Original Research Article

Assessing Risk of Disease Progression and Pharmacological Management of Autosomal Dominant Polycystic Kidney Disease: A Canadian Expert Consensus

Steven Soroka[1], Ahsan Alam[2], Micheli Bevilacqua[3], Louis-Philippe Girard[4], Paul Komenda[5], Rolf Loertscher[6], Philip McFarlane[7], Sanjaya Pandeya[8], Paul Tam[9], and Daniel G. Bichet[10]

Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder worldwide. The disease is characterized by renal cysts and progressive renal failure due to progressive enlargement of cysts and renal fibrosis. An estimated 45% to 70% of patients with ADPKD progress to end-stage renal disease by age 65 years. Although both targeted and nontargeted therapies have been tested in patients with ADPKD, tolvaptan is currently the only pharmacological therapy approved in Canada for the treatment of ADPKD. The purpose of this consensus recommendation is to develop an evidence-informed recommendation for the optimal management of adult patients with ADPKD. This document focuses on the role of genetic testing, the role of renal imaging, predicting the risk of disease progression, and pharmacological treatment options for ADPKD. These areas of focus were derived from 2 national surveys that were disseminated to nephrologists and patients with ADPKD with the aim of identifying unmet needs in the management of ADPKD in Canada. Specific recommendations are provided for the treatment of ADPKD with tolvaptan.

Abrégé

La polykystose rénale autosomique dominante (PKRAD) est le trouble rénal héréditaire le plus fréquent dans le monde. La maladie est caractérisée par la présence de kystes rénaux et par une insuffisance rénale progressive provoquée par l'élargissement progressif des kystes et par une fibrose rénale. Environ 45 à 70% des patients atteints de PKRAD verront leur état évoluer vers l'insuffisance rénale terminale avant l'âge de 65 ans. Bien que les thérapies ciblées et non ciblées aient été testées chez des patients atteints de PKRAD, le tolvaptan est le seul médicament approuvé au Canada pour le traitement de la PKRAD. L'objectif de cette recommandation consensuelle est l'élaboration de recommandations fondées sur des données probantes pour une prise en charge optimale des patients adultes atteints de PKRAD. Ce document met l'accent sur le rôle du dépistage génétique et de l'imagerie rénale, sur les façons de prédire le risque de progression de la maladie et sur les options de traitement pharmacologique de la PKRAD. Ces domaines d'action dérivent de deux enquêtes nationales diffusées aux néphrologues et aux patients canadiens atteints de PKRAD, et qui avaient pour but d'identifier les besoins non satisfaits dans la prise en charge le la PKRAD au Canada. Des recommandations spécifiques sont fournies pour le traitement de la PKD avec le tolvaptan.

Why is this review important

This consensus review was done to develop evidence-informed recommendations for Canadian nephrologists to guide optimal management of adult patients with ADPKD.

What are the key messages

1. Based on existing data, genetic testing is only required for a subset of patients with ADPKD, and it is not needed prior to initiating treatment options.

2. Although the gold standard for imaging is MRI, other less costly and more readily available imaging modalities should be used in routine clinical practice for diagnosis and determination of risk of progression.

3. Blood pressure targets and ADPKD-specific treatment options are recommended for patients who fulfill specific criteria.

4. We recommend treatment with tolvaptan for patients who fulfill the enrollment criteria of the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes (TEMPO) 3:4 study: 18 to 50 years of age, Cockcroft-Gault GFR >60 mL/min, and TKV >750 mL. In the absence of Cockcroft-Gault GFR, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) >45 mL/min may be used, and in the absence of TKV, ultrasound (US) kidney length (KL) >16.5 cm may be used.

5. We suggest treatment with tolvaptan for patients who, according to the Mayo Classification, are classified as 1D or 1E with eGFR in CKD stage 3 or higher. Treatment with tolvaptan should be considered for patients who are classified as 1C and are younger than 50 years or have other risk factors for rapid progression.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder, with a prevalence of 1:500 to 1:1000.[1] ADPKD accounts for 7% to 11% of patients on renal replacement therapy in Europe and approximately 5% of patients requiring dialysis in the United States.[2] ADPKD is characterized by bilateral renal cysts and may be associated with kidney pain, urinary tract infection, hematuria, nephrolithiasis, hypertension, and progressive renal failure due to progressive enlargement of cysts and fibrosis.[3-5] Cyst growth displaces and destroys normal kidney tissue, culminating in fibrosis, renal architectural derangement, and ultimately kidney failure.[6,7] An estimated 45% to 70% of patients with ADPKD progress to end-stage renal disease (ESRD) by age 65 years.[8]

Several targeted pharmacological therapies have been tested in patients with ADPKD, including mammalian target of rapamycin (mTOR) inhibitors, somatostatin analogues, and the vasopressin V2-receptor antagonist tolvaptan[2]; however, tolvaptan is the only approved therapy in Canada for the treatment of ADPKD.[9] The purpose of this consensus recommendation is to develop an evidence-informed recommendation for the optimal management of adult patients with ADPKD. The focus will be on the role of genetic testing, the role of renal imaging, risk prediction of disease progression, and pharmacological treatment options. These areas of focus were derived from 2 national surveys that were disseminated to nephrologists and patients with ADPKD.

Nephrologists' Survey

With the goal of identifying the top needs in the management of ADPKD from the perspective of nephrologists, a survey was disseminated to members of the Canadian Society of Nephrology. A total of 73 physicians completed the survey. The survey results are summarized in Table 1.

Patients' Survey

A second survey was disseminated to patient members of the PKD Foundation of Canada. A total of 88 patients completed the survey that was designed to assess what symptoms of ADPKD have the greatest effect on their lives, and what they perceive to be the greatest unmet needs in the management of ADPKD. The results of the survey are summarized in Table 2.

Methods

The present consensus recommendations are based on the experience and opinions of the authors, and on a literature search conducted in PubMed, the Cochrane Library, and Google Scholar using the search terms *ADPKD* or *polycystic kidney* in combination with the following terms: *CKD* or

[1]Division of Nephrology, Dalhousie University, Halifax, Nova Scotia, Canada

[2]Division of Nephrology, Royal Victoria Hospital, McGill University, Montreal, Québec, Canada

[3]Division of Nephrology, St. Paul's Hospital, University of British Columbia, Vancouver, Canada

[4]Division of Nephrology, Foothills Medical Centre, University of Calgary, Alberta, Canada

[5]Division of Nephrology, Seven Oaks General Hospital, University of Manitoba, Winnipeg, Canada

[6]Division of Nephrology, Lakeshore General Hospital, McGill University, Pointe-Claire, Québec, Canada

[7]Division of Nephrology, St. Michael's Hospital, University of Toronto, Ontario, Canada

[8]Division of Nephrology, Halton Healthcare Services, Oakville, Ontario, Canada

[9]The Scarborough Hospital, Ontario, Canada

[10]Division of Nephrology, Département de Médecine et de Physiologie Moléculaire et Intégrative, Hôpital du Sacré-Cœur de Montréal, Université de Montréal, Québec, Canada

Corresponding Author:

Steven Soroka, Division of Nephrology, Dalhousie University, QEII - Dickson Building, Suite 5088 Dickson Building, 5820 University Avenue, Halifax, Nova Scotia, Canada B3H 2Y9.

Email: Steven.Soroka@nshealth.ca

Table 1. Results of the survey disseminated to members of the Canadian Society of Nephrology.

What treatment guidelines/algorithm, if any, do you use to treat your patients with ADPKD?
  82% None
  11% Clinical guidelines developed by the Caring for Australians with Renal Impairment
  7% Workshop results in Kidney International, literature-guided therapy, evidence-based literature, control of BP, and encouragement of increased water consumption
What screening tools do you use to diagnose ADPKD?
  92% Ultrasonography
  3% Magnetic resonance imaging
  3% Molecular genetic testing
  1% Computed tomography
  1% None
  0% Urinary biomarkers
What treatments have you used for your patients with ADPKD?
  42% Surgery
  29% Tolvaptan
  24% Other types of therapy (eg, BP monitoring, interventional radiology)
  3% Mammalian target of rapamycin inhibitors (eg, everolimus, sirolimus)
  1% Somatostatin analogues (eg, octreotide, lanreotide, pasireotide)
What do you perceive to be the top needs in the management of ADPKD in Canada?
  Lack of general practitioners' awareness of ADPKD
  Lack of management guidelines and care pathways
  Lack of knowledge of comprehensive integrated and accepted guidelines for the evaluation of extrarenal manifestations of ADPKD
  Lack of established diagnostic algorithms integrating clinical signs and symptoms with kidney imaging and genetic testing
  Lack of consensus on the optimal approach to predict prognosis
  Lack of therapeutic options
  Lack of clarity on subgroups of patients that may benefit from existing treatment

Note. ADPKD = autosomal dominant polycystic kidney disease; BP = blood pressure.

Table 2. Results of the Survey Disseminated to Patient Members of the PKD Foundation of Canada.

What symptoms bother you the most?
  Pain
  Fatigue
  Enlarged abdomen/bulky organs/bloating
  Edema
  Hypertension
  Side effects of therapy
In your opinion, what should the priorities be for research on ADPKD?
  Finding a cure
  Finding therapy that will stop/slow disease progression/cyst growth
  Finding therapy that could reduce cysts to a manageable size or prevent cyst development
  Identifying nonpharmacological therapies that could be used to delay the initiation of pharmacological therapies
  Providing better access to transplantation
  Improving the longevity of transplants
  Finding treatments with improved efficacy and safety
  Identifying molecular-based therapies that could correct the gene defect
  Identifying modifiable lifestyle factors

Note. ADPKD = autosomal dominant polycystic kidney disease.

chronic kidney disease or diagnosis or end-stage renal disease or ESRD or gene or imaging or management or mTOR inhibitor or risk or pharmacological or screening or somatostatin or surgery or TKV or total kidney volume or height adjusted TKV or tolvaptan or transplantation or treatment. We selected publications that were published in the past 10 years but did not exclude highly regarded older publications. In addition, we searched the reference lists of articles identified by this search strategy and selected additional relevant references. For topics that were beyond the scope of this consensus document, review articles are cited to guide readers to sources with more details. The authors reached a consensus on the recommendations published herein. The following aspects of the disease are addressed: genetic testing, renal imaging, predicting disease progression, and pharmacological treatment options.

Genetic Testing in ADPKD

ADPKD is genetically heterogeneous with 2 genes identified: *PKD1* (chromosome 16p13.3) and *PKD2* (4q21).[10] Mutations in the *PKD1* gene occur in 85% to 90% of cases of ADPKD, whereas mutations in the *PKD2* gene account for the remainder of cases.[11,12] The *PKD1* and *PKD2* genes encode 2 proteins, polycystin-1 and polycystin-2, that constitute the transient receptor potential polycystin subfamily of transient receptor potential channels.[10] Genic, allelic, and gene modifier effects contribute to the high phenotypic variability of ADPKD, and truncating *PKD1* mutations are associated with more severe disease and earlier decline in kidney function compared with nontruncating *PKD1* mutations.[13] According to the PKD Foundation of Canada, there are currently 2323 known mutations in the *PKD1* gene and 278 known mutations in the *PKD2* gene (Autosomal Dominant Polycystic Kidney Disease Mutation Database [PKDB], http://pkdb.mayo.edu/).

Genetic testing for ADPKD can be carried out using DNA linkage analysis, gene-based mutation screening (also referred to as Sanger sequencing), or, in the near future, next-generation sequencing (NGS). Up-to-date information regarding laboratories currently offering genetic testing for ADPKD can be obtained from GeneTests (www.genetests.

org), a valuable web-based resource funded by the National Institutes of Health.[14] The Web site provides a comprehensive list of academic and commercial facilities worldwide that offer testing for *PKD1* or *PKD2* mutations on a clinical or research basis.

DNA linkage analysis seeks to identify the presence of a segment of the chromosome at either the *PKD1* or *PKD2* locus that completely segregates with the disease. Thus, there is no need to identify the exact ADPKD mutation as the presence of these markers and not the mutations themselves is being tracked. There are currently 15 microsatellite markers for *PKD1* and 8 for *PKD2*.[15] DNA linkage analysis, however, is useful only in familial cases and requires a large family with at least 4 affected members in at least 2 generations, with radiological studies in both affected and unaffected individuals, for conclusive results. Results must be interpreted with caution if there are de novo mutations, mosaicisms, and hypomorphic alleles.

Gene-based mutation screening is the most commonly used method for genetic diagnosis of ADPKD. This approach seeks to identify the exact mutation in the *PKD1* and *PKD2* genes. Because most mutations are unique to a single family with no clear "hot spots," exon-by-exon screening of these genes is necessary to ensure high sensitivity in detecting disease-causing mutations in *PKD1* and *PKD2*.[16] Challenges of gene-based mutation screening include the difficulty in differentiating disease-causing missense mutations from benign variants, the detection of a definitive mutation in no more than 65% to 75% of patients tested, and the lack of a confirmed pathogenic mutation in approximately 8% of patients with ADPKD.[13]

NGS, also known as high-throughput sequencing, refers to a number of different modern sequencing technologies that can sequence millions of small fragments of DNA in parallel and use bioinformatic analyses to piece together these fragments and provide accurate data on genetic mutations.[17] Compared with gene-based mutation screening, NGS offers the benefits of high fidelity, high throughput, and high speed.[18] NGS was validated in a cohort of 25 patients who had previously undergone genetic testing using gene-based mutation screening.[19] NGS identified 250 genetic variants in the *PKD1* and *PKD2* genes, including all 16 pathogenic mutations and 3 novel mutations that gene-based mutation screening did not identify. In this study, NGS showed sensitivity of 99.2% and specificity of 99.9%, with cost and turnaround time reduced by approximately 70% compared with gene-based mutation screening sequencing.

Although genetic testing for ADPKD mutations is indicated in some patients, it is not indicated for all patients. Genetic testing is not needed when a firm positive or negative diagnosis can be made by imaging alone or, as in the case of a patient with suspected ADPKD, when a diagnosis can be made based on the imaging results of the patient's parents or based on the presence of extrarenal manifestations. Genetic testing should be considered in potential living related donors to confirm the absence of any mutations for ADPKD, in patients without a family history of ADPKD (especially if radiographic presentation is atypical, if renal disease is mild, if extrarenal symptoms are atypical, or if prognostic information is required), in families with atypical radiographic patterns of kidney cysts to possibly exclude other cystic kidney diseases, in families affected by early-onset polycystic disease, and in patients who want a prenatal or preimplantation diagnosis.[15,20]

Family history can be highly predictive of the genetic mutation.[21] A family history of having at least one family member with early-onset ESRD ≤55 to 58 years of age has a positive predictive value (PPV) of 100% for the presence of a mutation in the *PKD1* gene. In contrast, a family history of having at least one family member who remained renal sufficient or developed ESRD ≥68 to 70 years of age had a PPV of 100% for a mutation in the *PKD2* gene. Applying these 2 criteria can correctly predict the *PKD1* or *PKD2* mutation in approximately 75% of cases.

Recommendations

1. Based on existing data, genetic testing is not necessary for selecting treatment options for patients with a confirmed diagnosis of ADPKD.
2. If genetic testing is to be done, it should be done by a Clinical Laboratory Improvement Amendments (CLIA)-certified center and interpreted by those familiar with ADPKD genetics.

Renal Imaging

Several imaging modalities are currently available to diagnose and evaluate ADPKD, including abdominal ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). In terms of diagnosis, our nephrologist survey indicated that 92% of clinicians are using US as their diagnostic modality. US has robust performance in this setting; age-based criteria and diagnostic performance have been previously published and serve as good criteria for imaging-based diagnosis.[22] MRI and high-resolution US have greater sensitivity for imaging-based diagnosis at younger ages than conventional US,[23] but the availability of these tests in some centers may be limited.

For size determination, MRI appears to be the preferred imaging modality; it has greater accuracy and precision when compared with US, and although CT performs well, it requires radiation exposure.[24,25] US is a more practical and more cost-effective approach; however, there are concerns that, compared with CT or MRI, US is more user-dependent and has higher variability making it difficult to obtain accurate and reproducible results.[26] Emerging US techniques, including 3-dimensional and high-resolution US, have some data in the diagnosis of ADPKD,[23] but these modalities are not widely available, and their performance in size determination has not been evaluated.[27]

In ADPKD, kidney volume can be divided into cystic and noncystic components; however, changes in overall total kidney volume (TKV) are less variable than changes in either of these components individually, and TKV is easier to obtain.[28] For these reasons, TKV is the more commonly used measure, and in most cases, it is unnecessary to divide the volume into cystic and noncystic components.

TKV is typically obtained either by stereology or various formulae that estimate volume from a more limited set of measurements.[28,29] Stereology can be quite labor-intensive but is presently considered the gold standard for the measurement of TKV.[28] The most common method of estimation is the ellipsoid equation, which has been shown to approximate the stereological approach accurately and is less labor-intensive.[29] Another estimation formula based on a single midcoronal measurement has also been shown to yield volumes that are highly correlated with stereology measures.[30] More recently, automated methods of TKV determination have been reported to yield results similar to stereology; for these measures, patients are classified based on height-adjusted (ht) TKV and age.[31,32]

The nephrologist survey indicated that US is the first imaging modality in the majority of cases; the information extracted from these already available US images should be maximized, but it is important to consider the performance of this test. When measuring TKV, US tends to be more variable than MRI and tends to overestimate volume. Therefore, it may be useful to group patients into broad categories of kidney size.[26] Of the component measurements, US kidney length has less variability than the other dimensions.[26] US kidney length was recently found to correlate well with htTKV measured by MRI and seemed to predict the development of stage 3 chronic kidney disease (CKD) in a similar manner.[33]

Before interpreting TKV measurements, patients should be categorized according to the recently published Mayo Clinic Classification (Figure 1)[29] (http://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754). According to this system, patients with typical symmetric, bilateral, diffuse cyst distribution are categorized as class 1 (approximately 90% of patients), whereas patients with atypical, asymmetric, or segmental cyst distribution are categorized as class 2 (Table 3). Class 1 patients can be further divided into subclasses A through E by integrating htTKV with age. Classes 1C, 1D, and 1E show the highest propensity for developing early-onset renal disease. There are subtypes of class 2 (atypical) enlargement, and class 2 patients are generally not thought to be at risk of rapid renal progression, although the original studies had too few class 2 patients to definitively comment on renal progression in this group.[29]

There are limited data on the role of repeated imaging.[24,34] In patients where serial measurements are taken, an increase of >5% per year in TKV, corresponding to the threshold for class 1D, appears to correlate well with predicting rapid renal progression.[29] Recent recommendations by the European Renal Association-European Dialysis and Transplant
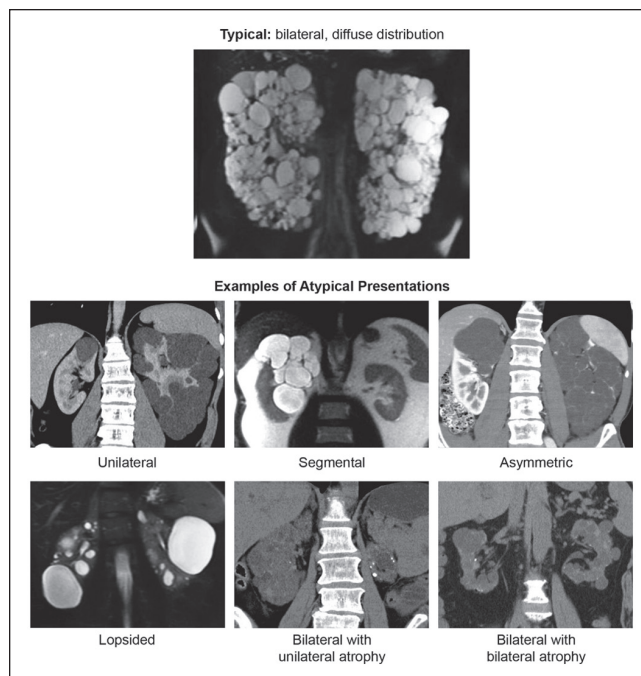
Figure 1. Mayo clinic classification of autosomal dominant polycystic kidney disease.
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Association (ERA-EDTA) and the Japanese regulatory authorities also proposed that patients with an increase in TKV of >5% annually should be placed in a higher risk category for renal disease progression.[35,36] If repeated measurements are obtained by the clinician, the performance of these tests should be considered. With MRI, differences in TKV can be detected with as little as a 6-month interval between measurements.[37] Conversely, although US can detect differences in kidney size over many years, it is not suitable for short-term follow-up as the inherent inaccuracy in US measurements is approximately the same as the annual rate of growth.[38]

Recommendations

1. We recommend that before quantifying the size of the kidneys, patients should be classified according to the Mayo Clinic classification for typical versus atypical morphology with renal imaging.

2.1. We recommend that a baseline assessment of renal size be undertaken in patients with ADPKD. The objective of these measurements is to determine which patients are suitable candidates to be considered for therapeutic intervention based on their risk of progression.

2.2. Although the gold standard for measuring TKV is MRI stereology, we recommend the use of ellipsoid TKV or US to determine TKV in routine clinical

Table 3. Classification of ADPKD Based on Imaging Characteristics According to the Mayo Clinic Classification.

Class, subclass, and term	Description
1. Typical ADPKD	Bilateral and diffuse distribution, with mild, moderate, or severe replacement of kidney tissue by cysts, where all cysts contribute similarly to TKV
2. Atypical ADPKD	
Unilateral	Diffuse cystic involvement of one kidney causing marked renal enlargement with a normal contralateral kidney, defined by a normal kidney volume (<275 mL in men; <244 mL in women) and having 0-2 cysts
Segmental	Cystic disease involving only one pole of one or both kidneys and sparing the remaining renal tissue
Asymmetric	Diffuse cystic involvement of one kidney causing marked renal enlargement with mild segmental or minimal diffuse involvement of the contralateral kidney, defined by a small number of cysts (>2 but <10) and volume accounting for <30% of TKV
Lopsided	Bilateral distribution of renal cysts with mild replacement of kidney tissue with atypical cysts where ≤5 cysts account for ≥50% TKV (the largest cyst diameter is used to estimate individual cyst volume)
Bilateral presentation with acquired unilateral atrophy	Diffuse cystic involvement of one kidney causing moderate to severe renal enlargement with contralateral acquired atrophy
Bilateral presentation with bilateral kidney atrophy	Impaired renal function (serum creatinine ≥1.5 mg/dL) without significant enlargement of the kidneys, defined by an average length <14.5 cm, and replacement of kidney tissue by cysts with atrophy of the parenchyma

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Note. ADPKD = autosomal dominant polycystic kidney disease; TKV = total kidney volume.

practice. We suggest that MRI or CT htTKV is currently the most accurate method of assessing renal size in patients with ADPKD.

2.3. In the absence of MRI, imaging by CT may be used to determine TKV. In situations where an MRI or CT is not easily obtainable, we suggest US-measured KL as a suitable surrogate. US can be used to determine TKV; however, TKV obtained using US may introduce error and does not provide an advantage over KL.

3. We recommend that routine assessment of TKV or KL should not exceed a frequency of once yearly.

Predicting Disease Progression

Prognostic factors related to disease progression in ADPKD include TKV, the type of genetic mutation, vasopressin activity, uric acid, and the presence of certain urine biomarkers, as

Table 4. Prognostic Factors Related to Disease Progression in ADPKD.

Imaging-based prognostic factors
- TKV shows a strong inverse association with the slope of GFR[28,41]
- Height-adjusted TKV shows a good correlation with GFR at baseline ($r = 0.22$), and an even stronger correlation after 3 years and 8 years ($r = 0.44$ and $r = 0.65$, respectively)[42]

Genetic prognostic factors
- *PKD1* mutations are associated with an earlier onset of ESRD compared with *PKD2* mutations[43]
- Truncating *PKD1* mutations are associated with an average onset of ESRD at 55 years of age, whereas nontruncating *PKD1* mutations and *PKD2* mutations are associated with an average onset of ESRD at 67 and 79 years of age, respectively[44]
- Hypomorphic alleles are associated with milder disease as polycystin activity is not completely abrogated; if these alleles are coupled with another mutation, a more severe disease progression may develop[45]

Urinary biomarkers
- Urinary neutrophil gelatinase–associated lipocalin and interleukin-18 levels increased over 3 years in the CRISP study; however, the increases in these 2 urine biomarkers did not correlate with changes in TKV or kidney function[46]

Other prognostic factors
- Higher levels of vasopressin activity (measured using 24-h urine osmolality as a surrogate marker) were associated with greater declines in GFR from year 1 to 6 in the CRISP study[47]
- Increased vasopressin activity (measured using copeptin levels as a surrogate marker) was associated with higher morning urine osmolality, higher BP, increased TKV, and decreased GFR in the CRISP study[48]
- Elevated serum uric acid levels are associated with disease progression; a 5.8% increase in TKV and a 4.1% increase in TKV/body surface area for every 1-mg/dL increase in uric acid have been demonstrated[49]

Note. ADPKD = autosomal dominant polycystic kidney disease; TKV = total kidney volume; GFR = glomerular filtration rate; ESRD = end-stage renal disease; CRISP = Consortium of Renal Imaging Studies in Polycystic Kidney Disease; BP = blood pressure.

summarized in Table 4.[39] Disease progression in ADPKD is characterized by loss of renal function, defined as a decline of ≥5 mL/min/1.73 m² in 1 year, or average decline of ≥2.5 mL/min/1.73 m² over 5 years, measured by creatinine clearance using the Cockcroft-Gault equation or by estimated glomerular filtration rate (eGFR) using the CKD-EPI equation.[29,40] However, in the early stages of disease, there is little change in renal function yet detectable changes in TKV. As such, TKV is a more sensitive measure of disease progression.[28]

Risk Prediction Using PROPKD Score

Cornec-Le Gall et al developed the PROPKD score as a prognostic model to predict renal outcomes in patients with ADPKD on the basis of genetic and clinical data from 1341 patients

Table 5. The PROPKD Scoring System.

Factor	Points
Male	1
Hypertension before age 35 y	2
First urological event before age 35 y	2
PKD2 mutation	0
Nontruncating *PKD1* mutation	2
Truncating *PKD1* mutation	4

from the Genkyst cohort.[50] The scoring system assigns points as shown in Table 5. Thus, an individual's PROPKD score can range from 0 to 9 points. Three risk categories of progression to ESRD were subsequently defined: low (0-3 points), intermediate (4-6 points), and high (7-9 points). The predicted median age of onset for ESRD and predicted disease progression for these 3 risk categories are listed in Table 6. Of note, the PROPKD scoring system cannot be applied to patients with no history of urological events or hypertension and has not been widely validated in independent cohorts.

Risk Prediction Using Genetic Scoring

For some patients, such as those younger than 35 years and those missing clinical data, the Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) score cannot be applied.[50] In these cases, genetic scoring may be carried out, comprising only genetic data and gender. In this scoring system, patients fall into 1 of 4 prognostic groups:

- patients with *PKD2* mutations (1 point)
- patients with nontruncating *PKD1* mutations (2 points)
- women with truncating *PKD1* mutations (3 points)
- men with truncating *PKD1* mutations (4 points)

Patients with a genetic score ≥2 points have a predicted onset of ESRD before age 65 years. Although genetic scoring is less accurate than the PROPKD score, it offers good prediction of ESRD.

Risk Prediction Using Mayo Classification

The proposed Mayo Classification defines groups of patients with different risks for eGFR decline.[29] As shown in Figure 2A, class 1 patients are categorized into subclasses 1A through 1E based on htTKV and age at baseline, which, in turn, predicts decline in eGFR, as shown in Figure 2B. The Mayo Classification, although a useful clinical tool, was developed with the aim of identifying patients eligible to participate in clinical trials.

Recommendations

1. We recommend that in current clinical practice, patients with a TKV measurement be categorized in terms of their risk of progression as per the Mayo Clinic classification or other validated clinical tools. We highlight that the application of the Mayo Classification to clinical practice has not yet been delineated; however, it appears to be the most robust clinical prediction tool as it pertains to the important marker of htTKV.

2. Currently available TKV-based prognostication tools should not be applied to class 2 (atypical morphology) patients, as we suggest that these patients are unlikely to be rapid progressors. Certain patients may require further clinical evaluation.

3. We suggest that patients who are classified as Mayo class 1C, D, or E be considered to be at risk of rapid progression of their ADPKD renal disease.

4. We recommend that patients who demonstrate a sequential increase of >5% annually in TKV on imaging should be considered at risk of rapid progression of their ADPKD-related renal disease.

5. We recommend that patients with an US KL of >16.5 cm bilaterally should be considered at high risk of progression of their ADPKD-related renal disease. A KL >16.5 cm has been shown to correlate with a TKV of 750 mL; however, direct measurement of TKV would be required if more accurate assessment is needed.

6. We suggest that baseline TKV and KL are important determinants of renal progression of ADPKD; however, serial TKV and KL measurements have not been established as markers to monitor response to therapy.

Nontargeted Treatment Options

Nontargeted treatment options for ADPKD include protein restriction, increased fluid intake, and blood pressure (BP) control. To date, no study has been able to demonstrate the benefit of protein restriction in patients with ADPKD.[51]

Increased fluid intake has received a great deal of attention as a therapeutic approach to improving disease progression in ADPKD; however, there are currently no compelling data to support increased water intake as a treatment option to prevent disease progression in ADPKD. A recent study demonstrated no benefit on disease progression in ADPKD among patients in the high water intake group compared with the free water intake group.[52]

Rigorous BP control (95/60-110/75 mm Hg) was associated with a significantly lower annual rate of increase in TKV compared with a standard BP target (120/70-130/80 mm Hg): 5.6% versus 6.5%; $P = .006$.[53] Patients in the tighter BP control group also experienced a reduction in urinary albumin excretion per year (-3.8%) versus an increase (2.4%) in the standard BP group ($P < .001$), but there was no significant difference between the 2 groups in annual change in eGFR (-2.9 mL/min/1.73 m^2 vs -3.0 mL/min/1.73 m^2, respectively; $P = .55$). Similarly, a post hoc analysis of the

Table 6. Predicted Median Age of Onset of ESRD and Predicted Disease Progression by PROPKD Risk Category.

	PROPKD risk category for progression to ESRD		
	Low risk (0-3 points)	Intermediate risk (4-6 points)	High risk (7-9 points)
Predicted median age of onset for ESRD, y	70.6	56.9	49.0
Predicted disease progression	Excludes progression to ESRD before 60 years of age (negative predictive value of 81.4%)	Prognosis is unclear	Rapid progression to ESRD before 60 years of age (positive predictive value of 90.9%)

Note. ESRD = end-stage renal disease.
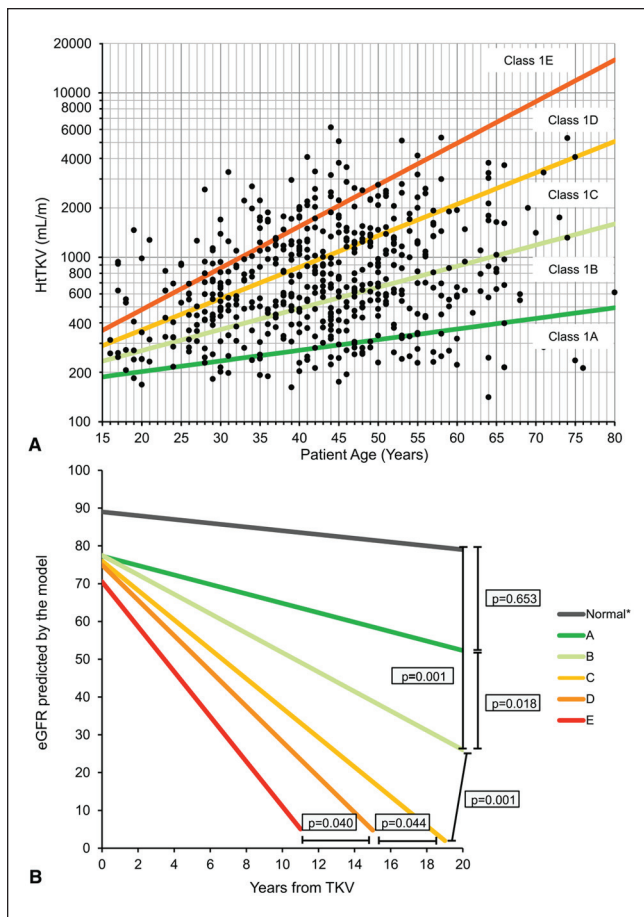
Figure 2. A, Subclassification of patients with class 1 autosomal dominant polycystic kidney disease at baseline based on htTKV and age at baseline. B, Predicted change in eGFR over time in class 1 patients (slopes shown are those for men).
Source. Republished from Irazabal et al[29] with permission of the American Society of Nephrology; permission conveyed through Copyright Clearance Center, Inc.
Note. htTKV = height-adjusted total kidney volume; eGFR = estimated glomerular filtration rate; TKV = total kidney volume.

early ADPKD population in the Halt Polycystic Kidney Disease (HALT-PKD) Study A demonstrated a stronger benefit of rigorous BP control on TKV increase, as well as a stronger benefit on eGFR decline, in the subgroup of patients with severe disease (classes 1D and E).[54]

Recommendation

1. We recommend that patients with ADPKD who are younger than 50 years with eGFR >60 mL/min/1.73 m^2 and without significant cardiovascular comorbidities should have a target BP of ≤110/75 mm Hg, realizing that in some patients an individual target may be needed.

ADPKD-Specific Treatment Options

A recent meta-analysis of 4 randomized, controlled trials of the mTOR inhibitor sirolimus in adults with ADPKD showed a positive impact on TKV but not on eGFR.[55] Similar results have been reported with the mTOR inhibitor everolimus.[56] Thus, sirolimus and everolimus are effective in reducing the increase in TKV in patients with ADPKD but have not been shown to slow or improve loss of renal function.

Treatment with the somatostatin analogue octreotide in its standard or long-acting formulation inhibits or slows renal enlargement in patients with ADPKD but has not been shown to improve loss of renal function.[57-59] The efficacy of pravastatin in the treatment of ADPKD has been demonstrated in pediatric patients.[60] At the end of 3 years of treatment with pravastatin, a significant decrease in percent change in htTKV was observed when adjusted for age, sex, and hypertension status, compared with placebo (23 ± 3% vs 31 ± 3%, respectively, *P* = .02). Further studies are required to assess efficacy in adults.

Tolvaptan, a selective vasopressin V2-receptor antagonist approved by Health Canada in 2015, is indicated to slow the progression of kidney enlargement in patients with ADPKD.[9,61] Tolvaptan received approval based on the results of the phase 3, double-blind TEMPO 3:4 trial.[62] In this 3-year trial, 1445 ADPKD patients aged 18 to 50 years with a TKV ≥750 mL and a creatinine clearance of ≥60 mL/min, as estimated by the Cockcroft-Gault formula, were randomized to either tolvaptan (highest of 3 doses based on tolerability) or placebo. The annual rate of change in TKV (primary
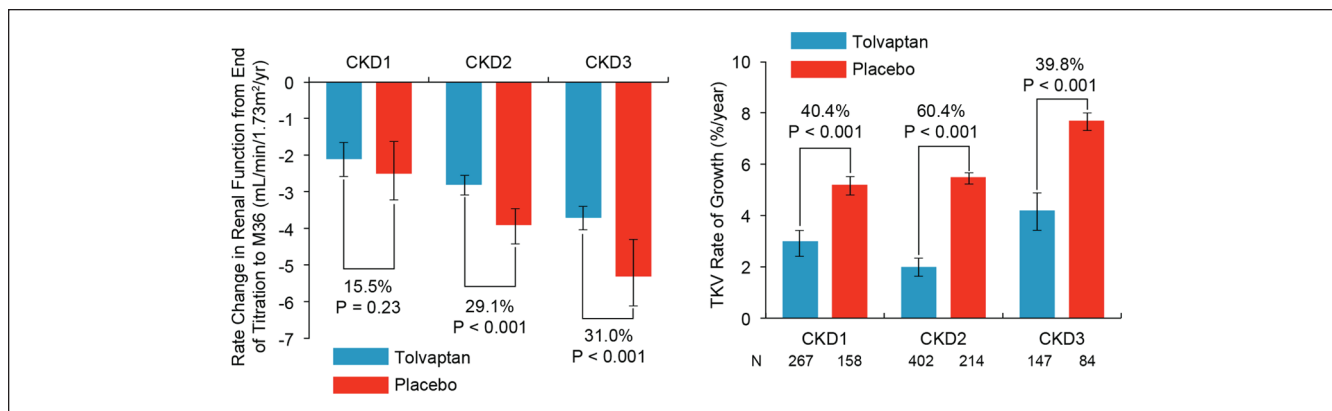
Figure 3. Effect of tolvaptan on eGFR (left panel) and TKV (right panel) by CKD stage in the TEMPO 3:4 trial.
Source. Republished from Torres et al[63] with permission of the American Society of Nephrology; permission conveyed through Copyright Clearance Center, Inc.
Note. eGFR = estimated glomerular filtration rate; TKV = total kidney volume; CKD = chronic kidney disease.

endpoint) was 2.8% with tolvaptan, compared with 5.5% with placebo ($P < .0001$). The rate of growth was reduced by 2.7 percentage points per year with tolvaptan, and the ratio of the geometric means of growth rate was 0.97 ($P < .001$). Loss in kidney function, determined as the reciprocal of the serum creatinine level, from the end of dose escalation to month 36, was significantly reduced with tolvaptan (slope of -2.61 $[\text{mg/mL}]^{-1}$ per year) compared with placebo (slope of -3.81 $[\text{mg/mL}]^{-1}$ per year).[62] The overall treatment effect was an increase of 1.20 $(\text{mg/mL})^{-1}$ per year ($P < .001$). Analysis of the annual estimated GFR slope (which gave results similar to those of the slopes of the reciprocal of the serum creatinine level) showed an estimated GFR slope of -2.72 mL per minute per 1.73 m^2 per year in the tolvaptan group versus -3.70 in the placebo group (treatment effect, an increase of 0.98 mL per minute per 1.73 m^2 per year; 95% confidence interval, 0.60 to 1.36; $P < .001$).[63] Figure 3 shows the effect of tolvaptan on TKV growth and eGFR stratified by CKD stage.[63] Tolvaptan also significantly reduced the occurrence of clinically significant kidney pain—defined as pain necessitating medical leave, pharmacological treatment (opioid or last-resort analgesic agents), or invasive intervention—compared with placebo (hazard ratio [HR] 0.64; $P = .007$).[62]

A post hoc analysis of TEMPO 3:4 clinical data was carried out using Mayo Classification to exclude 10% of the original patient population who had a lesser risk for progression (classes 1A-B and 2), resulting in a patient population enriched in categories 1C-E.[64] A comparison of the enriched population to the original cohort showed that the effect of tolvaptan on TKV and eGFR slopes increased in classes 1C to E: TKV was significantly lower with tolvaptan versus placebo (5.8% vs 2.9%; $P < .001$; 2.8% in TEMPO 3:4) and reduced the decline in the eGFR slope (-3.93 mL/min/1.73 m^2 per year to -2.82 mL/min/1.73 m^2 per year; $P < .001$; -2.78 mL/min/1.73 m^2 per year in TEMPO 3:4), and

significantly reduced the risk of clinical progression (HR 0.84; $P = .0032$).

Cost-effectiveness of Tolvaptan

There have been no published manuscripts addressing the cost-effectiveness of tolvaptan. The Canadian Agency for Drugs and Technologies in Health (CADTH) recently recommended that tolvaptan not be listed on provincial formularies to slow the progression of kidney enlargement in patients with ADPKD.[65] The manufacturer submitted a cost-utility analysis comparing tolvaptan with the standard of care that suggested a base-case incremental cost utility ratio (ICUR) of \$244 402 per quality-adjusted life year (QALY).[66] From their conclusions, it appears that the model is sensitive to varying assumptions around rate of disease progression and lower drug efficacy, which inflate the ICUR considerably. Although we are unable to comment directly on how sensitive the model is to pricing of the drug, it is logical that the model would be exquisitely sensitive to this parameter. If we assume a liberal willingness-to-pay threshold of \$100 000 per QALY to fund new health interventions, further negotiation on pricing may influence decisions to list this medication on provincial formularies moving forward. Therefore, at the time of writing this article, tolvaptan is only available through private insurance, and our recommendations are predicated on patients having private health care insurance that will cover the cost of the drug.

Recommendations

1. We suggest that all patients be referred to a nephrologist for initial assessment to determine what treatment should be initiated, in particular to initiate tolvaptan as soon as possible in patients determined to be appropriate candidates who would benefit from this therapy.

2. We recommend treatment with tolvaptan for patients who fulfill the enrollment criteria of the TEMPO 3:4 study: 18 to 50 years of age, Cockcroft-Gault GFR >60 mL/min, and TKV >750 mL. In the absence of Cockcroft-Gault GFR, CKD-EPI >45 mL/min may be used, and in the absence of TKV, US KL >16.5 cm may be used.

3. We suggest treatment with tolvaptan for patients who, according to the Mayo Classification, are classified as 1D or 1E with eGFR in CKD stage 3 or higher. Treatment with tolvaptan should be considered for patients who are classified as 1C and are younger than 50 years or have other risk factors for rapid progression. We do not recommend tolvaptan for patients classified as 1A or 1B.

4. We suggest that treatment with tolvaptan be stopped when the patient develops ESRD. In the predialysis setting, there are no data to guide when treatment with tolvaptan should be stopped.

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Declaration of Conflicting Interests

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