Modern Assessment and Management of Autosomal Dominant Polycystic Kidney Disease

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BC Provincial Renal Agency PKD Medical Lead
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Outline

• Epidemiology of PKD
• Approach and differential diagnosis of bilateral renal cystic diseases
• Natural History of PKD
• Determining renal prognosis
• Delaying renal progression of renal progression
• Extra-renal manifestations of PKD
Disclosures

• Relevant to this topic, I disclose the following from Otsuka Canada Pharmaceuticals Inc:
  • An unrestricted grant to the BC Renal Agency to assist in creation of the BC PKD registry
  • Honoraria for scientific advisory work related to PKD imaging and treatment
Epidemiology and Natural History of PKD
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.

• There is no racial predilection; it affects all groups equally

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

• Polycystin 1 and 2 localize to primary cilia. These are involved in tubulogenesis, maintenance of tubular structure and sensing of urinary flow to maintain normal orientation
• Abnormalities in these genes and the resultant loss of polarity can result in cyst formation
• What is clear in PKD is that intracellular cAMP levels are increased, and of its many effects, two that are relevant to the disease process occur:
  – Increase cell proliferation, including through the mTOR pathway
  – Activation of the CFTR chloride channel leading to calcium secretion at the apical membrane
2\textsuperscript{nd} (or 3\textsuperscript{rd}, or 4\textsuperscript{th}) hits

- Only a small minority of nephrons develop cysts
- There is much more than the PKD1/2 complex at play in the phenotypic presentation of ADPKD
- These other facilitating or attenuating factors account for much of the variability seen in ADPKD
The disease course is a variable one, with the early portion of the 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.
Diagnosis of PKD

Essentially two presentations:
- initial presentation with multiple renal cysts
- screening in a known family

**Screening**
- Our ability to detect cysts is quite good, so it is easier to confirm the diagnosis than it is to rule it out
- NPV is not adequate until later in life

**These criteria apply to patients with known family history**

New imaging findings of multiple cysts
- Need to consider ddx of multiple cysts

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Differential diagnosis of multiple renal cysts

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>Family history</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal-recessive polycystic kidney disease</td>
<td>AR</td>
<td>Siblings (25%)</td>
<td>~1 in 20,000. Neonatal deaths in 30%; Potter’s phenotype; biliary dysgenesis (congenital hepatic fibrosis, intrahepatic bile duct dilatation), resulting in portal hypertension and cholangitis.</td>
</tr>
<tr>
<td>Renal cysts and diabetes syndrome (RCAD/MODY5/ HNF-1B)</td>
<td>AD</td>
<td>De novo mutations (often deletions) in 50%</td>
<td>Renal cysts or malformation in 90%, diabetes mellitus in 45%, hypomagnesemia in 40%, genital tract abnormalities in 20%, hyperuricemia in 20%, elevated liver enzymes in 15%.</td>
</tr>
<tr>
<td>Tuberous sclerosis complex</td>
<td>AD</td>
<td>Absent in two thirds of families</td>
<td>~1 in 10,000 live births. Skin lesions (facial angiofibroma, periungual fibroma, hypomelanotic macules, shagreen patch), &gt;90% cerebral pathology (cortical tuber, subependymal giant cell astrocytoma), 90%; renal (polycystic kidneys, angiomyolipoma), 50–70%; retinal hamartomas, 50%; lymphangioleiomyomatosis.</td>
</tr>
<tr>
<td>PKD1-TSC contiguous gene syndrome</td>
<td>AD</td>
<td>Spontaneous presentation frequent</td>
<td>Presentation of severe ADPKD at an early age, with polycystic kidneys with renal angiomylipomas frequently present after the first year of age.</td>
</tr>
<tr>
<td>von Hippel-Lindau disease</td>
<td>AD</td>
<td>De novo mutations in 20%</td>
<td>~1 in 35,000. Cerebellar and spinal hemangioblastoma; retinal angiomas; serous cystadenomas and neuroendocrine tumors of pancreas; pheochromocytoma; renal cell carcinoma.</td>
</tr>
<tr>
<td>Medullary cystic kidney disease</td>
<td>AD</td>
<td>Rare</td>
<td>Slowly progressive kidney disease; medullary cysts (but uncommon in families with type 2 MCKD [now known as ADTKD-UMOD]); hyperuricemia and gout in type 2 MCKD (now known as ADTKD-UMOD); small- to normal-sized kidneys.</td>
</tr>
<tr>
<td>Medullary sponge kidney</td>
<td>Unclear</td>
<td>Familial clustering reported</td>
<td>~1 in 5000. Medullary nephrocalcinosis; kidney stones; 'brush' or linear striations on intravenous pyelogram.</td>
</tr>
<tr>
<td>Simple renal cysts</td>
<td>Acquired</td>
<td>None</td>
<td>Common; increase in number and size with age; normal renal function; normal-sized kidneys.</td>
</tr>
<tr>
<td>Acquired cystic kidney disease</td>
<td>Acquired</td>
<td>None</td>
<td>Common in patients with chronic renal failure or ESRD; multiple cysts associated with normal- or small-sized kidneys.</td>
</tr>
</tbody>
</table>

**Table 2 | Differential diagnosis of other renal cystic diseases**

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Chapman et al, 2015
Typical radiographic morphology of ADPKD

Diffuse, bilateral cystic involvement of both kidneys
In most cases these can be differentiated radiographically by two key radiographic features of ADPKD:
- Multiple simple cysts throughout the kidneys
- Renal enlargement
A key new understanding of PKD: Hyperfiltration

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

Maintained GFR in the setting of renal parenchymal loss = hyperfiltration.

The disease course is variable, 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.
Genetics in PKD

PKD1

PKD2
Genetics are only part of the story…

While PKD1 on average portends a worse prognosis than PKD2 there is substantial variation and overlap.

Family history can suggest genotype in the extremes:
• Affected family member with ESRD <55 years, 100% PPV for PKD1
• Affected kin without ESRD >70 – 100%PPV PKD2

For everything else there is substantial overlap.
It is more complicated than 1 vs 2...

Mayo PKD mutation database
- PKD1 – 2323 known mutations, 868 clear pathogenic significance
- PKD2 – 278 mutations, 168 clear pathogenic significance

In any case, genetics only tells you about average disease course, not your individual patient

It is very difficult to get detailed genetic analysis in BC
## Genetic analysis methods

<table>
<thead>
<tr>
<th></th>
<th>DNA linkage analysis</th>
<th>Gene-based mutation screening</th>
<th>NGS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PKD1</td>
<td>PKD2</td>
<td>PKD1</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>n/a</td>
<td>n/a</td>
<td>~$1000</td>
</tr>
<tr>
<td><strong>Availability (# of sites worldwide)</strong></td>
<td>1</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td><strong>Interpretation</strong></td>
<td>Should be interpreted with caution given the possibility of de novo mutations, mosaicism, and hypomorphic alleles (Torra-Balcells and Ars-Criach, 2011)</td>
<td>May be difficult to differentiate missense mutations from benign variants; mutations detected in approximately 65%-75% of subjects, approximately 8% of patients have no confirmed pathogenic mutation (Heyer et al., 2016)</td>
<td>Offers sensitivity of 99.2% and specificity of 99.9% in identifying mutations in PKD1 and PKD2 (Tan et al., 2014)</td>
</tr>
</tbody>
</table>
Role of genetics

• Due to the difficulty obtaining genetics, the accuracy of image-based diagnosis of PKD and the limited prognostic information provided by genetics (more later) this plays a minor role in clinical PKD management
  • Potential donors
  • Uncertain imaging
  • New presentations with unusual manifestations
  • Family planning

In BC, this is only covered if approved by a medical geneticist
Take home points: Natural history

• Imaging based diagnosis of PKD is age dependent
• Decline in GFR is a late finding in PKD – by the time that happens there has been substantial disease progression
• PKD is a hyperfiltering and fibrotic disease
• Genetics have some prognostic value but there is substantial variation in the disease course of individual patients
Symptom burden in PKD
Over ¼ of people with GFR >60 have abdominal symptoms related to their PKD.
Other complications of PKD

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


Health related quality of life in PKD

- Even early stage (CKD1) PKD patients show impacts of PKD on their life.
- In other studies, PKD patients score lower on HR-QoL scores than CKD peers at similar GFRs.

Oberdhan; ASN 2015
Patient perspectives of PKD

The physical symptoms and complications are only one aspect of the total burden of PKD.
Take home points: Symptom burden and impact of PKD

• Although renal dysfunction in a late finding, complications and symptoms often present before GFR decline
• Even early stage PKD has a substantial symptom burden, impact on quality of life and psychological impact on patients
Predicting renal prognosis in PKD
Predictors of progression in PKD

Other studies exist which confirm these criteria, as well as changes in albuminuria and urine concentrating capacity. These are not predictors of progression, they are signs that substantial progression has already occurred.

HR for risk of ESRD at 60yrs
Clinical markers and the PRO-PKD score

<table>
<thead>
<tr>
<th>Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension before age 35</td>
<td>2</td>
</tr>
<tr>
<td>First urologic event before age 35</td>
<td>2</td>
</tr>
<tr>
<td>PKD2 mutation</td>
<td>0</td>
</tr>
<tr>
<td>Non truncating PKD1 mutation</td>
<td>2</td>
</tr>
<tr>
<td>Truncating PKD1 mutation</td>
<td>4</td>
</tr>
</tbody>
</table>

- A scoring system based on a mix of clinical and genetic factors
- Can only be used in patients with a history of urologic events
Kidney size/Total kidney volume (TKV)

• In many cases, genetics are too variable to firmly predict progression, and clinical markers appear too late in the disease course

• Since kidney size precedes renal dysfunction, changes in kidney size have been examined as a marker of prognosis and disease progression. A dynamic marker like this would help quantify the progression of an individual patient

• Much of the following data has come from the CRISP investigators
Change in kidney size precedes change in renal function

• While a statistically significant difference in GFR did not arise until 6 years of follow-up, a detectable and significant change in TKV was detectable at 1 year follow-up.
TKV as a predictor of renal outcomes

In this study of the CRISP cohort, total kidney Volume (TKV) at baseline was found to be a better predictor of risk of GFR <60 over 8 years of follow-up than baseline age, baseline renal function or proteinuria.

At present, this appears to be the best predictor of renal progression for early stage PKD.
Mayo classification categorizes rate of kidney growth

<table>
<thead>
<tr>
<th>Class</th>
<th>Average annual change in TKV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>&lt;1.5%</td>
</tr>
<tr>
<td>1B</td>
<td>1.5-3</td>
</tr>
<tr>
<td>1C</td>
<td>3-4.5</td>
</tr>
<tr>
<td>1D</td>
<td>4.5-6</td>
</tr>
<tr>
<td>1E</td>
<td>&gt;6%</td>
</tr>
</tbody>
</table>

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

Mayo class predicts rate of GFR loss

<table>
<thead>
<tr>
<th>Class</th>
<th>Average annual change in TKV</th>
<th>Average annual decrease in eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>&lt;1.5%</td>
<td>0.23</td>
</tr>
<tr>
<td>1B</td>
<td>1.5-3</td>
<td>1.33</td>
</tr>
<tr>
<td>1C</td>
<td>3-4.5</td>
<td>2.63</td>
</tr>
<tr>
<td>1D</td>
<td>4.5-6</td>
<td>3.48</td>
</tr>
<tr>
<td>1E</td>
<td>&gt;6%</td>
<td>4.78</td>
</tr>
</tbody>
</table>

The average GFR comes from >8 years of CRISP and Mayo clinic follow-up data
Take home points: Predicting progression of PKD

Clinical/ lab abnormalities predict disease progression but they are late findings
Assessment of kidney size is the best early predictor of renal prognosis

- Providing patients with an individualized prognostication of their renal disease (based on assessment of renal size in early stages) is becoming standard of care
- Disease modifying treatments will target early stage patients and there is a substantial symptom burden even in early stage PKD
Take home point: Early management of PKD

• All PKD patients should have a detailed clinical assessment including prognostication of renal progression

For this reason, early referral to nephrology is recommended for all PKD patients

• This is a significant difference compared to the general CKD population where delayed referral is appropriate
Treatment of PKD

Measures to slow renal decline in ADPKD
Blood Pressure in Early Autosomal Dominant Polycystic Kidney Disease

Robert W. Schrier, M.D., Kaleab Z. Abebe, Ph.D., Ronald D. Perrone, M.D., Vicente E. Torres, M.D., Ph.D., William E. Braun, M.D., Theodore I. Steinman, M.D., Franz T. Winklhofer, M.D., Godela Brosnahan, M.D., Peter G. Czarnecki, M.D., Marie C. Hogan, M.D., Ph.D., Dana C. Miskulin, M.D., Frederic F. Rahbari-Oskouei, M.D., Jared J. Grantham, M.D., Peter C. Harris, Ph.D., Michael F. Flessner, M.D., Ph.D., Kyongtae T. Bae, M.D., Charity G. Moore, Ph.D., M.S.P.H., and Arlene B. Chapman, M.D., for the HALT-PKD Trial Investigators*
HALT-PKD trial

• P: 558 hypertensive PKD patients with GFR > 60ml/min
• I: Low blood pressure target (95/60-110/75)
• C: Standard BP target (120/70-130/80)
(Also looked at combination RAS blockade – negative results, will not discuss here)
• O: Primary outcome was change in TKV. Secondary outcomes included decrease in renal function and proteinuria
• Study design: Double-blind RCT
Young: Age 37
Preserved kidney function: eGFR 90
Rapid progressing disease: Big kidneys at a young age
Achieved BP
Effect on TKV

A. Changes in Total Kidney Volume over Time

- Standard blood pressure
- Low blood pressure

- Low blood pressure, 5.6%/yr
- Standard blood pressure, 6.6%/yr
- Difference, -1.0 percentage points/yr (95% CI, -1.6 to -0.2)
- P = 0.006

Follow-up (mo)
Effect on rate of GFR decline

B  Changes in eGFR over Time

- Standard blood pressure
- Low blood pressure

Observed eGFR (ml/min/1.73 m²)

Low blood pressure, -2.9 ml/min/1.73 m²/yr
Standard blood pressure, -3.0 ml/min/1.73 m²/yr
Difference, -0.1 ml/min/1.73 m²/yr (95% CI, -0.3 to 0.6)
P = 0.55
Secondary outcomes

• Albuminuria was reduced by 3.77% in the low target group vs 2.43% in the standard target group (p<0.001)

• Dizziness/light-headedness were more common in the low target group [80.7 vs 69.4 (p=0.02)]. Despite this, >75% of participants completed the study at their assigned BP target
Opinion: How Goldilocks got misinterpreted

Crumbly diabetic vasculopathy

Average CKD patient

PKD or other isolated hyperfiltering renal disease

Incidence of Primary Outcome, %

Systolic Blood Pressure, mm Hg

Water

• Theoretical basis – inhibition of ADH release and therefore less activity via V2R

• Numerous studies with conflicting results – no demonstrable impact on renal progression

• Low risk treatment, many patients do this as far as tolerated

• Data from tolvaptan studies demonstrate that it is possible to drink enough water to suppress ADH, but it is very difficult and only a minority of patients can do so
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 Higashihiara, 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*
Refresher on ADPKD pathophysiology
TEMPO 3:4 trial

- P: 1445 patients 18-50 years old with ADPKD and TKV >750 ml and GFR > 60ml/min
- I: Tolvaptan; dosed BID, titrated to max tolerated dose with goal 90/30mg
- C: Placebo. High fluid intake and hypertension management with RAS blockade in both groups
- O: Primary outcome was change in TKV. Secondary outcomes included decrease in renal function and pain events
- Study design: Double-blind, placebo controlled RCT
Young: Age 39

Preserved kidney function: eGFR 81

Rapid progressing disease: Big kidneys at a young age
• 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
- 23% vs. 13.8% in the placebo group discontinued the drug
- 8.3% of all tolvaptan patients discontinued due to aquaretic symptoms
- 1.3% of patients in the tolvaptan group discontinued the drug due to liver enzyme abnormalities

**HyperNa 2.8% vs. 1.0% (NS)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Tolvaptan (N = 961)</th>
<th>Placebo (N = 483)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thirst</td>
<td>531 (55.3)↑</td>
<td>99 (20.5)</td>
</tr>
<tr>
<td>Polyuria</td>
<td>368 (38.3)↑</td>
<td>83 (17.2)</td>
</tr>
<tr>
<td>Nocturia</td>
<td>280 (29.1)↑</td>
<td>63 (13.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>240 (25.0)</td>
<td>120 (24.8)</td>
</tr>
<tr>
<td>Pollakiuria*:</td>
<td>223 (23.2)↑</td>
<td>26 (5.4)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>154 (16.0)</td>
<td>59 (12.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>128 (13.3)</td>
<td>53 (11.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>131 (13.6)</td>
<td>47 (9.7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>109 (11.3)</td>
<td>42 (8.7)</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>100 (10.4)↑</td>
<td>17 (3.5)</td>
</tr>
<tr>
<td><strong>Adverse events more common</strong></td>
<td><strong>in placebo group</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>309 (32.2)</td>
<td>174 (36.0)</td>
</tr>
<tr>
<td>Renal pain</td>
<td>259 (27.0)↓</td>
<td>169 (35.0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>210 (21.9)</td>
<td>111 (23.0)</td>
</tr>
<tr>
<td>Back pain</td>
<td>132 (13.7)</td>
<td>88 (18.2)</td>
</tr>
<tr>
<td>Increased creatinine level</td>
<td>135 (14.0)</td>
<td>71 (14.7)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>75 (7.8)↑</td>
<td>68 (14.1)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>80 (8.3)↑</td>
<td>61 (12.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>98 (10.2)</td>
<td>57 (11.8)</td>
</tr>
</tbody>
</table>

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

**Serious adverse events more common in tolvaptan group**
- Alanine aminotransferase elevation 9 (0.9) vs. 2 (0.4)
- Aspartate aminotransferase elevation 9 (0.9) vs. 2 (0.4)
- Chest pain 8 (0.8) vs. 2 (0.4)
- Headache 5 (0.5) vs. 0

**Serious adverse events more common in placebo group**
- Pyelonephritis 5 (0.5) vs. 5 (1.0)
- Renal-cyst infection 6 (0.6) vs. 4 (0.8)
- Renal-cyst hemorrhage 3 (0.3) vs. 4 (0.8)
- Renal pain 1 (0.1) vs. 4 (0.8)
- Appendicitis 1 (0.1) vs. 4 (0.8)
- Nephrolithiasis 2 (0.2) vs. 3 (0.6)
- Urinary tract infection 1 (0.1) vs. 3 (0.6)
- Hypertension 1 (0.1) vs. 3 (0.6)
Adverse effects – increased transaminases

• Overall, 4.9% with tolvaptan vs. 1.2% in the placebo group had abnormal liver enzymes

• 2 patients (0.02%) in the tolvaptan arm had AST/ALT >3xULN and bilirubin >2xULN. This pharmacologic entity is a specific type of drug induced liver damage deemed ‘Hy’s Law’ and carries an approximate 10% mortality
  • The two patients that met this criteria had their liver injury occur at 4 and 5 months of treatment. The first had complete recovery at 3 months, the second had mild persistent increase in transaminases

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

As a result there is Health Canada mandated hepatic monitoring when using tolvaptan (‘Blood for drug’)
Applicability of findings to other ADPKD patients

- TEMPO 3:4 enrolled a very specific group of ADPKD patients in that they had relatively preserved (but not normal) renal function and massive kidneys at about age 40; in other words they were at high risk of declining rapidly.
- The fact that the placebo arm had a -3.7 ml/min/year GFR slope reinforces this.
- There are ongoing trials on these patients as well as patients with lower GFR.

### Variable | TEMPO inclusion criteria | Actual mean values of pts entered
--- | --- | ---
Age | 18-50 | 39
GFR | >60 ml/min, randomization stratified to >80 or <80 | 81 ml/min. ~25% < 80 ml/min, remainder >80 ml/min
TKV | >750 ml | ~1700 ml
BP | Not a criterion, randomization stratified to present or absent | 128/82. Hypertension present in ~80% of patients, ~72% on RAAS blockade
Proteinuria | Not a criterion | 7-8 mg/mmol
Identifying candidates for tolvaptan

• Essentially the current data points to efficacy in patients who are rapidly progressing but still early in their disease course
• This indication may change when more data is published
• Canadian guidelines for treatment will be published later this year
• Early prognostication of all PKD patients is critical to help identify the rapidly progressing patients who will be candidates for this, and any other treatments that emerge
  • The future will likely be multi-targeted treatment of PKD, directed at rapid progressors, early in their disease course
  • In the pipeline: mTOR inhibitors, SS analogues, TZDs, metformin, statins
Delaying renal progression in PKD

- A stricter blood pressure target may help slow progression of PKD
- Not all patients can tolerate such low blood pressure, but the young, early stage PKD patients here tolerated it quite well
  - I would attempt aggressive target in most PKD patients, especially with preserved GFR
  - If they do not tolerate the low target, back off
- High fluid intake may have some benefit and is fairly benign
- Tolvaptan (and other disease modifying treatments) is likely to be most effective in those with preserved renal function but rapidly progressing disease
Extra-renal manifestations of PKD
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
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, 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

**Opinion** for those with ICAs, this is another reason for aggressive BP control
Liver involvement in PKD

- Liver cysts occur in >80% of PKD patients
- Most are asymptomatic; ~20% have abdominal symptoms
- Impact on liver function is rare, but occurs
- Estrogen is a risk factor – more common in women, avoid HRT
- The renal treatments we will discuss do not impact liver cysts
  - Somatostatin analogues are being studied
Summary

• There is substantial disease progression including symptoms and impact on patients that occur before you see any change in GFR

• There are imaging based tools available to help predict patient’s disease course in PKD
  • PKD patients should all have at least one assessment of renal size

• There is good data for a lower blood pressure target in PKD
  • This is a good time to review blood pressure control in your PKD patients

• Tolvaptan can be considered in patients with rapidly enlarging kidneys but preserved GFR
Summary

Early assessment of PKD patients and identification of rapid progressors is the cornerstone of modern PKD management

- Please consider early nephrology referral for all your PKD patients, at least for an initial assessment

- Remember to ask about affected family members and any screening
What we have done with PKD 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 BP in the normal range and do your bloodwork. See you in 6-12 months.

When your GFR drops, we’ll start talking about transplant and dialysis.
What we should aim for 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 as early as possible.

We will discuss treatments like BP and water that apply to everyone with PKD and will assess whether you are a candidate for disease specific treatments.
Questions?

Thank you for attending this talk and for your interest!

If any questions arise, feel free to contact me at: Mike.bevilacqua@bcpra.ca