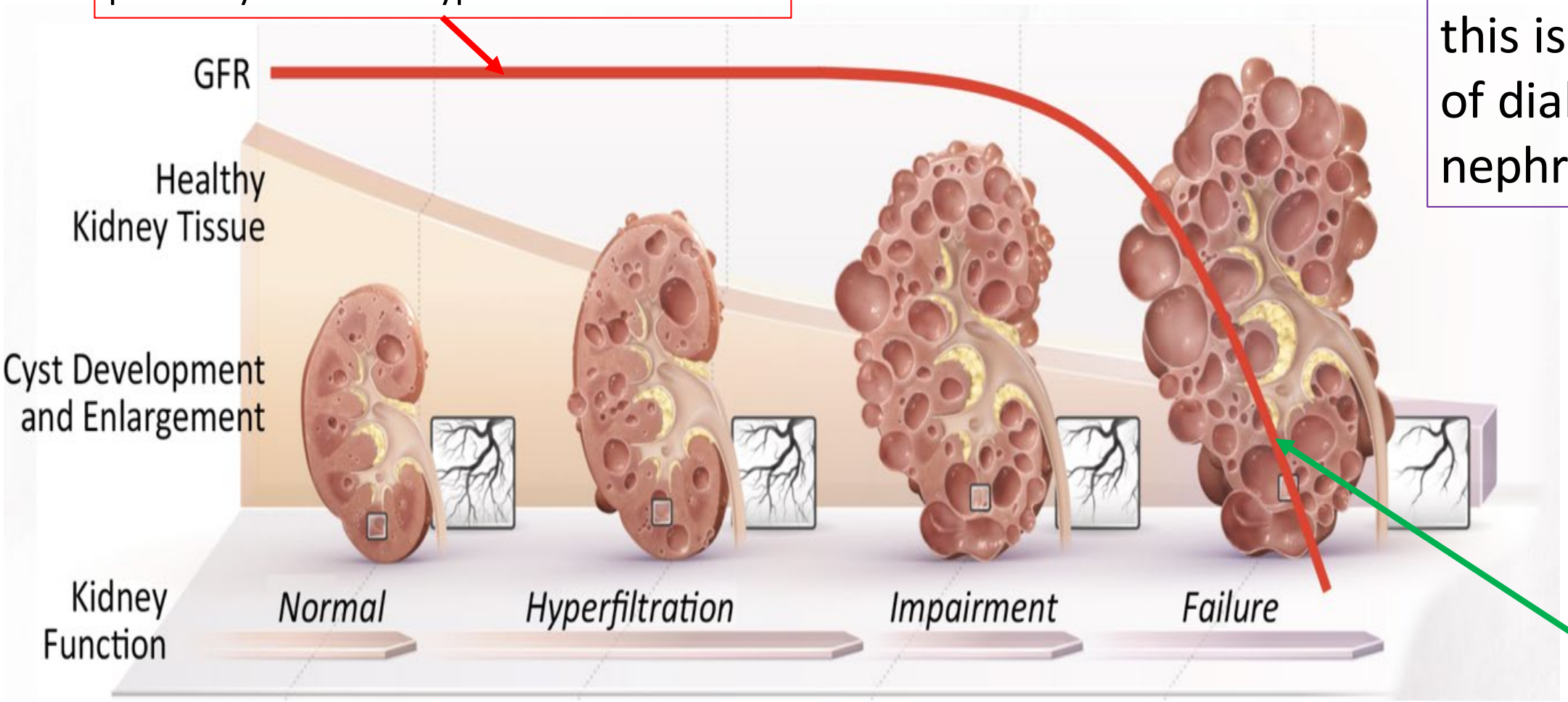
- Autosomal dominant polycystic kidney disease (ADPKD) is **the most common inherited renal disorder**, affecting between 1-2.5/1000 live births
  - Although exact provincial numbers are lacking, this estimate would mean there are somewhere from **4600 to over 10000** British Columbians living with the disease.

- Of patients with an identifiable etiology of ESRD, ADPKD is the 4th leading cause of ESRD in Canada

Modern understanding of ADPKD disease course

Maintained GFR in the setting of renal parenchymal loss = hyperfiltration

A good way to conceptualize this is to think of diabetic nephropathy



Upwards of 5ml/year decline

The disease course is variable one, with the early disease marked by cyst proliferation and expansion with little renal dysfunction followed by a precipitous decline. The corollary here is that by the time there is a change in GFR, significant cyst expansion and proliferation has already occurred

Changes in kidney size precede change in renal function

Significant changes in kidney volume can be detected years before changes in GFR

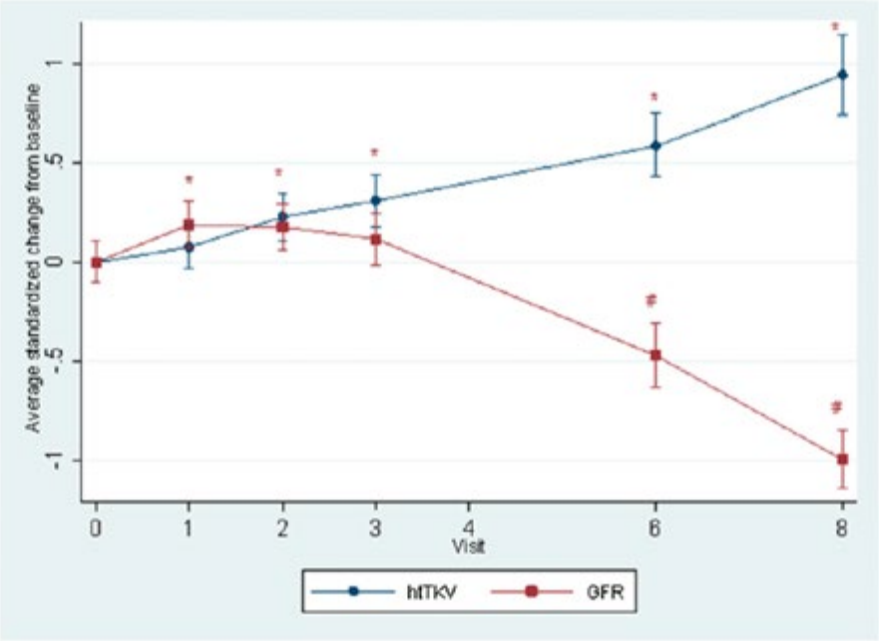
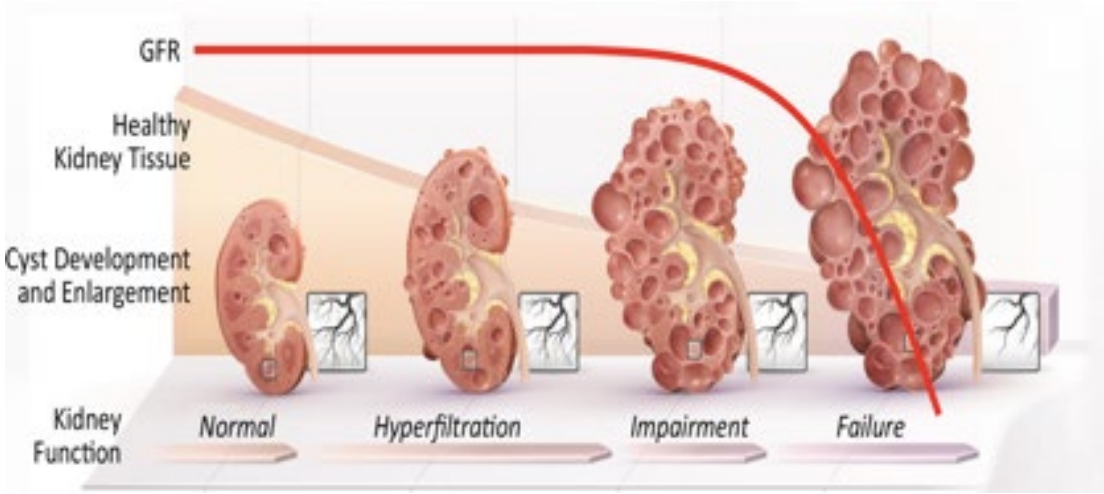


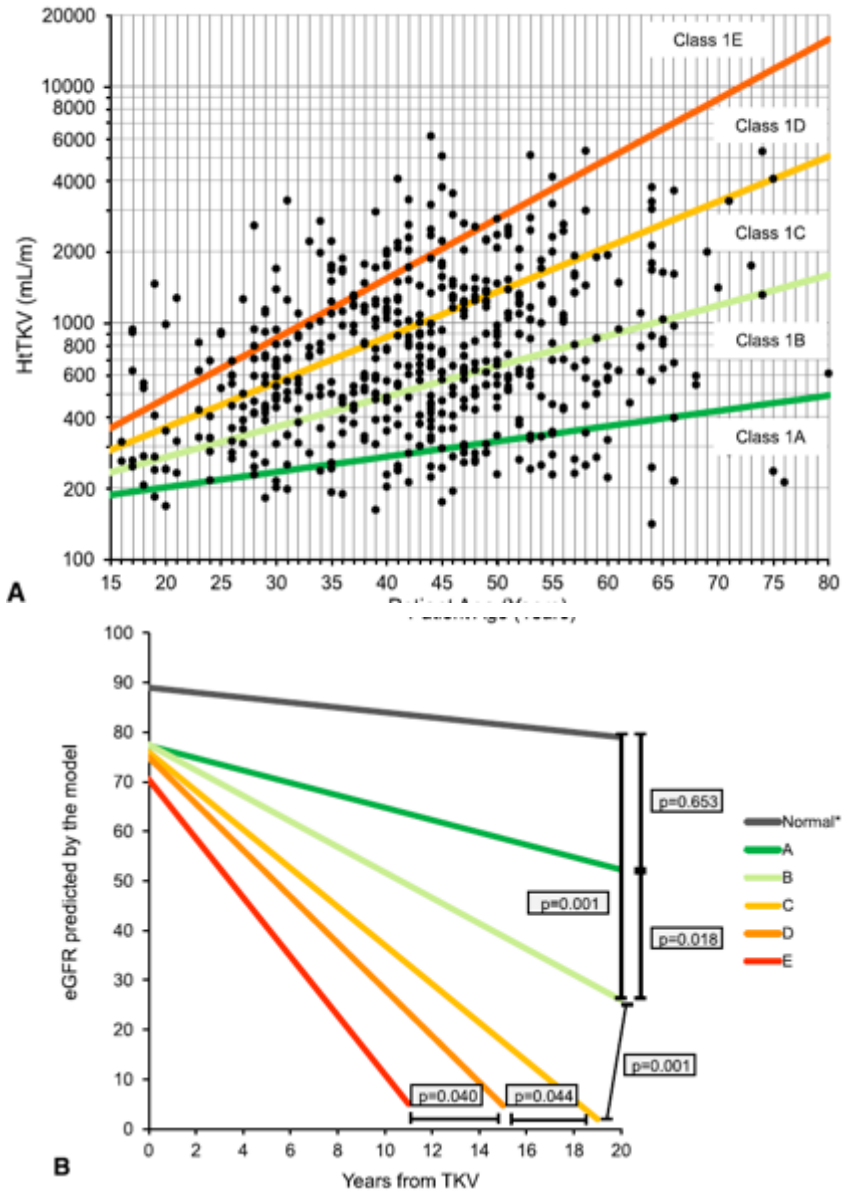
Figure 2. | Average standardized change in htTKV and iothalamate GFR. htTKV determined at baseline and iothalamate GFR at baseline and five subsequent visits until year 8 (n=93 with complete data). P<0.01 based on paired t test comparing each year to baseline for htTKV (*) and GFR (#). htTKV, height-adjusted total kidney volume.



Clin J Am Soc Nephrol 7: 479–486, 2012.

Total Kidney Volume (TKV)-based prognostication: the Mayo classification

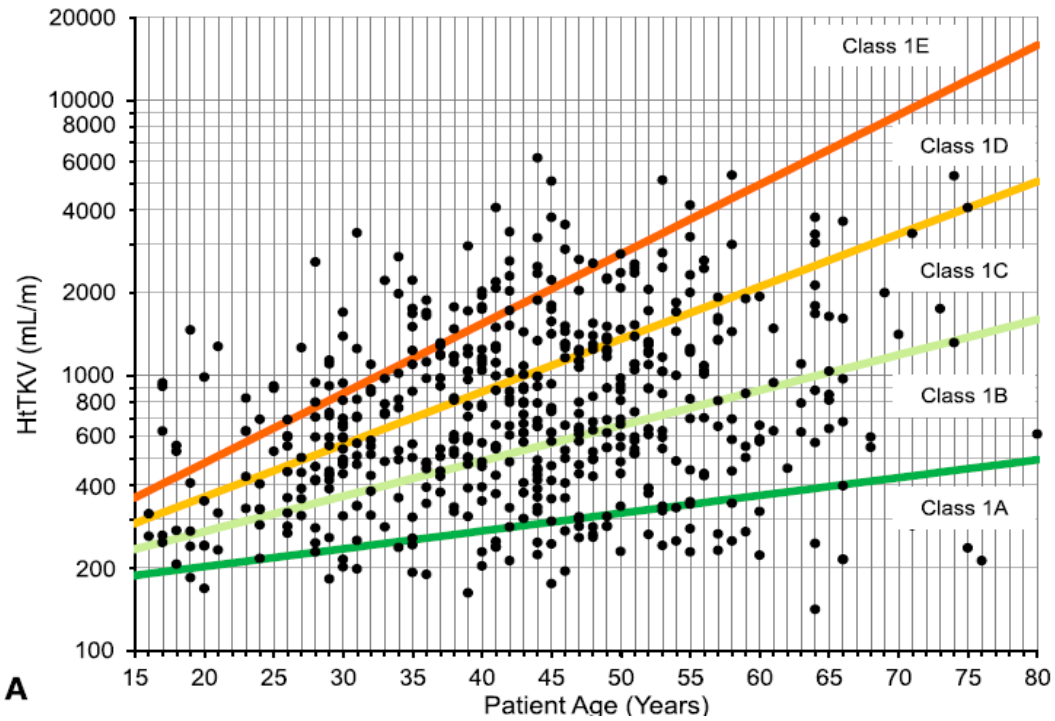
At present this appears to be the most robust individualized predictor of **early stage** progression in PKD patients (i.e., before GFR declines)



J Am Soc Nephrol 26: 160–172, 2015.

Mayo classification categorizes rate of kidney growth

Class	Average annual change in TKV
1A	<1.5%
1B	1.5-3
1C	3-4.5
1D	4.5-6
1E	>6%



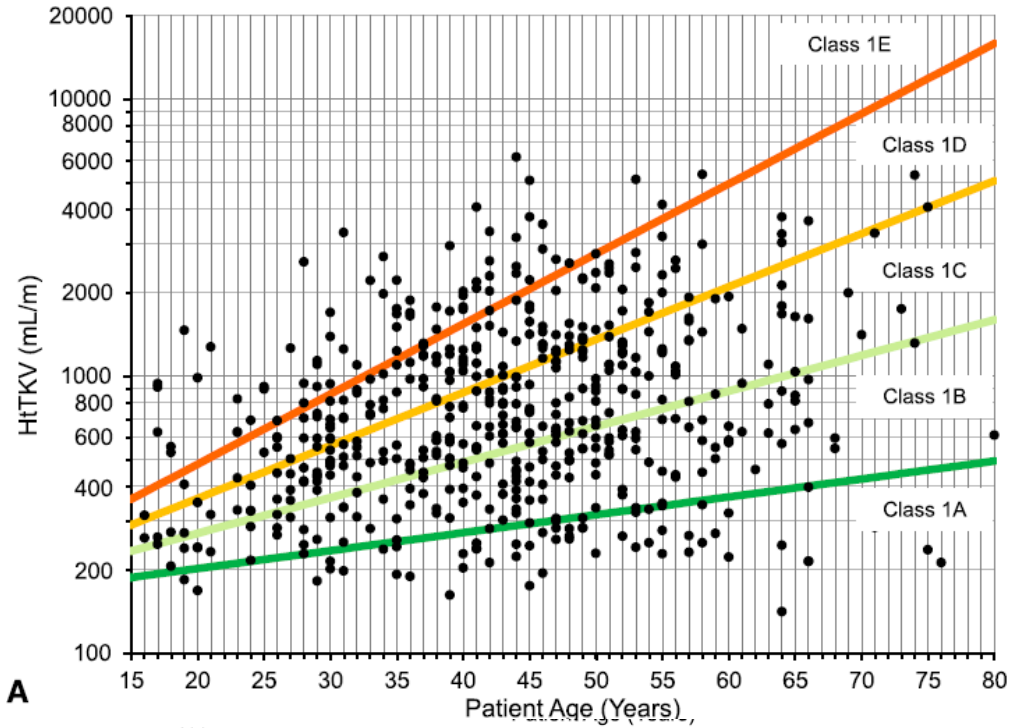
The 1A-1E classification is best thought of as a ***velocity of growth classification*** – the classes refer to the average annual growth in htTKV

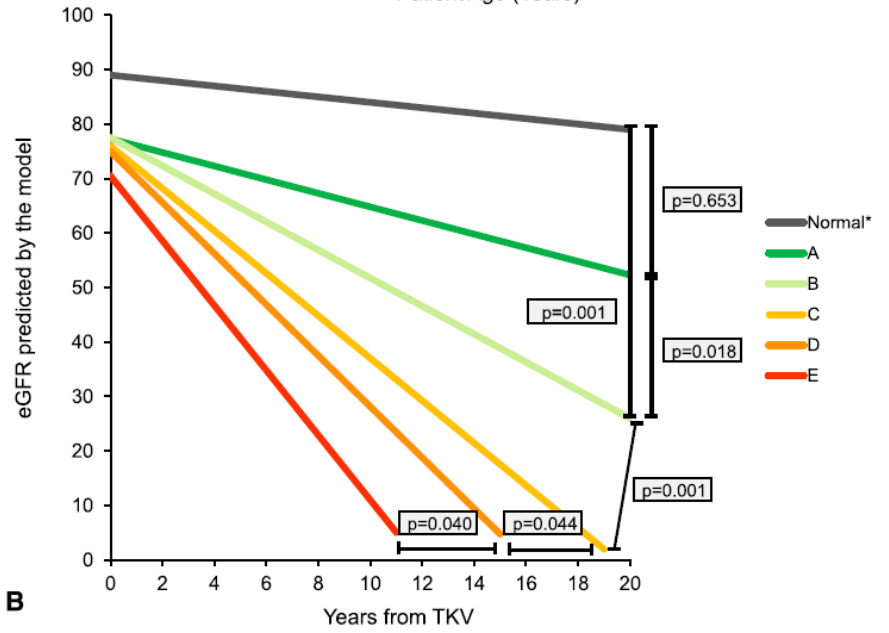
J Am Soc Nephrol 26: 160–172, 2015.

Mayo class predicts rate of GFR loss

Class	Average annual change in TKV	Average annual decrease in eGFR
1A	<1.5%	0.23
1B	1.5-3	1.33
1C	3-4.5	2.63
1D	4.5-6	3.48
1E	>6%	4.78

The average GFR comes from >8 years of CRISP and Mayo clinic follow-up data





J Am Soc Nephrol 26: 160–172, 2015.

Disease modifying treatment for ADPKD

ORIGINAL ARTICLE

Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease

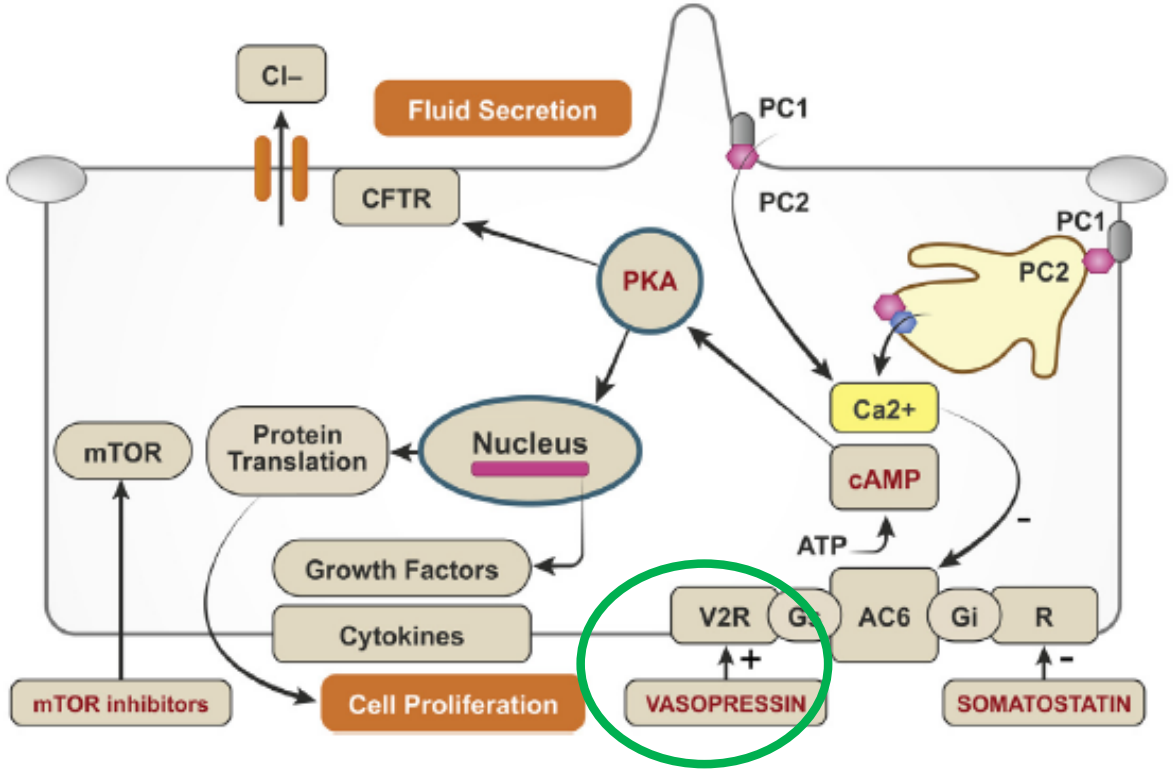
Vicente E. Torres, M.D., Ph.D., Arlene B. Chapman, M.D., Olivier Devuyst, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D., Jared J. Grantham, M.D., Eiji Higashihara, M.D., Ph.D., Ronald D. Perrone, M.D., Holly B. Krasa, M.S., John Ouyang, Ph.D., and Frank S. Czerwiec, M.D., Ph.D., for the TEMPO 3:4 Trial Investigators*

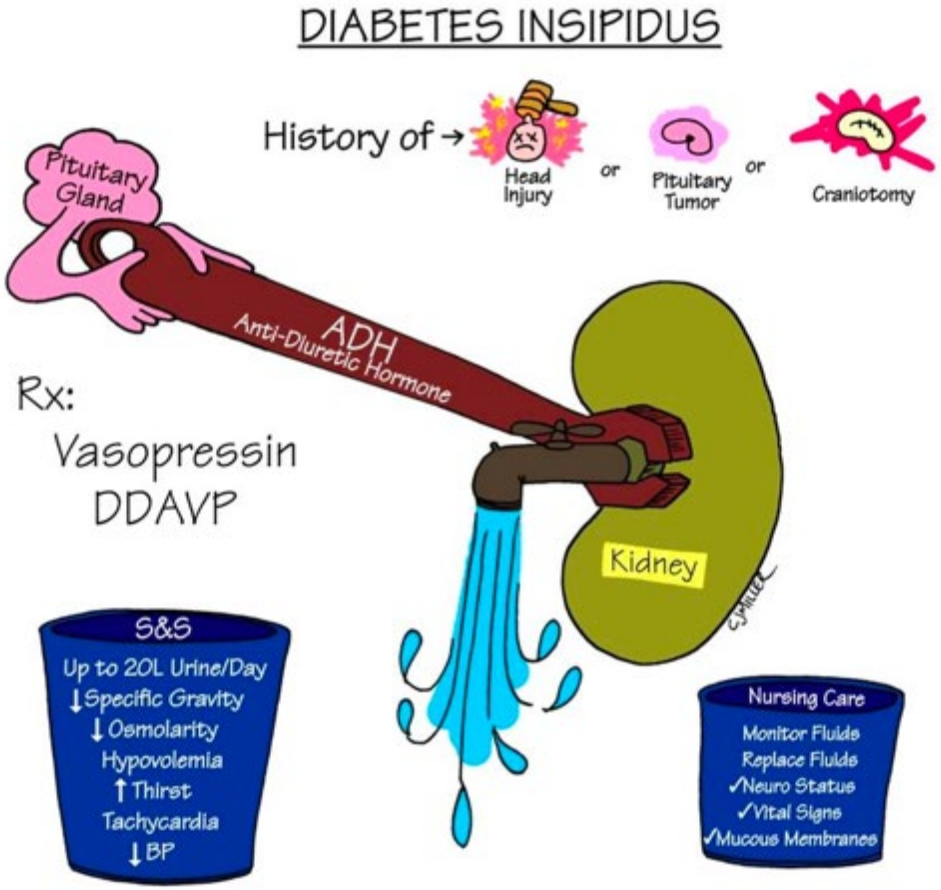
ORIGINAL ARTICLE

Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease

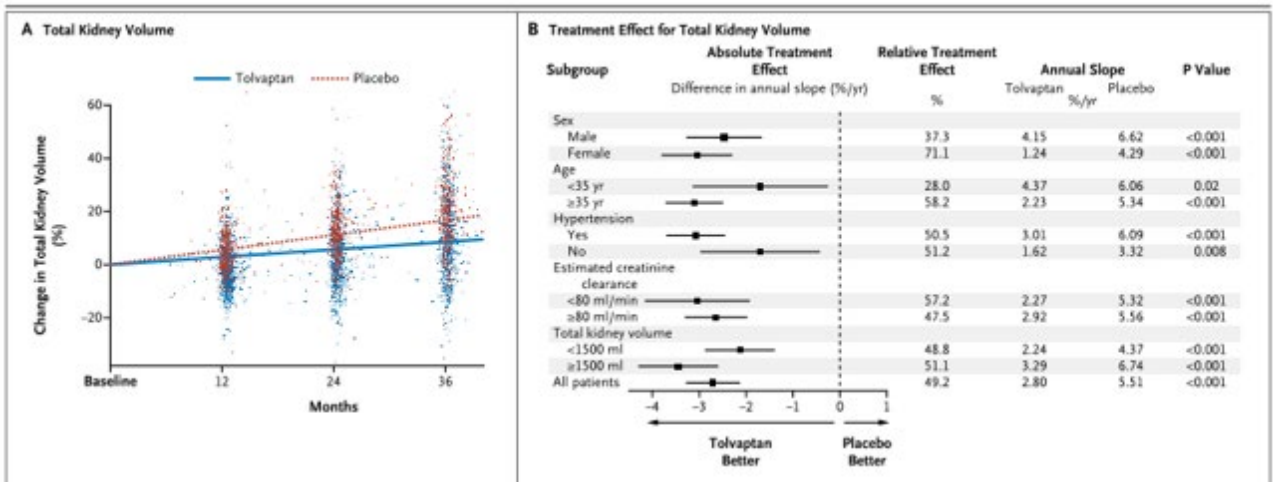
Vicente E. Torres, M.D., Ph.D., Arlene B. Chapman, M.D., Olivier Devuyst, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D., Ronald D. Perrone, M.D., Gary Koch, Ph.D., John Ouyang, Ph.D., Robert D. McQuade, Ph.D., Jaime D. Blais, Ph.D., Frank S. Czerwiec, M.D., Ph.D., and Olga Sergeyeva, M.D., M.P.H., for the REPRISE Trial Investigators*

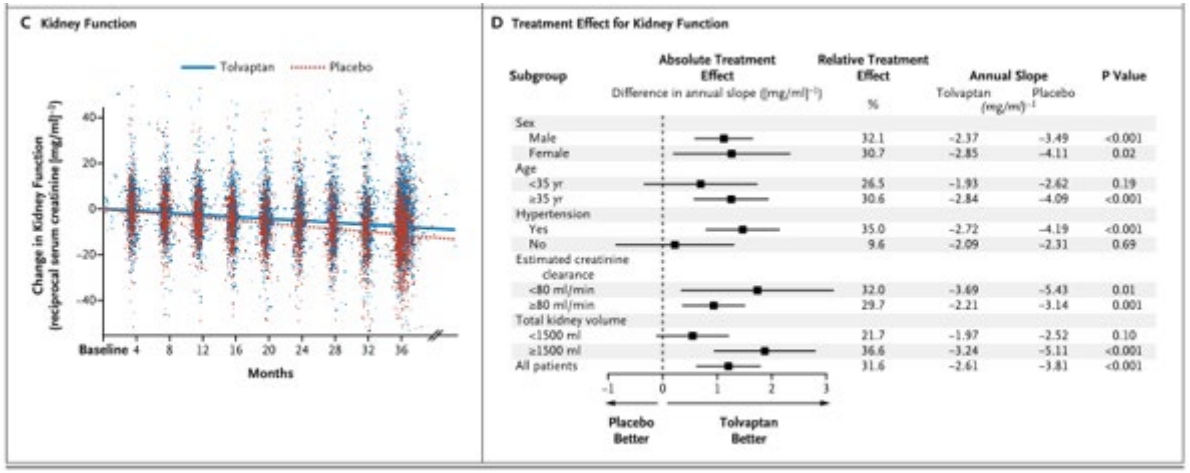
How tolvaptan (vasopressin 2 receptor antagonist) works





Results in (earlier) stage patients

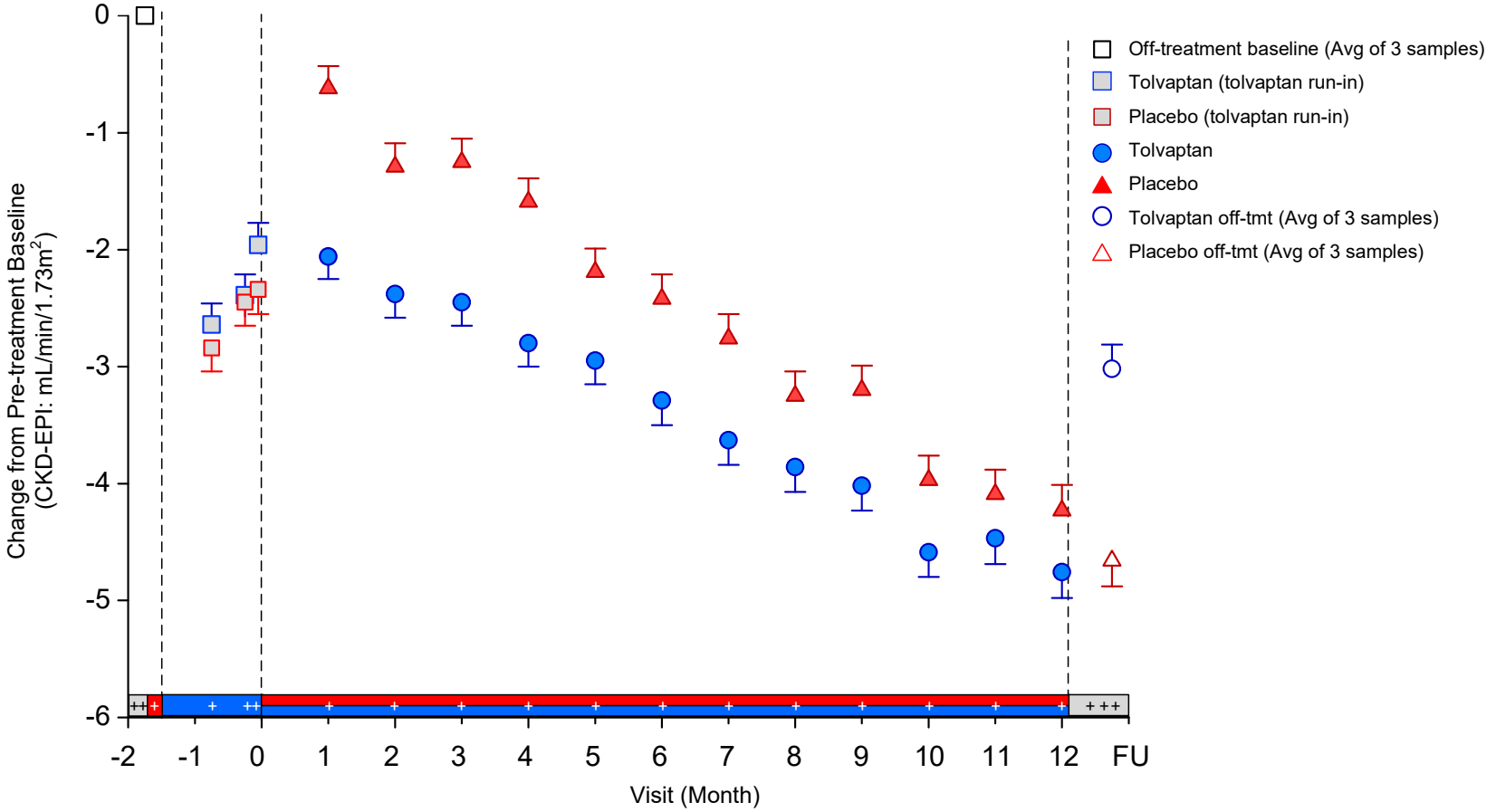


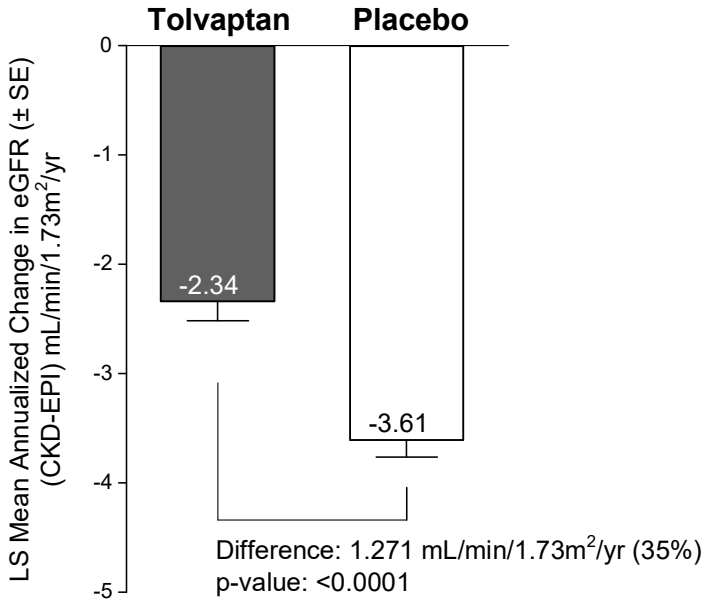


Increase in TKV was 2.8%/year(2.3-3.1%) in the tolvaptan group vs. 5.5%/year (5.1-6.0%) in the placebo group

Slope of reciprocal of creatinine (which varies directly with GFR) was-2.61/year compared to -3.81/year in the placebo group. This corresponds to a GFR slope of -2.72ml/min/year vs. -3.70ml/min/year

Results in later stage patients



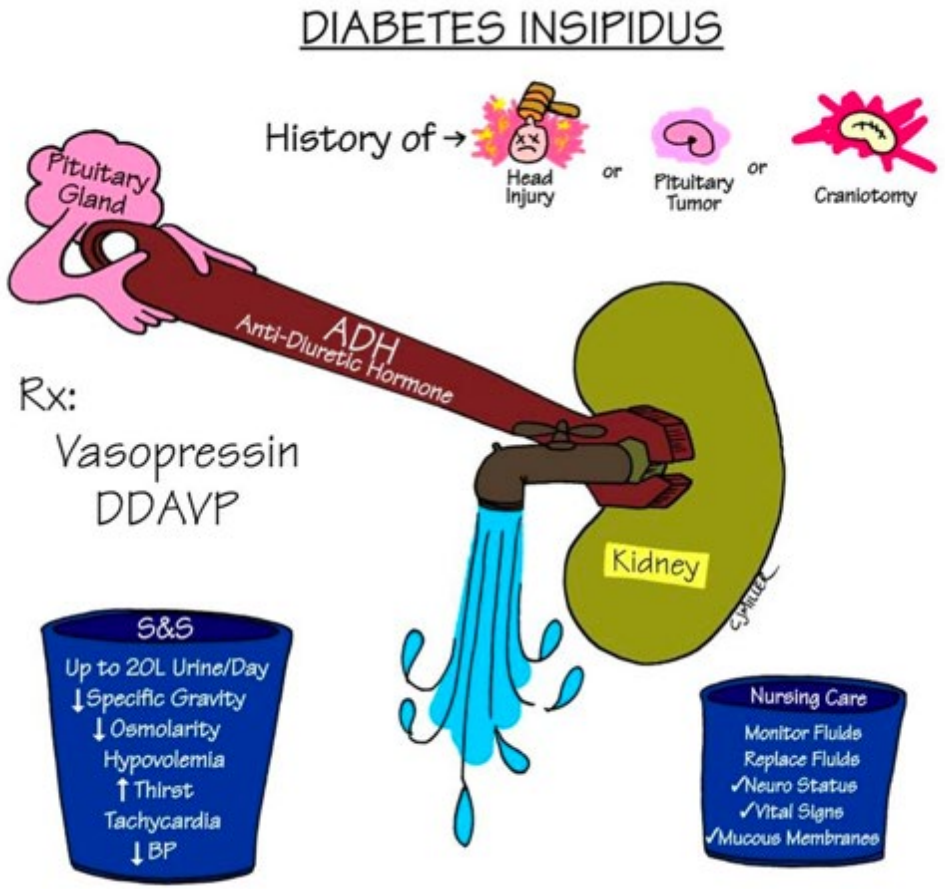


Adverse effects - aquaretic symptoms

This is a difficult drug for patients to work into their lives

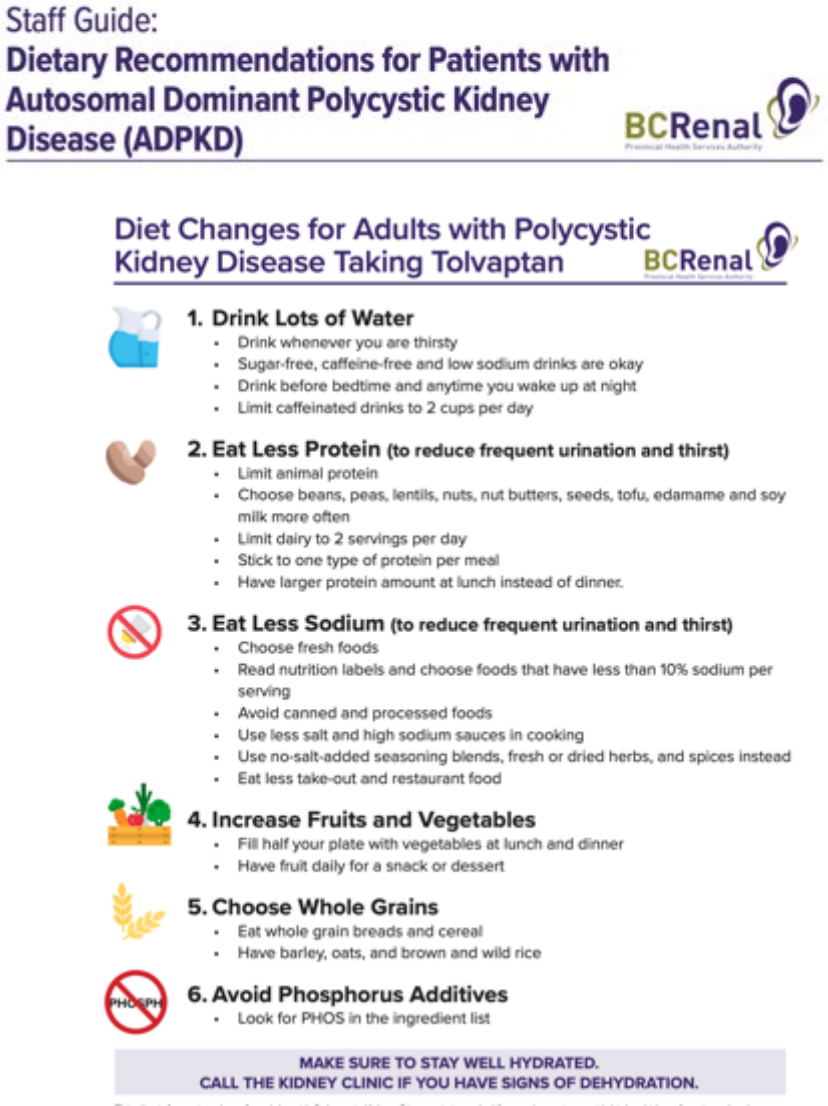
I think of it as inducing a different disease to slow the existing one

- There is a high rate of side effects and discontinuation



Dealing with aquaretic symptoms

- Judicious approach to dose titration
  - “Do you think you could carry on with this for the rest of your life”
- **Minimizing and distributing dietary solute intake (primarily salt and protein)**
- Treat this as a ‘sick day’ medication
- AND also a ‘convenience day’ or ‘cheat day’ medication



Staff Guide:

Dietary Recommendations for Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Diet Changes for Adults with Polycystic Kidney Disease Taking Tolvaptan

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1. Drink Lots of Water

- Drink whenever you are thirsty
- Sugar-free, caffeine-free and low sodium drinks are okay
- Drink before bedtime and anytime you wake up at night
- Limit caffeinated drinks to 2 cups per day

2. Eat Less Protein (to reduce frequent urination and thirst)

- Limit animal protein
- Choose beans, peas, lentils, nuts, nut butters, seeds, tofu, edamame and soy milk more often
- Limit dairy to 2 servings per day
- Stick to one type of protein per meal
- Have larger protein amount at lunch instead of dinner.

3. Eat Less Sodium (to reduce frequent urination and thirst)

- Choose fresh foods
- Read nutrition labels and choose foods that have less than 10% sodium per serving
- Avoid canned and processed foods
- Use less salt and high sodium sauces in cooking
- Use no-salt-added seasoning blends, fresh or dried herbs, and spices instead
- Eat less take-out and restaurant food

4. Increase Fruits and Vegetables

- Fill half your plate with vegetables at lunch and dinner
- Have fruit daily for a snack or dessert

5. Choose Whole Grains

- Eat whole grain breads and cereal
- Have barley, oats, and brown and wild rice

6. Avoid Phosphorus Additives

- Look for PHOS in the ingredient list

MAKE SURE TO STAY WELL HYDRATED.
CALL THE KIDNEY CLINIC IF YOU HAVE SIGNS OF DEHYDRATION.

Increased transaminases and need for monitoring

- Overall, there is a 4-5% rate of increased liver enzymes with tolvaptan

  To compare to other drugs associated with AST/ALT increases:
  - INH: up to 20%
  - MTX: 15%
  - Amiodarone: 3-6%
  - Lipitor: <2%

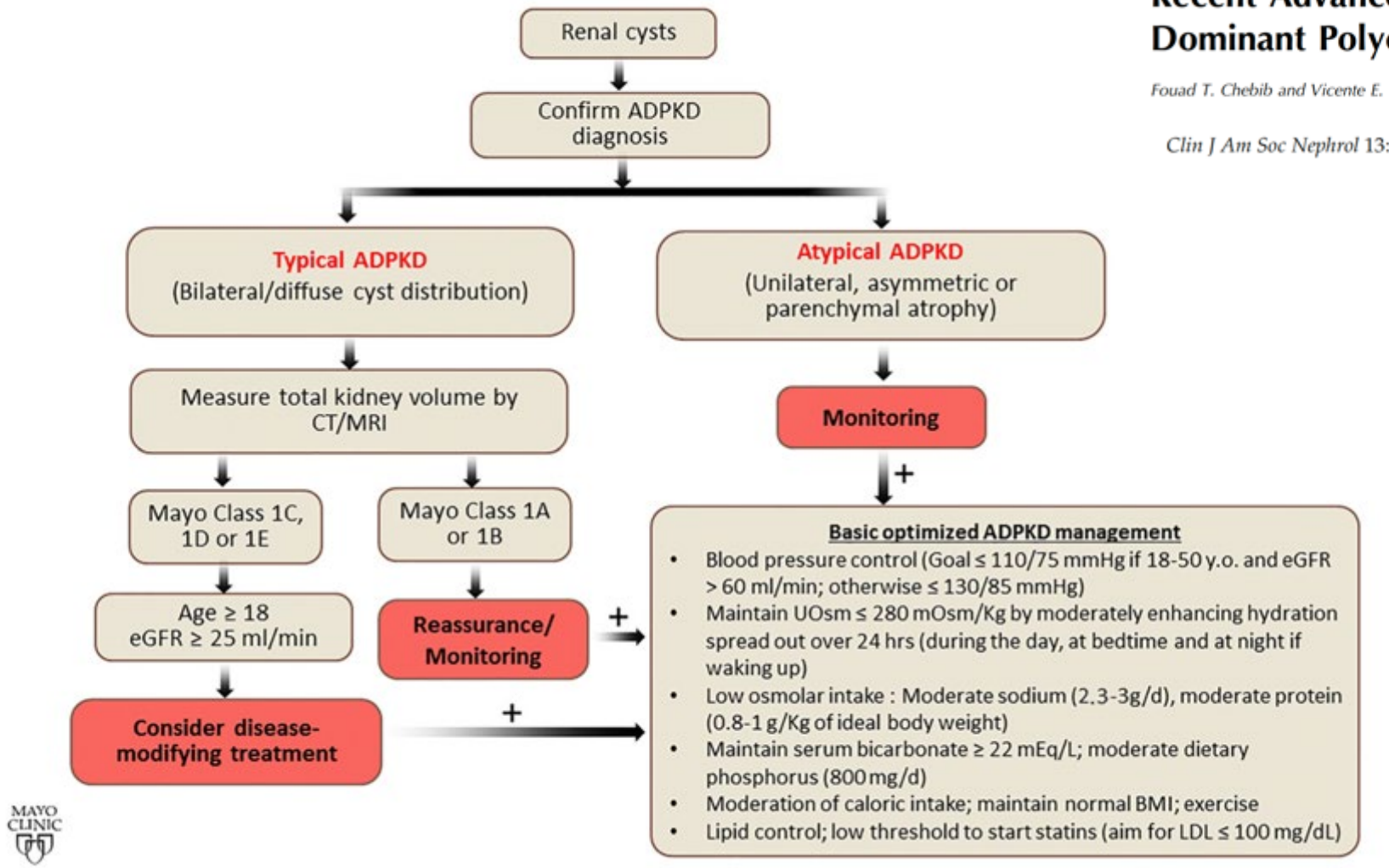
- But in the trials, 3 patients had AST/ALT >3xULN *and* bilirubin >2xULN.
  - Signal of much worse liver injury called **Hy's Law**

- **The injury is reversible with drug discontinuation if done in a timely fashion**

- There is **mandatory** hepatic monitoring while on tolvaptan (monthly at first then q3 months)
- With this monitoring pathway, although there are incidents of transaminitis, there have been no Hy's Law patients in Canada (nearing 2000 patients treated)

A new management paradigm for ADPKD

Targeted and non-target treatments



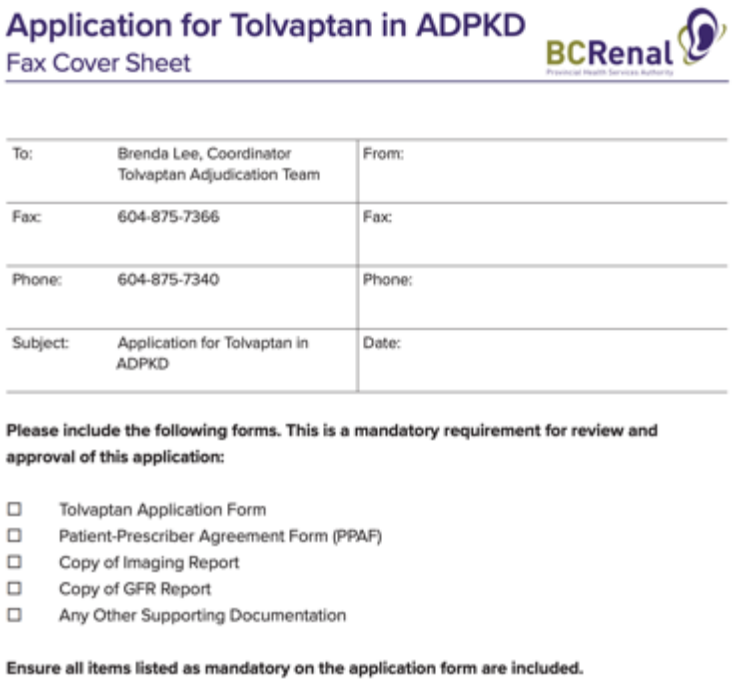
Recent Advances in the Management of Autosomal Dominant Polycystic Kidney Disease

Fouad T. Chebib and Vicente E. Torres

Clin J Am Soc Nephrol 13: ●●●–●●●, 2018. doi: https://doi.org/10.2215/CJN.03960318

Note that when talking about disease modifying treatment, the goal is selection of **rapid progressors**

Application for tolvaptan



Application for Tolvaptan in ADPKD

Fax Cover Sheet

BCRenal

To:	Brenda Lee, Coordinator Tolvaptan Adjudication Team	From:	
Fax:	604-875-7366	Fax:	
Phone:	604-875-7340	Phone:	
Subject:	Application for Tolvaptan in ADPKD	Date:	

Please include the following forms. This is a mandatory requirement for review and approval of this application:

- ☐ Tolvaptan Application Form
- ☐ Patient-Prescriber Agreement Form (PPAF)
- ☐ Copy of Imaging Report
- ☐ Copy of GFR Report
- ☐ Any Other Supporting Documentation

Ensure all items listed as mandatory on the application form are included.

☐ **Group A**: Patients 18-55 years old who are similar to those in clinical trials[1,2]:

eGFR >25 mL/min/1.73 m^2 **AND** Evidence of renal enlargement
Renal enlargement can be documented as any of:

- ☐ TKV >750 mL in those with eGFR >45 mL/min/1.73m^2
- ☐ Class 1C, 1D or 1E on the Mayo Clinic Classification

Although not a criterion in the REPRISE trials, documentation of renal enlargement has been included here as a criterion. In those patients with advanced or rapidly progressive CKD without enlarged kidneys, an alternate diagnosis for CKD should be investigated.

☐ **Group B**: Patients 55-65 years old who would have met criteria for the REPRISE trial[2], and who also have evidence of rapid disease progression. **All three of these criteria must be met:**

- ☐ eGFR of 25 to 44 mL/min/1.73 m^2

AND

- ☐ Historical evidence of a decline in eGFR >2.0 mL/min/1.73 m^2/year

AND

- ☐ Class 1D or 1E on the Mayo Clinic Classification

Although not a criterion in the REPRISE trial, documentation of renal enlargement has been included here as a criterion to ensure that only the more rapidly progressing patients are chosen for tolvaptan treatment. In those patients with advanced or rapidly progressive CKD without enlarged kidneys, an alternate diagnosis for CKD should be investigated.

☐ **Group C**: Patients 18-65 years of age with eGFR ≥25 mL/min/1.73 m^2 who do not otherwise fit into the trial criteria may also be considered if they display other markers of rapid disease progression, including those listed below. Not all factors in this group in isolation would meet criteria for tolvaptan treatment. Therefore, all or many of these factors should be considered together:

- ☐ Annual decrease in eGFR of >2.5 mL/min/1.73 m^2 and alternate CKD diagnoses have been excluded
- ☐ Increase in TKV of >5% per year
- ☐ Mayo Clinic Classification groups 1D or 1E
- ☐ PKD 1 protein truncating mutation
- ☐ Classified as high risk via the PROPKD risk score (7-9 points)
- ☐ MRI or CT cannot be done to assess TKV and patient has large kidney lengths (e.g. >20cm) on ultrasound. Ultrasounds are not as strong of a predictor of progression as total kidney volume and should only be considered if TKV is not possible to obtain
- ☐ Consideration can be given to patients with high symptom burden related to renal expansion, but this alone is not generally an indication for tolvaptan treatment. Symptom burden should be considered in addition to other clinical criteria.

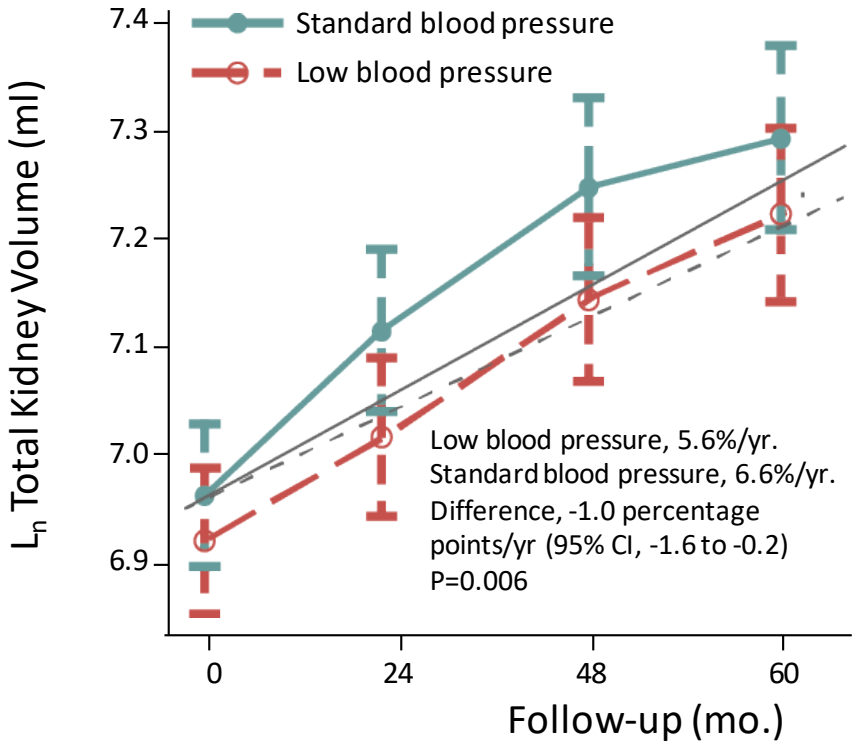
The goal is to identify rapid progressors

- Higher bar set for older patients because if that have made it to that point they are less likely to be a rapid progressor

Targeting a Lower Blood Pressure: Evidence from the HALT-PKD Study

- Double-blind, placebo-controlled trial
- 558 hypertensive participants with ADPKD
  - 15 to 49 years old
  - Baseline eGFR >60 mL/min/1.73 m^2
- Randomized to BP target range:
  - Standard: 120/70 to 130/80 mmHg
  - Low: 95/60 to 110/75 mmHg
- Followed for 5 years
- Primary efficacy outcome: Annual % change in TKV

Low BP target led to lower rate of total kidney volume growth



- **Standard BP: 6.6%/yr**
- **Low BP: 5.6%/yr**
- **Absolute difference: -1.0 percentage points/yr (95% CI, -1.6 to -0.2) P=0.006**
- **Relative difference: 14.2%**

Adapted from Schrier RW, *et al. N Engl J Med* 2014;371(24):2255-66.

Canadian Expert Consensus on Blood Pressure Management in ADPKD

1. For patients with ADPKD who are **less than 50** years old, with an **eGFR greater than 60** mL/min/1.73 m^2:

Target Blood Pressure: ≤ 110/75 mm Hg

An individualized target may be needed for some patients

2. Salt restriction should be followed as per current guidelines published by Hypertension Canada

The evidence for lower BP is in earlier disease (young age, intact GFR)

Can **try** an aggressive target beyond this, but be prepared to **back off** if there are any issues

Soroka S, *et al. Can J Kidney Health Dis* 2018;*5*(1). https://doi.org/10.1177/2054358118801589..

Extra-renal manifestations of PKD

KIDNEY-RELATED

Pain and discomfort

Kidney stones

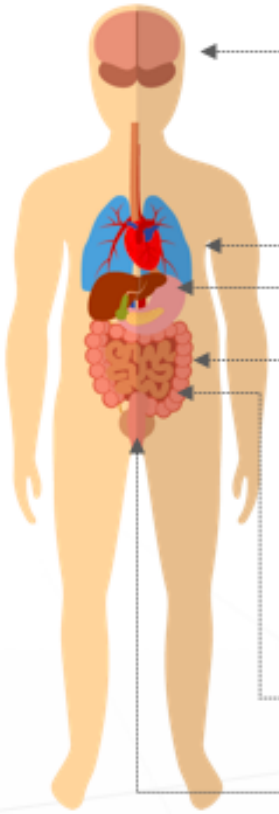
Cyst bleeds

Infected cysts

High blood pressure

Blood in urine

Worsening kidney function / kidney failure



NON-KIDNEY-RELATED

Brain aneurysm*

Cardiovascular*
(e.g., heart valve problems)

Liver cysts

Hernias of the abdomen

Diverticulosis*
(outpouchings of the large intestine)

Seminal vesicle cysts

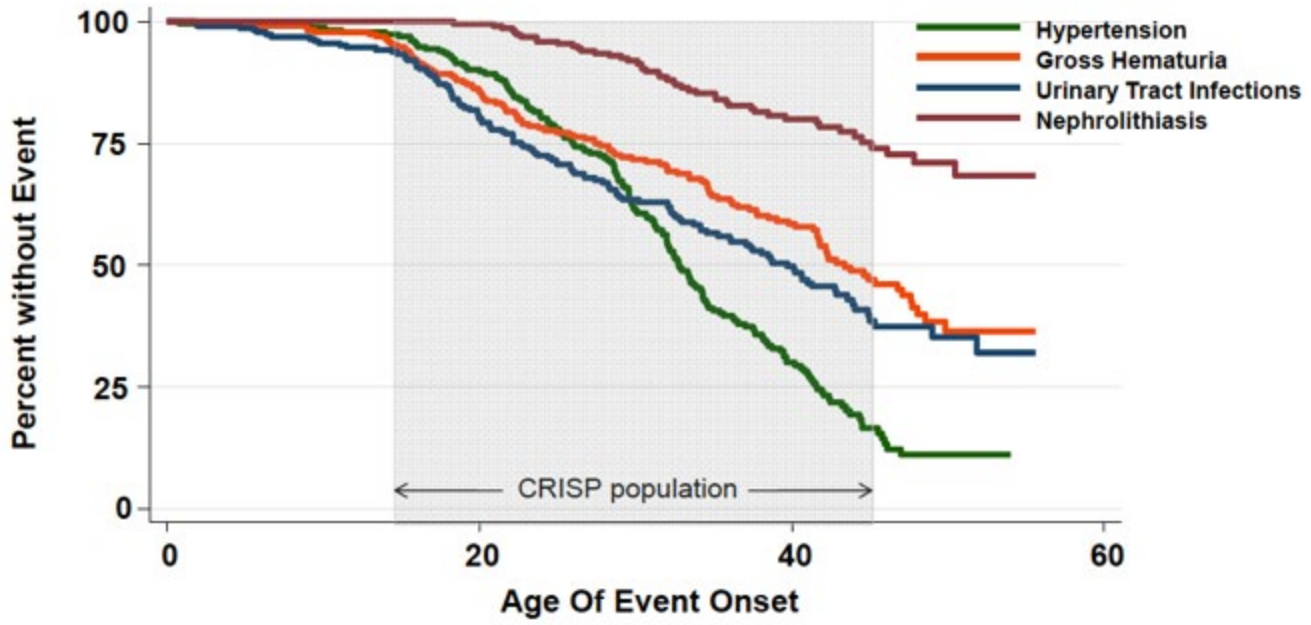
Not everybody with ADPKD will experience all of these complications

*Less frequent

ADPKD: Autosomal Dominant Polycystic Kidney Disease

Adapted from www.endpkd.ca; and Harris PC, et al. Gene Reviews, last updated June 11, 2015.

Other complications of PKD



By age 30, over 50% have at least one complications

NIH CRISP Studies; Chapman *J. Amer. Soc. Neph*, 21:384A, 2010.

CK-35

Pain, hematuria, infection and stones can occur early in the disease course

- Up to 25% of PKD patients present with these symptoms in the setting of **preserved renal function**
- The occurrence of these symptoms does not completely coincide with their renal disease course

Gabow PA, Duley I, Johnson AM. Clinical profiles of gross hematuria in autosomal dominant polycystic kidney disease. Am J Kidney Dis. 1992 Aug;20(2):140–3.

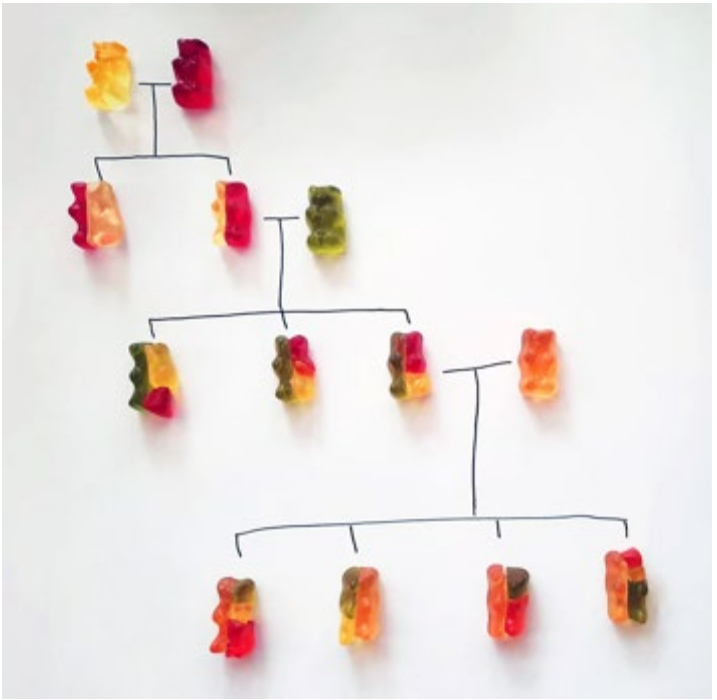
Bajwa ZH, Sial KA, Malik AB, Steinman TI. Pain patterns in patients with polycystic kidney disease. Kidney international. 2004;66(4):1561–9.

Screening At-risk Family Members

This is a complex issue, but the most important point is to have a detailed conversation with your patient who can make an informed choice to test or not

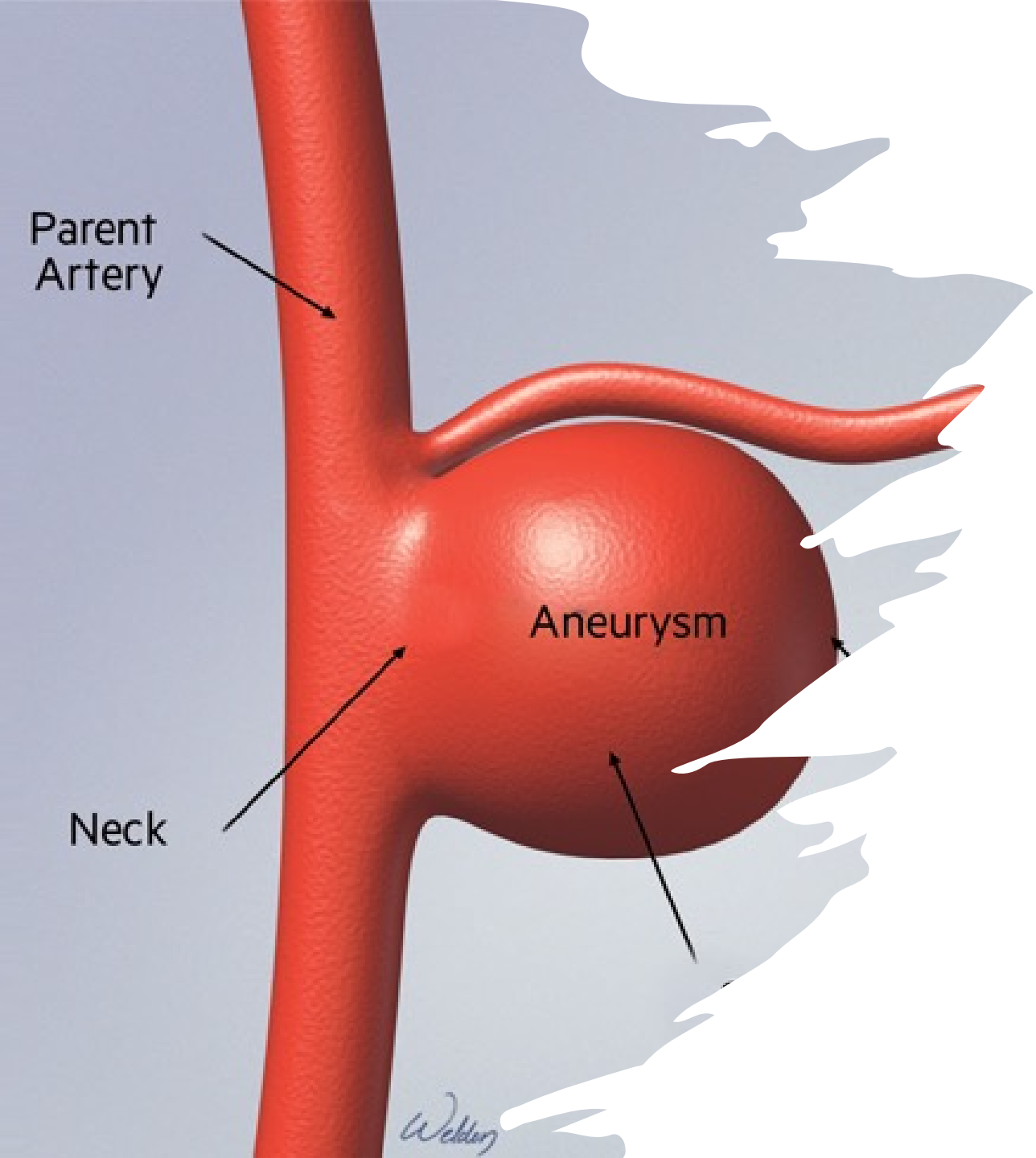
- Potential benefits of pre-symptomatic diagnosis usually outweigh the risks among adults in ADPKD families
  - Remember that treatments to slow renal decline are most effective earlier in the disease process
- In families with intracranial aneurysms, it may be desirable to establish a diagnosis of ADPKD to decide who might benefit from screening
- When screening is pursued, the test of choice is a renal ultrasound
- See our dedicated documents for more details (including children)

Screening and Testing for Autosomal Dominant Polycystic Kidney Disease (ADPKD) BCRenal



Pregnancy and Family Planning in Autosomal Dominant Polycystic Disease (ADPKD) BCRenal

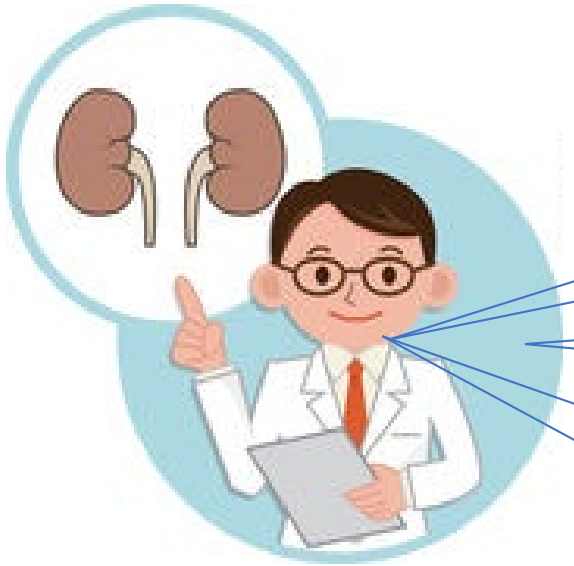
Adapted from Perkins D, et al. Autosomal Dominant Polycystic Kidney Disease: Recommendations for the Canadian Primary Care Practitioner. Elsevier Canada, 2017.



Intracranial Aneurysms

- Occur in ~10% of PKD compared to ~2-3% in general population
- The only clear risk factor is a family history of ICA rupture
- Role of screening unclear
  - Mostly small ICA of unclear significance
  - Repair risky
- Screening recommended for those with:
  - Prior ICA rupture, family Hx, high risk profession, **patient anxiety**
- If doing screening and monitoring (MRA or CTA)
  - Repeat q6–24 months if positive
  - Repeat q5-10 years if negative
- The most important part about screening is to know what to do with the results
  - Experienced neurosurgical input can be very valuable

What we have done with ADPKD in the past

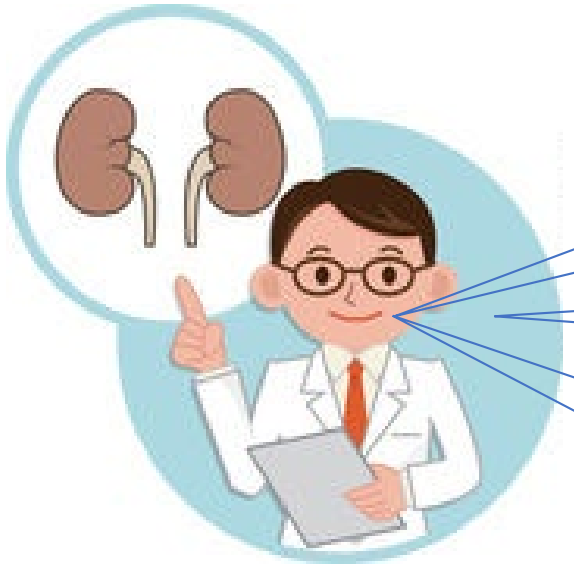


Let’s confirm the diagnosis and then we will tell you about screening your family members

Drink lots of water, keep your blood pressure in the normal range and do your bloodwork. See you back in 6-12 months.

When your GFR drops, we’ll start talking about transplant and dialysis

What we need to do with ADPKD now



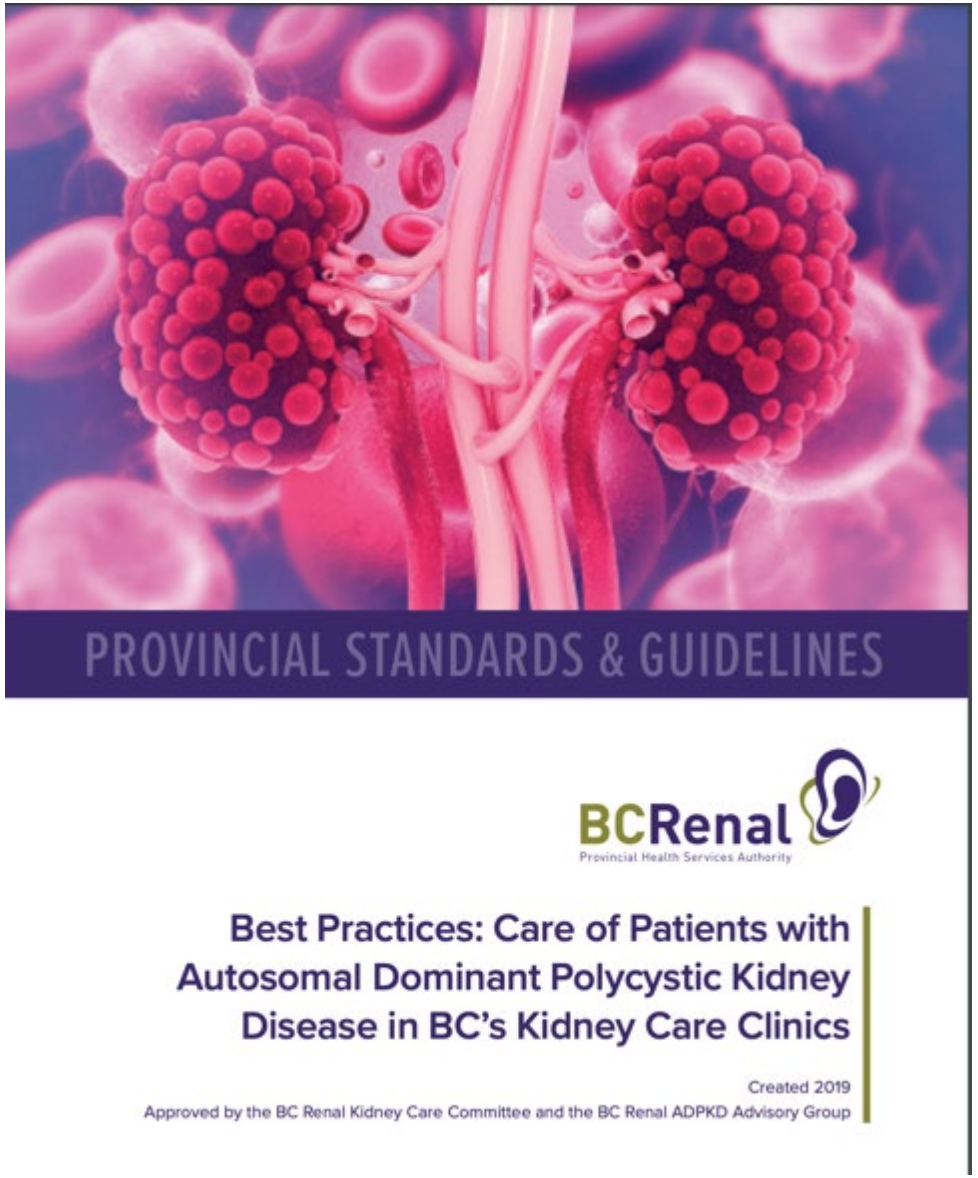
Tell us what your family screening, reproductive, financial, symptom and renal failure concerns are and we will discuss those

We will use imaging and other tools to more accurately predict your renal progression

We will discuss conventional treatments like BP reduction that apply to everyone with PKD and will also assess whether you are a candidate for new disease specific treatments

ADPKD Best Practices

- Launched Nov 2019 ~2 yrs
- Aligned with KCC best practices
- Developed by KCC interdisciplinary team members across BC



Self-Management Resources for Patients

- Pain & ADPKD
- Pain Diary for ADPKD
- Pregnancy & Family Planning in ADPKD
- Screening & Testing for ADPKD

Pregnancy and Family Planning in Autosomal Dominant Polycystic Disease (ADPKD)

BCRenal

It's natural to wonder how ADPKD can affect fertility and pregnancy. For people with ADPKD, the ability to conceive children and have a healthy pregnancy is not that different than the general population. About 80% of pregnancies in women with ADPKD are safe and proceed with minimal complications; however, there are some additional risks that are important to be aware of. This means that extra monitoring and care throughout a pregnancy and when the baby is being born is recommended.

Pregnancy and a new diagnosis of ADPKD

Some women do not realize that they have ADPKD until they are pregnant and undergo certain tests. While this may be surprising for some women, it's not an uncommon way

Pain and Autosomal Dominant Polycystic Kidney Disease (ADPKD)

BCRenal

What is pain?

Pain is the feeling of hurt or discomfort in the body. While it is a common symptom of autosomal dominant polycystic kidney disease (ADPKD), each person experiences pain differently and therefore your pain is unique to you. The experience of pain can be influenced by a person's cultural background, expectations, behaviors, and physical and emotional health.

This symptom can range from mild to intense and can be temporary or ongoing. Pain is the body's way of signaling that there is a health problem that needs attention. For this reason, it's helpful to monitor your pain and to know when to consult your care team.

What kinds of pain are there?

Acute pain usually starts suddenly and is caused by something specific. It goes away when there is no longer an underlying cause for the pain.

Chronic pain is ongoing pain that's common in people with ADPKD. About 6 in 10 people who have been diagnosed with the condition experience chronic pain.

What causes pain?

Understanding the cause of your pain will help your healthcare team treat it in the best way. Some things that might cause or worsen pain include:

- Some illnesses or diseases
- Medical procedures and tests
- Stress, anxiety or depression
- The emotional, social, and spiritual impact

Screening and Testing for Autosomal Dominant Polycystic Kidney Disease (ADPKD)

BCRenal

ADPKD is a genetic disorder that can affect whole families, meaning it is passed on from parents to children. In some cases, the disease may also occur randomly in a person without a family history of the disease.

ADPKD is most often caused by changes in specific genes linked to ADPKD with the two most common being PKD1 and PKD2[1], and less often by changes in other genes. Many people with ADPKD don't know which gene causes their disease. The information in this resource applies to all cases, regardless of which gene is causing ADPKD for you and/or your family members.

Not everyone who has ADPKD shows obvious symptoms. But because the condition can be inherited and affect family members, it is important to discuss family screening and testing with your kidney care team. This resource can be used to inform your decision on whether or not to pursue testing for ADPKD.

How is ADPKD inherited?

A common question among parents is

Pain Diary for Autosomal Dominant Polycystic Kidney Disease (ADPKD)

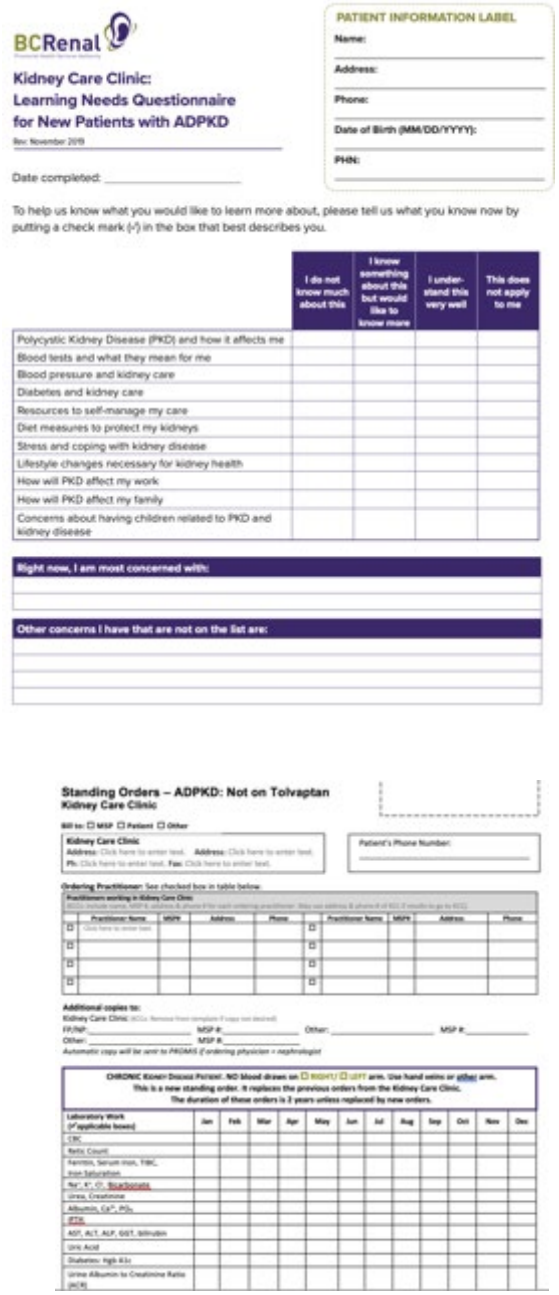
BCRenal

Often, doctors ask patients to describe their pain using a scale from 1 to 10, where 0 is no pain and 10 is extreme pain. This scale also describes how pain is impacting your quality of life and/or ability to complete daily activities. You can use the infographic included in this pain diary to determine how to rate your pain.

Pain Intensity	0 No pain	1-2 Mild Pain		3-5 Moderate Pain			6-7 Severe Pain		8-9 Very Severe Pain		10 Worst Pain Possible
Impact on Quality of Life (QoL)	Normal Quality of Life										Non-Functioning
	• Work/ volunteer, normal activities each day • Social life outside of work • Take an active part in family life	• Work/ volunteer, be active 8 hours daily • Outside social activities limited • Take part in family life	• Work/ volunteer, at least 6 hours daily • Have energy to make plans for 1 social activity weekly • Active on weekends	• Work/ volunteer, a few hours daily • Active at least 5 hours a day • Do simple activities on the weekend	• Work/ volunteer, limited hours • Take part in limited social activities on weekends	• Work/ volunteer, minimal hours possible • Do simple chores around house • Minimal activities outside of home 2 days a week	• Not able to work/ volunteer • Struggle but fulfill daily home responsibilities • No outside activity	• Get dressed in morning • Minimal activities at home • Contact with friends via phone, email	• Get out of bed but don't get dressed • Stay at home all day	• Stay in bed at least half the day • Have no contact with outside world	• Stay in bed all day • Feel hopeless and helpless about life

ADPKD KCC Tools

- Learning needs questionnaire for new patients with ADPKD (PDF fillable available)
- SAMPLE Standing Lab Work Orders for ADPKD Patients (modifiable by KCC)



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Kidney Care Clinic:
Learning Needs Questionnaire
for New Patients with ADPKD

Rev: November 2019

PATIENT INFORMATION LABEL
Name:
Address:
Phone:
Date of Birth (MM/DD/YYYY):
PHN:

Date completed: _____

To help us know what you would like to learn more about, please tell us what you know now by putting a check mark (✓) in the box that best describes you.

	I do not know much about this	I know something about this but would like to know more	I understand this very well	This does not apply to me
Polycystic Kidney Disease (PKD) and how it affects me				
Blood tests and what they mean for me				
Blood pressure and kidney care				
Diabetes and kidney care				
Resources to self-manage my care				
Diet measures to protect my kidneys				
Stress and coping with kidney disease				
Lifestyle changes necessary for kidney health				
How will PKD affect my work				
How will PKD affect my family				
Concerns about having children related to PKD and kidney disease				

Right now, I am most concerned with:

Other concerns I have that are not on the list are:

Standing Orders – ADPKD: Not on Tolvaptan
Kidney Care Clinic

Bill to: ☐ MSP ☐ Patient ☐ Other

Kidney Care Clinic
Address: Click here to enter text. Address: Click here to enter text.
Ph: Click here to enter text. Fax: Click here to enter text.

Patient's Phone Number: _____

Ordering Practitioner: See checked box in table below

Practitioners working in Kidney Care Clinic

	Practitioner Name	MSP#	Address	Phone		Practitioner Name	MSP#	Address	Phone
☐	Click here to enter text.				☐				
☐					☐				
☐					☐				
☐					☐				

Additional copies to:
Kidney Care Clinic (ECC: Remove from template if copy not desired)
FP/NP: _____ MSP #: _____ Other: _____ MSP #: _____
Other: _____ MSP #: _____
Automatic copy will be sent to PROMIS if ordering physician = nephrologist

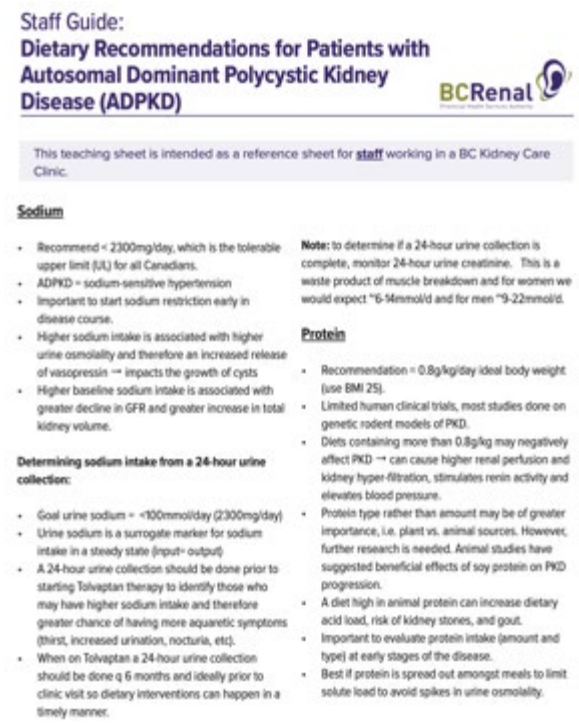
CHRONIC Kidney Disease Patient: NO blood draws on ☐ RIGHT/ ☐ LEFT arm. Use hand veins or other arm.
This is a new standing order. It replaces the previous orders from the Kidney Care Clinic.
The duration of these orders is 2 years unless replaced by new orders.

Laboratory Work (✓ applicable boxes)	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
CBC												
Retic Count												
Ferritin, Serum Iron, TIBC, Iron Saturation												
Na+, K+, Cl-, Bicarbonate												
Urea, Creatinine												
Albumin, Ca^{++}, PO_4												
eGFR												
AST, ALT, ALP, GGT, bilirubin												
Uric Acid												
Diabetes: high A1c												
Urine Albumin to Creatinine Ratio (ACR)												

ADPKD Staff Resources

Staff Guide: Dietary Recommendations for Patients with ADPKD

Supporting Evidence Documents



Staff Guide:
Dietary Recommendations for Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

BCRenal

This teaching sheet is intended as a reference sheet for **staff** working in a BC Kidney Care Clinic.

Sodium

- Recommend < 2300mg/day, which is the tolerable upper limit (UL) for all Canadians.
- ADPKD = sodium-sensitive hypertension
- Important to start sodium restriction early in disease course.
- Higher sodium intake is associated with higher urine osmolality and therefore an increased release of vasopressin → impacts the growth of cysts
- Higher baseline sodium intake is associated with greater decline in GFR and greater increase in total kidney volume.

Determining sodium intake from a 24-hour urine collection:

- Goal urine sodium = <100mmol/day (2300mg/day)
- Urine sodium is a surrogate marker for sodium intake in a steady state (input= output)
- A 24-hour urine collection should be done prior to starting Tolvaptan therapy to identify those who may have higher sodium intake and therefore greater chance of having more aquaretic symptoms (thirst, increased urination, nocturia, etc).
- When on Tolvaptan a 24-hour urine collection should be done q 6 months and ideally prior to clinic visit so dietary interventions can happen in a timely manner.

Note: to determine if a 24-hour urine collection is complete, monitor 24-hour urine creatinine. This is a waste product of muscle breakdown and for women we would expect ~6-14mmol/d and for men ~9-22mmol/d.

Protein

- Recommendation = 0.8g/kg/day ideal body weight (use BMI 25).
- Limited human clinical trials, most studies done on genetic rodent models of PKD.
- Diets containing more than 0.8g/kg may negatively affect PKD → can cause higher renal perfusion and kidney hyper-filtration, stimulates renin activity and elevates blood pressure.
- Protein type rather than amount may be of greater importance, i.e. plant vs. animal sources. However, further research is needed. Animal studies have suggested beneficial effects of soy protein on PKD progression.
- A diet high in animal protein can increase dietary acid load, risk of kidney stones, and gout.
- Important to evaluate protein intake (amount and type) at early stages of the disease.
- Best if protein is spread out amongst meals to limit solute load to avoid spikes in urine osmolality.

Supportive Evidence Document:
BLOOD PRESSURE MONITORING AND TARGETS IN ADPKD

BCRenal

Introduction

Hypertension is a common complication of ADPKD, and it precedes the onset of renal decline in 50%-75% of cases (1). It is estimated to occur in 30% of children with ADPKD, and the median age at diagnosis of hypertension is within the third decade of life (32 years in males, 34 years in females) (2).

Hypertension increases the rate of renal decline (3). In ADPKD patients, it is implicated in the development of left ventricular hypertrophy (1), and it may also contribute to cerebral hemorrhage, aneurysmal subarachnoid hemorrhage, and cardiovascular death (3). In one 5-year study of patients aged 4 to 21 years that compared hypertensive and normotensive children/young adults, it was found that hypertensive individuals demonstrated a greater but not statistically significant increase in renal volume over time, as well as higher left ventricular mass index (LVMI) throughout the study (4).

It is therefore important to detect hypertension as early as possible and to treat to appropriate blood pressure (BP) targets using non-pharmacological measures +/- antihypertensives.

Summary of the Evidence

Blood Pressure Monitoring

Office BP monitoring:
The utility of office BP measurements is limited in patients with white coat hypertension or masked hypertension. In essential hypertensives, both home BP monitoring and ambulatory blood pressure monitoring (ABPM) have been shown to be more accurate than office BP monitoring (5).

Home BP monitoring:
Home BP monitoring is useful for diagnosing sustained hypertension (5). In patients with essential hypertension, there is evidence suggesting that it is more accurate in predicting cardiovascular risk than office BP monitoring (5). However, it cannot be used to detect nocturnal hypertension or to determine whether patients have normal "dipping" of BP overnight.

24-hour ambulatory BP monitoring (ABPM):
There is increasing evidence that 24-hour ABPM is a useful tool in the ADPKD population, and it is endorsed in several ADPKD expert reviews and guidelines (Table 1). A summary of the evidence for 24-hour ABPM in ADPKD is presented in Table 2.

Three studies demonstrated that 24-hour ABPM was useful in detecting hypertension that would otherwise have been missed through office BP or home BP measurements (6-8).

Supportive Evidence Document:
ANTIHYPERTENSIVE AGENTS IN ADPKD

BCRenal

Introduction

Due to the risks of cardiovascular complications and renal progression associated with hypertension in ADPKD, it is important to treat to blood pressure (BP) targets with appropriate therapies. Further information about BP targets is outlined in the "Blood Pressure Monitoring and Targets in ADPKD" Supporting Document.

Although non-pharmacological measures for BP control have not been specifically studied in ADPKD patients, they remain an important component of BP therapy. These include regular exercise, weight loss, smoking cessation, and sodium restriction. A multidisciplinary approach is key to provide optimal education about these measures.

However, antihypertensive agents are often necessary to reach BP targets in ADPKD patients. The magnitude of benefit of antihypertensive agents on cardiovascular and renal outcomes may differ depending on the class used. In addition, concerns with the effects of certain antihypertensive classes on disease progression have been outlined in numerous expert reviews (1-3).

Summary of the Evidence

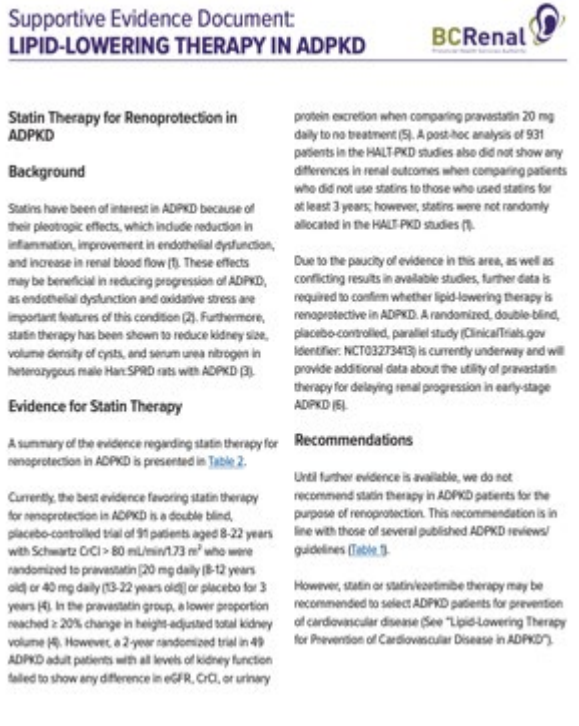
A summary of published clinical studies involving antihypertensives in ADPKD is provided in Table 2.

Angiotensin-Converting Enzyme (ACE) Inhibitors or Angiotensin Receptor II Blockers (ARBs)

The renin-angiotensin-aldosterone system (RAAS) appears to play a large role in the pathogenesis of hypertension in ADPKD (1). It is thought that the compression of renal cysts on renal vasculature stimulates RAAS (1). This leads to increased angiotensin II, which not only increases BP, but also acts as a growth factor for cyst growth (1). Accordingly, RAAS blockade with ACE-inhibitors or ARBs is generally considered to be first-line therapy (1). This is in line with all published guidelines and expert reviews that provide recommendations for BP management in ADPKD, as indicated in Table 1.

Due to the general consensus that RAAS blockade is the cornerstone of BP management in ADPKD, the majority of studies evaluating antihypertensives have compared RAAS blockade with other antihypertensive classes (1), and select studies are summarized in the subsequent antihypertensive class sections below.

Only one study randomized patients to RAAS blockade or no RAAS blockade specifically in the ADPKD population, and this was done in 57 young patients aged 4-21 years who were either normotensive with severe ADPKD or borderline hypertensive (4). Patients were randomized to enalapril (or losartan if enalapril was not tolerated) or to treatment with no ACE-inhibitor to reach a target BP of ≤50th or ≤90th percentile (4).



Supportive Evidence Document:
LIPID-LOWERING THERAPY IN ADPKD

BCRenal

Statin Therapy for Renoprotection in ADPKD

Background

Statins have been of interest in ADPKD because of their pleotropic effects, which include reduction in inflammation, improvement in endothelial dysfunction, and increase in renal blood flow (1). These effects may be beneficial in reducing progression of ADPKD, as endothelial dysfunction and oxidative stress are important features of this condition (2). Furthermore, statin therapy has been shown to reduce kidney size, volume density of cysts, and serum urea nitrogen in heterozygous male Han:SPRD rats with ADPKD (3).

Evidence for Statin Therapy

A summary of the evidence regarding statin therapy for renoprotection in ADPKD is presented in Table 2.

Currently, the best evidence favoring statin therapy for renoprotection in ADPKD is a double blind, placebo-controlled trial of 91 patients aged 8-22 years with Schwartz CrCl > 80 mL/min/1.73 m^2 who were randomized to pravastatin (20 mg daily (8-12 years old) or 40 mg daily (13-22 years old)) or placebo for 3 years (4). In the pravastatin group, a lower proportion reached ≥ 20% change in height-adjusted total kidney volume (4). However, a 2-year randomized trial in 49 ADPKD adult patients with all levels of kidney function failed to show any difference in eGFR, CrCl, or urinary protein excretion when comparing pravastatin 20 mg daily to no treatment (5). A post-hoc analysis of 931 patients in the HALT-PKD studies also did not show any differences in renal outcomes when comparing patients who did not use statins to those who used statins for at least 3 years; however, statins were not randomly allocated in the HALT-PKD studies (1).

Due to the paucity of evidence in this area, as well as conflicting results in available studies, further data is required to confirm whether lipid-lowering therapy is renoprotective in ADPKD. A randomized, double-blind, placebo-controlled, parallel study (ClinicalTrials.gov Identifier: NCT03273413) is currently underway and will provide additional data about the utility of pravastatin therapy for delaying renal progression in early-stage ADPKD (6).

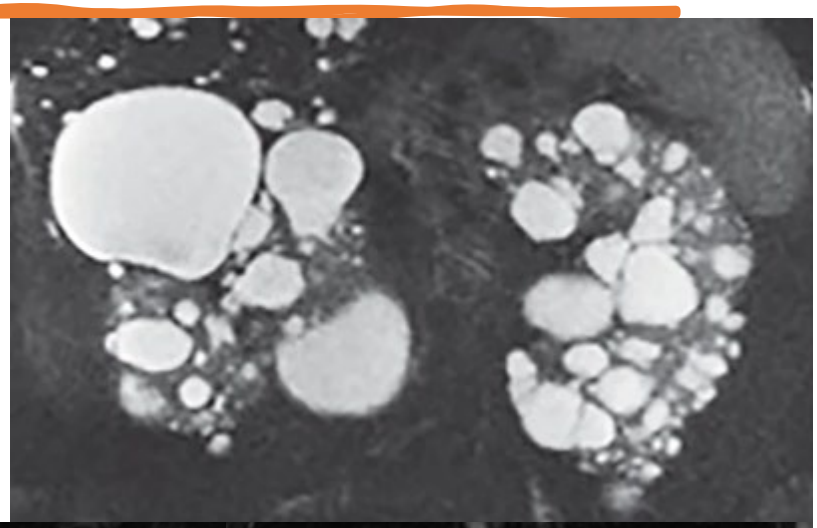
Recommendations

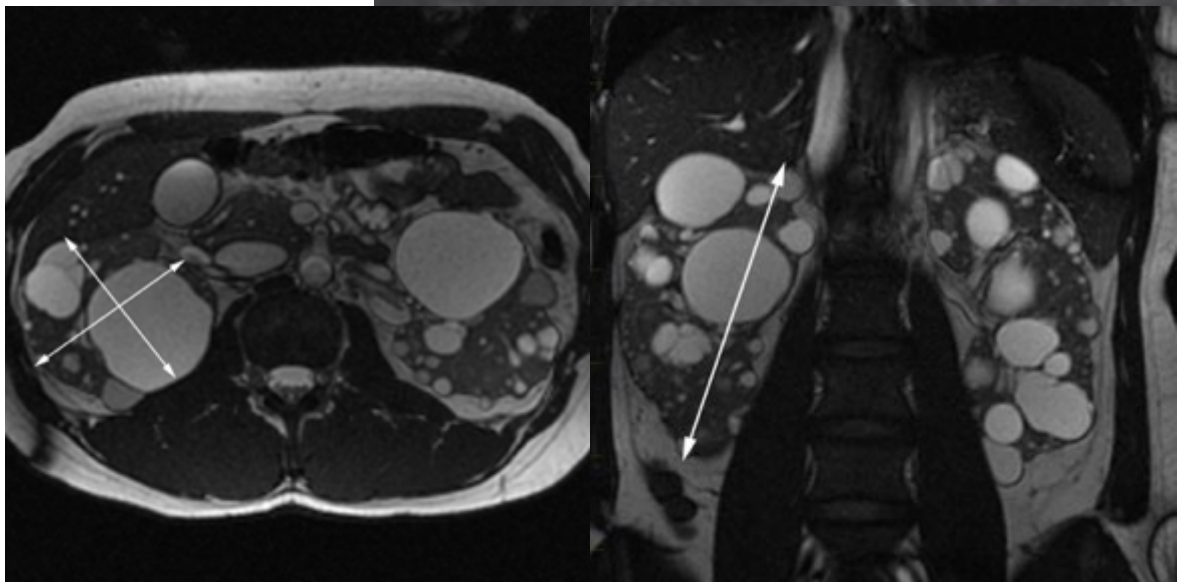
Until further evidence is available, we do not recommend statin therapy in ADPKD patients for the purpose of renoprotection. This recommendation is in line with those of several published ADPKD reviews/ guidelines (Table 1).

However, statin or statin/ezetimibe therapy may be recommended to select ADPKD patients for prevention of cardiovascular disease (See "Lipid-Lowering Therapy for Prevention of Cardiovascular Disease in ADPKD").

Imaging for ADPKD

- Dedicated MRI and Ultra-Low-Dose CT Imaging protocols for TKV measurement
- Standardized measurement instructions for TKV
- Approach to renal imaging in ADPKD
- Online tool for TKV calculation and mayo imaging classification of ADPKD





Tolvaptan for ADPKD

- Application for tolvaptan in ADPKD (with PPAF)
- Tolvaptan pharmacy information sheet
- Tolvaptan: FAQ's for prescribers
- Tolvaptan: FAQ's for patients
- Tolvaptan prescription for PKD

Tolvaptan
Frequently Asked Questions (for patients)

BCRenal
Provincial Health Services Authority

1. What is tolvaptan?

Tolvaptan is a medication that slows the growth of kidney cysts in patients with autosomal dominant polycystic kidney disease, also known as ADPKD. This may slow the progress of kidney problems in some patients.

2. How does tolvaptan work?

Tolvaptan blocks a hormone called vasopressin. Vasopressin helps the body hold onto water. Vasopressin is also one of many factors that lead to growth of kidney cysts in patients with ADPKD. Blocking this hormone may help to slow cyst growth.

3. Has tolvaptan been studied?

Health Canada has approved tolvaptan for use in patients with ADPKD based on studies that have been completed.

The largest study was called TEMPO 3:4. This study lasted 3 years and included 1,445 patients aged 18 to 50 with early stage ADPKD. All of the people in the study had large kidneys (a total kidney volume greater than 750 mL), but still had good kidney function (an average eGFR* of 80 mL/min/1.73 m^2).

Compared to those who did not take tolvaptan, those who took it had:

- Less growth in total kidney volume (TKV) each year
- Fewer episodes of pain in the kidneys
- Slower decline in kidney function

Another study called REPRISE lasted 1 year and included 1,370 patients who had lower levels of kidney function compared to the patients in TEMPO 3:4, as well as some patients who were older than those in TEMPO 3:4. There were two groups of patients studied:

- 18 to 55 years old with an eGFR of 25 to 65 mL/min/1.73 m^2
- 56 to 65 years old with an eGFR of 25 to 44 mL/min/1.73 m^2 that was decreasing by more than 2 mL/min/1.73 m^2 every year

Like the results from the TEMPO 3:4 study, the REPRISE study found that kidney function (eGFR) decreased by about 1 mL/min/1.73 m^2 less every year in patients who took tolvaptan, compared to those who did not.

Not all patients could tolerate tolvaptan. Side effects reported in both studies

PROMIS Updates

- PKD imaging data capture
- Tolvaptan refill request
- Tolvaptan discontinuation form
- Tolvaptan application form – in development

PROMIS
Patient Records and Outcome Management Information System

ADPKD Evaluation: PKD Indicator

- #/% of ADPKD patients followed in KCCs
- # of ADPKD patients with GFR>45

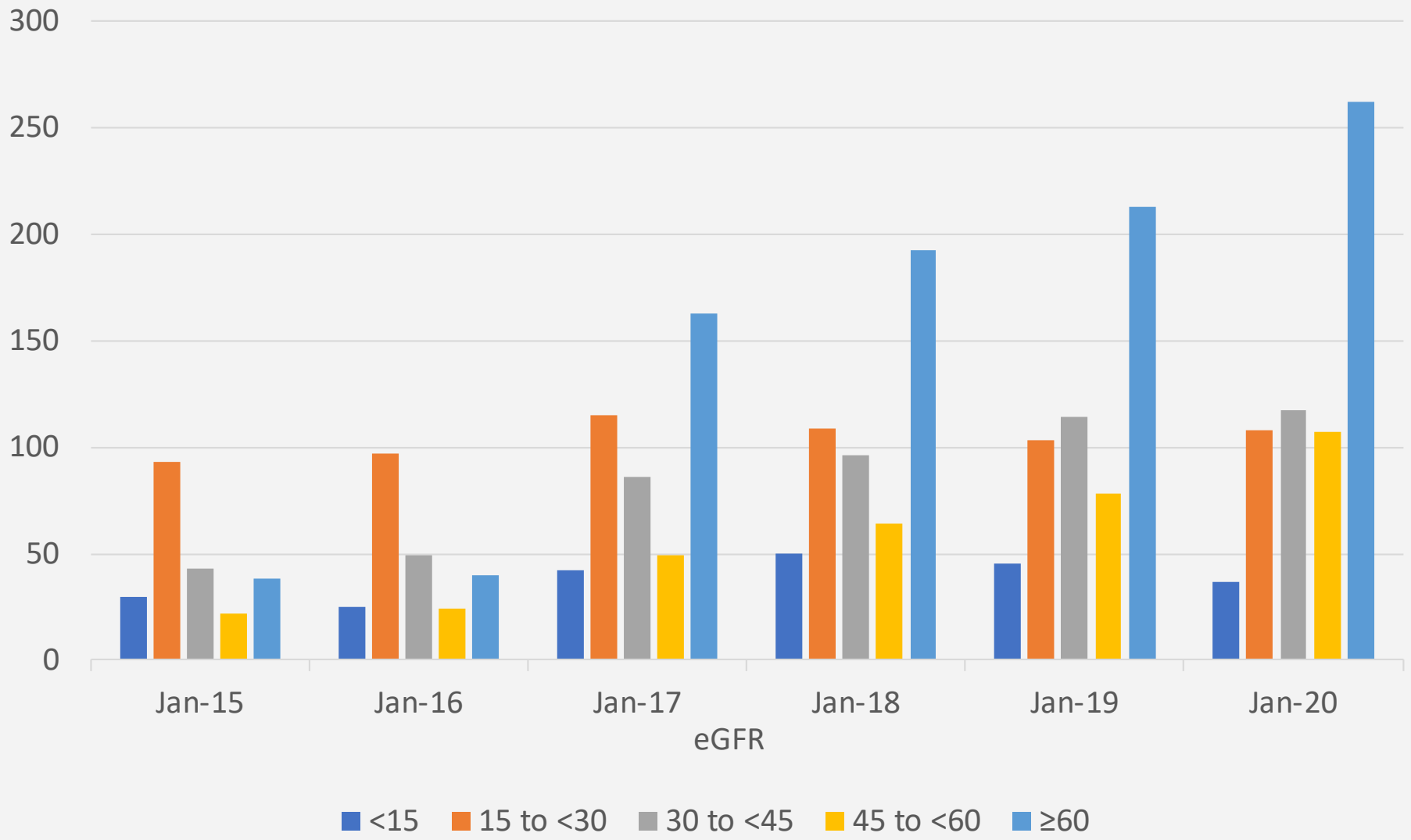
			Current Period (Oct 2020 - Mar 2021)																
			IHA						FHA			PHC/VCHA		VIHA			NHA	PHSA	BC
Category	Indicator	Measure	KGH	PRH	RIH	Williams Lake	West Koot (Trail)	East Koot (Cranbrook)	RCH	SMH	ARHCC	VGH	SPH	RJH	Nanaimo	North Island	UHNBC	BCCH	
KCC Patients as of March 31, 2021																			
Delaying Disease Progression & Managing Complications																			
Demographics	KCC pts [1]	#	915	345	1167	84	304	368	1464	1814	781	1547	1629	670	653	306	580	124	**12751**
ADPKD	ADPKD patients	#	19	6	47	1	7	1	29	96	18	66	140	21	17	6	14	0	**488**
	ADPKD patients with gfr > 45 [2]	#	7	2	26	0	5	0	10	42	5	34	73	12	5	0	1	0	**222**
	ADPKD patients with gfr > 45 [2]	%	36.8	33.3	55.3	0	71.4	0	34.5	43.8	27.8	51.5	52.1	57.1	29.4	0	7.1	0	**45.5**

[1] Includes all registered KCC patients as of the end of period, excluding parachute patients and previously transplanted patients.

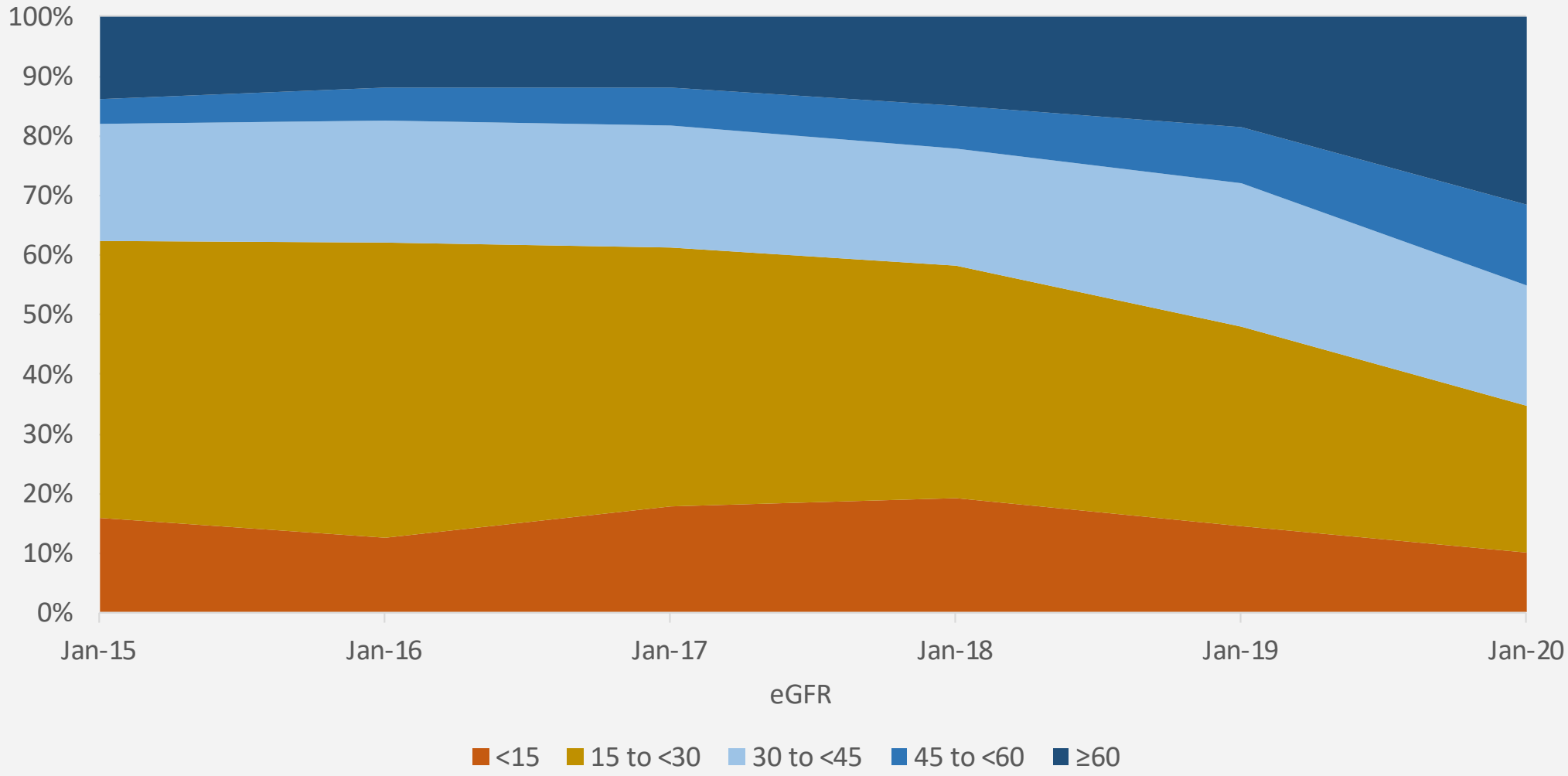
[2] Based on the last available eGFR within 12 months prior and 1 month post to end of period

Data Source: Data entered in PROMIS as of Sep 14, 2021

We are learning about people earlier in their disease course



More people with ADPKD come to multidisciplinary clinics, and they come earlier

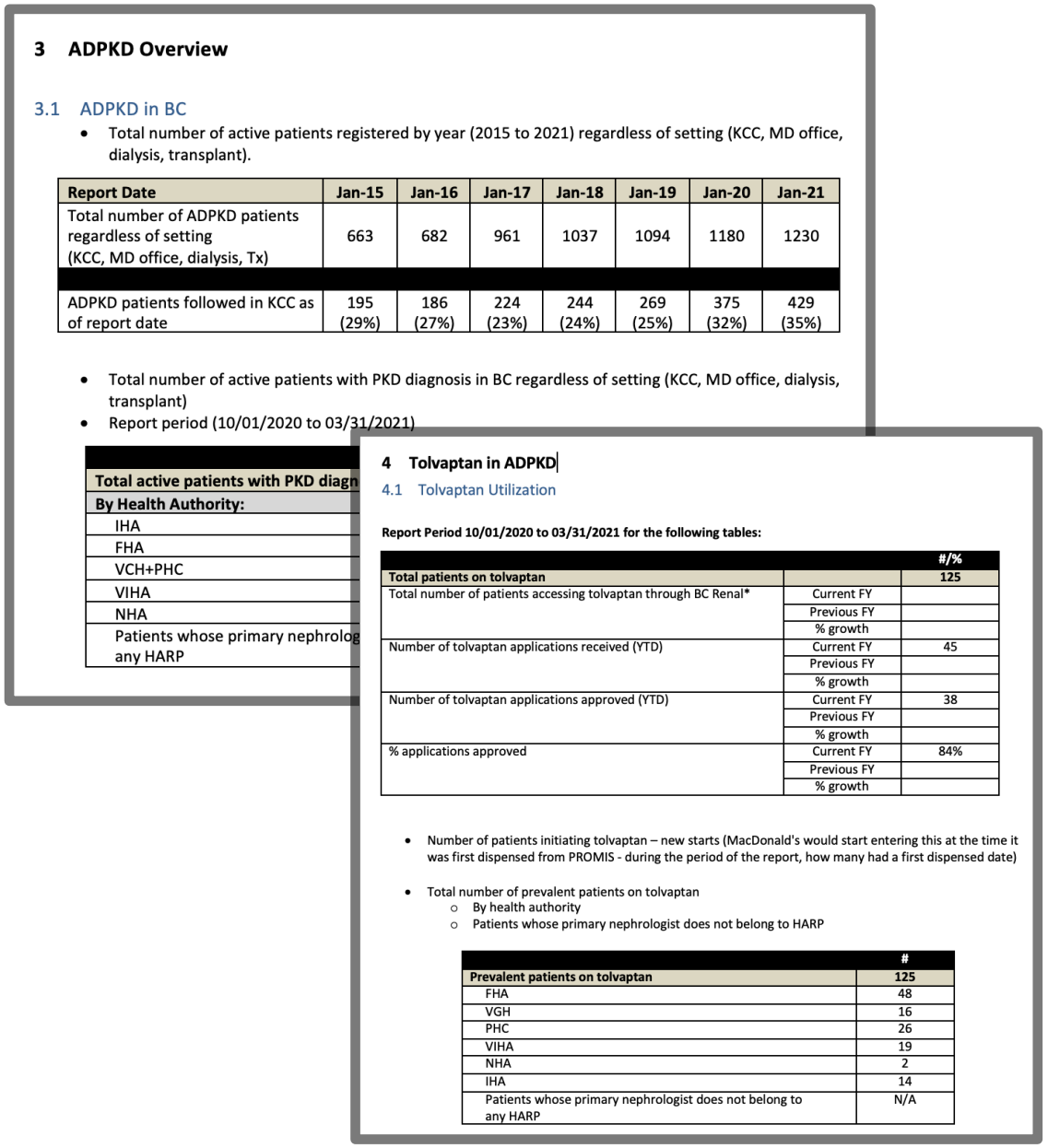


ADPKD Evaluation

ADPKD Atlas Annual Report

ADPKD PROVINCIAL ADVISORY GROUP

2021



3 ADPKD Overview

3.1 ADPKD in BC

- Total number of active patients registered by year (2015 to 2021) regardless of setting (KCC, MD office, dialysis, transplant).

Report Date	Jan-15	Jan-16	Jan-17	Jan-18	Jan-19	Jan-20	Jan-21
Total number of ADPKD patients regardless of setting (KCC, MD office, dialysis, Tx)	663	682	961	1037	1094	1180	1230
ADPKD patients followed in KCC as of report date	195 (29%)	186 (27%)	224 (23%)	244 (24%)	269 (25%)	375 (32%)	429 (35%)

- Total number of active patients with PKD diagnosis in BC regardless of setting (KCC, MD office, dialysis, transplant)
- Report period (10/01/2020 to 03/31/2021)

Total active patients with PKD diagn	
By Health Authority:	
IHA	
FHA	
VCH+PHC	
VIHA	
NHA	
Patients whose primary nephrolog any HARP	

4 Tolvaptan in ADPKD

4.1 Tolvaptan Utilization

Report Period 10/01/2020 to 03/31/2021 for the following tables:

		#/%
Total patients on tolvaptan		**125**
Total number of patients accessing tolvaptan through BC Renal*	Current FY	
	Previous FY	
	% growth	
Number of tolvaptan applications received (YTD)	Current FY	45
	Previous FY	
	% growth	
Number of tolvaptan applications approved (YTD)	Current FY	38
	Previous FY	
	% growth	
% applications approved	Current FY	84%
	Previous FY	
	% growth	

- Number of patients initiating tolvaptan – new starts (MacDonald's would start entering this at the time it was first dispensed from PROMIS - during the period of the report, how many had a first dispensed date)
- Total number of prevalent patients on tolvaptan
  - By health authority
  - Patients whose primary nephrologist does not belong to HARP

	#
Prevalent patients on tolvaptan	**125**
FHA	48
VGH	16
PHC	26
VIHA	19
NHA	2
IHA	14
Patients whose primary nephrologist does not belong to any HARP	N/A

ADPKD Evaluation: Interdisciplinary team survey

The purpose of the survey was to **assess knowledge and comfort** level with ADPKD and providing care for patients and families with ADPKD in KCCs

- Pre-survey (baseline) completed in fall 2019
- Post survey draft completed in spring 2021

Responses

- **48 surveys** were completed by KCC team members across the province as compared to 50 completed surveys from the baseline survey

- Overall a great response!!!

Survey Insights

- ✓Overall, **not a significant change** since baseline survey
- ✓More **strongly agree/agree to having the right resources** on hand
- ✓Most continue to agree that **more education** is required about ADPKD and caring for these patients in KCC
- ✓High level of **agreement** in the ability to **individualize care** for ADPKD patients by identifying their unique learning needs

Survey Insights: ADPKD Resources

- ADPKD best practices are “very useful”, whereas other ADPKD resources/tools indicate many KCC staff are “not using” them

- Further analysis of “usefulness” of ADPKD resources by clinician group shows:
  - Clinician groups (RN’s, RD’s, RX’s, SW’s) that are most likely to use each of the ADPKD resources are indicating that most resources are useful
  - However, there are a number of ADPKD resources that are still not being used by clinicians that could be using them
- More work needs to be done in promoting awareness and use of the ADPKD resources at the local level

ADPKD Provider Survey

The purpose of the survey was to evaluate clinicians' familiarity with, and usage of, novel evidence-based management tools for ADPKD

- In 2018 the online survey link was emailed to 65 nephrologists in current clinical practice in BC and in 2021 it was sent to 72
- Included nephrologists in academic and community settings
- Excluded nephrologists who practice exclusively in transplantation

Survey Measurements

Six domains were assessed at **baseline and post**:

- Sources of information
- Self-identified needs for optimal care delivery
- Prognostication
- Imaging tests
- Blood pressure targets
- Use of tolvaptan

Two domains were added and assessed in the **post survey**:

- Value of interdisciplinary care
- Usefulness of BC Renal ADPKD resources

Responses

Baseline

- 29 nephrologists responded to the survey = 45% response rate

Post

- 25 nephrologists responded to the survey = 35% response rate

Survey Insights

- ✓ Most providers indicated they see benefit from interdisciplinary KCC care for their ADPKD patients
- ✓ ADPKD resources are being used and found helpful
- ✓ A noted shift in the types of imaging used and BP targets for treatment in ADPKD that is in line with best practices
- ❑ Nephrologists rarely seek genetic testing and are uncomfortable interpreting the results
- ❑ Results indicate uncertainty around patient selection and use of tolvaptan

Considerations for Improvement

- Given the results around genetic testing for ADPKD, preferable to have a select group of nephrologists in BC to do this

- Support clinics better so they are comfortable with patient selection and use of tolvaptan via virtual health/co-management

ADPKD and Genetics: Update

- Collaboration with Medical Genetics (Mainland & Island)
  - Resources
    - Genetic testing and referral criteria for ADPKD
    - Standardized testing and approval package
    - Medical Genetics referral form
  - Implementation and Evaluation
    - 1-2 nephrologists/health authority
    - Nephrology and Genetics rounds


Q
A


Thank
You