Tolvaptan for ADPKD: Interpreting the NICE decision

Renal Association Working Group on Tolvaptan in ADPKD

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Conflict of interest (COI) declarations:

AO and JS were nominated clinical experts to the NICE Appraisal Committee on Tolvaptan; AO, TH, RS, JS, GW have received consultancy and lecture fees from Otsuka; TH reports that the PKD Charity received unrestricted donations from Otsuka Pharmaceutical UK Ltd in 2013 and 2014; CA, and RJS report no COIs.

Introduction

In October 2015, NICE recommended that Tolvaptan (JINARC®) therapy should be made available for selected patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) in England and Wales (http://www.nice.org.uk/guidance/TA358). In January 2016, the Scottish Medicines Consortium (SMC) also approved Tolvaptan for use in Scotland (https://www.scottishmedicines.org.uk/SMC_Advice/Advice/1114_15_tolvaptan_Jinarc/tolvaptan_Jinarc).

The recent approval of a targeted therapy Tolvaptan into clinical practice for patients with ADPKD, follows the pivotal TEMPO 3:4 trial which slowed the annual rate of kidney growth (total kidney volume, TKV) and reduced the rate of decline in kidney function (estimated glomerular filtration rate, eGFR) in treated patients (1). Currently Tolvaptan is being used in Canada, Japan, Korea and Switzerland for ADPKD and has been approved for use in Europe by the European Medicines Agency (EMA).

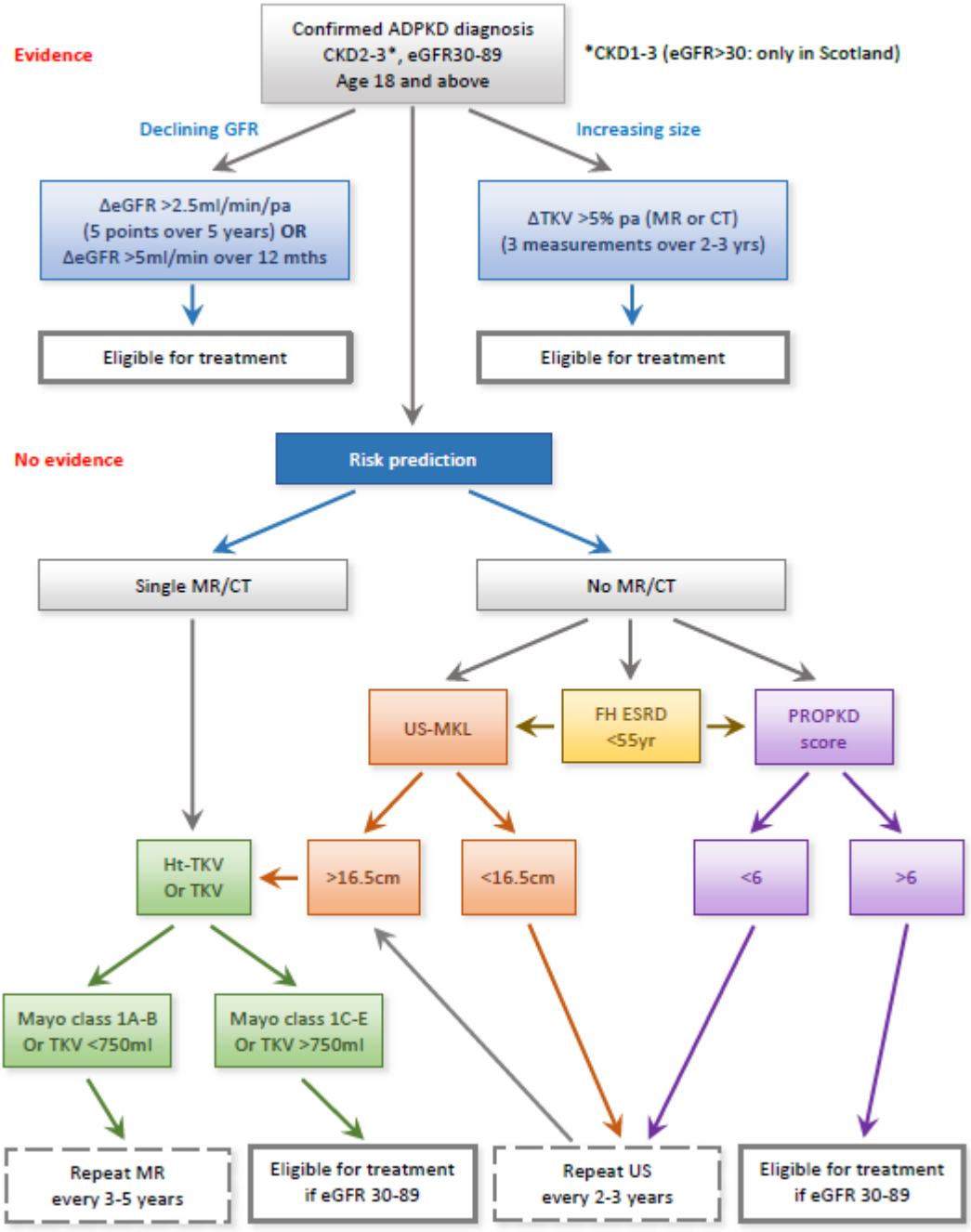
NICE concluded that patients with ADPKD who may be eligible for treatment must have Stage 2 or 3 chronic kidney disease (CKD) and 'evidence of rapidly progressing disease'. SMC have approved its use for Stages 1-3 CKD, similar to that recommended by the EMA. The definition and evaluation of 'rapid progressive disease' are however not established and have not been stipulated by NICE, SMC or the EMA.

Based on an estimated prevalence of under 1 in 2500, NICE estimated that 16,289 patients suffer from ADPKD of which 2,285 will be eligible for treatment in England. This equates to 4 per 100,000 population. NICE predicts a gradual but increasing uptake of treatment over the next few years.

The pharmaceutical company, Otsuka, have reached an agreement with the Department of Health to provide a discounted price under a patient access scheme, thus available only through hospital pharmacies. Apart from the cost of the therapy, there will be additional health care costs arising from the initial evaluation of eligible patients, titration and monitoring including mandatory monthly blood tests for liver function. It is expected that prescribing and monitoring will be carried out by nephrologists with a specialist interest in ADPKD in secondary or tertiary care, with the additional costs to be met by local Clinical Commissioning Groups. NICE have issued a costing template which includes a recommended enhanced tariff.

The Renal Association has commissioned a working group to develop practical guidance to facilitate the identification of eligible patients with ADPKD for consideration of treatment in an equitable and evidence-based manner.

A simple flow chart for assessing ADPKD patients for eligibility for treatment with Tolvaptan



TKV = Total Kidney Volume
Ht = Height-adjusted
MKL = Mean Kidney Length

RAWG on Tolvaptan in ADPKD 2016

Summary of recommendations

1. Evaluation of who to treat

1.1 At initiation of treatment, patients should be aged over 18 years of age

It is recommended that patients considered for treatment should be over 18 years of age. The inclusion criteria for the pivotal TEMPO 3:4 trial was within the age range of 18-50 years (1) and was confirmed in published recommendations by the ERA-EDTA (2). Results of the REPRISE study (https://clinicaltrials.gov/ct2/show/NCT02160145) which is currently investigating patients up to 55 years with eGFR 25-65ml/min/1.73m^2 and patients up to 65 years if eGFR is between 25-44ml/min/1.73m^2 will provide clearer evidence for the use of tolvaptan within a broader age and eGFR range. The trial data does not support its use under the age of 18 years.

The median age of end-stage renal failure (ESRF) for ADPKD patients requiring renal replacement therapy (RRT) in England and Wales is currently 55 years (3). Thus patients older than 50 years with stage 3 CKD are likely to reach ESRF at an older age (>55 years) and therefore fall into a better prognostic group. Symptoms such as chronic kidney pain associated with renal enlargement may benefit from treatment.

1.2 Eligible patients should have:

a) an established diagnosis of ADPKD either by genotype, age related modified Pei-Ravine imaging criteria (Appendix 1) (4), or if no family history, 10 cysts per kidney (using any imaging method) and exclusion of other forms of cystic kidney disease (5);

It is acknowledged that relatively few patients in the UK will have undergone genotyping to establish a diagnosis since this is not standard practice. However if this result is available, it will be informative for risk prediction (see 1.4).

AND

b) stage 2-3 CKD (30-89ml/min) measured by eGFR (using CKD-EPI) confirmed on 2 blood tests (over 72 hours apart) and without intercurrent illness (which may be associated with a reversible decline in kidney function); In Scotland, stage 1-3 CKD (>30ml/min) measured by the same criteria detailed.

The NICE guidance excluded patients with stage 1 CKD (eGFR ≥ 90ml/min/1.73m^2). This decision was based on a less favourable cost-benefit analysis of Tolvaptan (JINARC®) in patients with stage 1 CKD who showed a non-significant eGFR slope despite a significant reduction in TKV increase (6). It should be noted that changes in TKV are now accepted as earlier markers of disease progression (prior to changes in GFR) and baseline TKV has been accepted as a prognostic disease biomarker (in the context of eGFR and age) for clinical trial enrichment by the EMA (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500196569.pdf) and in the form of draft guidance by the Food and Drug Administration (FDA) (https://c-path.org/programs/pkd/regulatory-successes/) (7, 8). Changes in GFR tend to occur later in the natural history of disease due to initial compensatory glomerular hyperfiltration; hence eGFR may not be sufficiently sensitive to measure changes in the early course of disease ie stage 1 CKD (9, 10).

In hospitals where eGFR reporting does not differentiate between stages 1 and 2 (for example eGFR> 60ml/min/1.73m^2) CKD, it is recommended that the CKD Epidemiology Collaboration (CKD-EPI) equation (Appendix 2 or http://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/adults-si-unit-ckd-epi/Pages/default.aspx) be used to calculate an eGFR, based on a serum creatinine measured using a standardised method of laboratory IDMS (isotope-dilution mass spectrometry) correction.

AND

c) evidence of rapidly progressing disease (see 1.3).

1.3 Evidence of rapid disease progression

ADPKD is typically a slowly progressive disease with the development of ESRF occurring over many decades (10). There is however marked intra and interfamilial heterogeneity in the rate of progression and several risk prediction models have been developed to aid individual risk assessment (11-13) (see 1.4). In terms of current evidence and the most widely available measure in clinical practice, we propose that historical changes in eGFR over time provide the most robust *evidence* of disease progression.

Evidence of rapid disease progression in ADPKD can be defined as:

a) a sustained decline in eGFR of ≥2.5ml/min/1.73m^2 per year (with at least 5 measurements over 5 years);

OR

b) a sustained decline in eGFR of >5ml/min/1.73m^2 per year over 12 months (at least 2 measurements 6 months apart, with each measurement confirmed on 2 blood tests (over 72 hours apart)) in the absence of other confounding factors (for example nephropathy, medication, contrast nephropathy, nephrectomy).

These changes in eGFR are derived from a retrospective evaluation of 590 patients from the Mayo clinic and 177 patients from the CRISP study (11) and the Kidney Disease Improving Global Outcomes CKD guideline (14). If there is uncertainty regarding variability in eGFR measurements, this could be monitored over the next 6-12 months before a decision is made.

OR

c) an increase in total kidney volume (TKV) (≥5% per year) measured in at least 3 scans (CT or MRI) at least 6 months apart identifies rapid disease progression.

If historical eGFR results are not available, historical changes in TKV represent an alternative biomarker of disease progression (15). Nonetheless sequential (at least three) imaging scans (computed tomography (CT) or magnetic resonance imaging (MRI), 6-12 months apart) are likely to be available in only a few patients. In the CRISP cohort as well as the placebo groups of TEMPO3:4 and HALT A with early stage disease (eGFR>60), changes in TKV averaged 5.5% (1, 16, 17).

There is evidence to confirm a change in TKV can be reliably detected after 6 months (18) using MRI. Although ultrasound is cheaper and more widely accessible, it is insufficiently reliable, having inferior accuracy and is insufficiently reproducible (19).

1.4 Risk of rapid disease progression

Patients who lack evidence, as detailed above, to define rapid disease progression should be assessed for *risk* of disease progression and future eligibility for treatment. Patients not considered to have rapid disease progression should be re-evaluated periodically, at least every 3-5 years or earlier if there is a change in clinical parameters.

The following recommendations are supported by the best currently available evidence using risk prediction models of disease progression. The modality chosen to facilitate risk determination and prediction of rapid disease progression will depend on available information and may include imaging, genotype and clinical features including family history.

a) Patients who have had a single CT or MRI scan in which height adjusted TKV can be measured can be classified according to the Mayo Imaging classification. Patients who are defined as Class 1C-1E are at risk of rapid disease progression.

The Mayo Imaging classification (http://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754?_ga=1.42938278.2046346149.1449053926) is a research tool which is rapidly gaining acceptance as a sensitive prognostic marker in patients with "typical ADPKD" to predict the risk of disease progression. This model utilises a single measured or estimated TKV (based on MR or CT) adjusted for age and height (Appendix 3). The definition of 'typical ADPKD' (Class 1), present in the majority of patients, is the presence of bilateral, diffuse renal cysts which replace kidney tissue and contribute consistently to TKV (11). Class 1A-B and Class 2 ('atypical') patients are considered to have low risk of progression. It should be noted that a proportion of younger patients may move to a higher subclass (for example 1B to 1C) over time and therefore periodic reassessment by MR imaging eg every 3-5 years is advised (11).

If height measurements are not available, a single MRI-TKV of ≥750ml in the age range of could be used as a predictor of rapid disease progression since this was an inclusion criterion for patients in the TEMPO3:4 trial within the age range of 18-50 years and an eGFR greater than 60ml/min/1.73m^2 (1).

b) Patients in whom a mean kidney length has been measured on renal ultrasound should ideally be further evaluated with an MRI or CT to measure height adjusted TKV.

Based on the CRISP cohort, mean kidney length on ultrasound (>16.5cm) has been proposed as a sensitive prognostic marker in patients aged 18-45 years to predict future disease progression (19). However this has been disputed (20) and moreover is not age or height adjusted. Although ultrasound is cheaper than MRI and more widely available, we recommend that a more accurate measure of TKV (by MRI) should ideally be obtained as part of the evaluation of patients for Tolvaptan therapy.

c) Patients with a *PKD1* truncating mutation and early onset of symptoms (by 35 years of age) including hypertension or frank haematuria or cyst infection have an increased risk of rapid disease progression.

A large cohort study has confirmed the prognostic information of genotype, with a 20 year difference in age of onset of ESRF being reported between *PKD1* truncating and *PKD2* mutations (12). In the same cohort, a combined genetic and clinical score – the PROPKD score (Appendix 4) was developed to stratify progression to ESRF (13). A PROPKD score greater than 6 was associated with a significantly higher risk of disease progression with a positive predictive value of 90.9% for risk of progression to ESRF before the age of 60 years (13).

d) Patients with a family history of end stage renal failure (ESRF) in a family member aged younger than 55 years is predictive of rapid disease progression. We recommend a detailed family history is obtained and an MRI is arranged to enable accurate assessment of height adjusted TKV.

Although intra-familial variability occurs in ADPKD, age of ESRF in a family member could help predict risk of disease progression and indirectly the causal mutation (21). Patients who had a history of at least one family member who developed ESRF under 55 years of age had a positive predictive value (PPV) of 100% (sensitivity 72%) of having a *PKD1* mutation. In comparison, patients who had at least one affected family member who did not require renal replacement therapy until over 70 years was highly predictive of a *PKD2* mutation (PPV 100%, sensitivity 74%) (21).

e) Patients with stage 1 CKD (eGFR≥90ml/min/1.73m^2) – ongoing monitoring for risk of progression, except in Scotland where the SMC have approved the use of Tolvaptan in this group.

This group of patients are currently excluded from receiving Tolvaptan therapy in England and Wales (but not in Scotland) by the NICE decision but will include patients at risk of rapid disease progression. We therefore recommend that they should undergo risk evaluation at this stage by detailed review of clinical symptoms, family history and age at ESRF. Renal imaging should be undertaken with a minimum of kidney lengths measured on ultrasound recorded and ideally, height adjusted TKV determined by MRI, before their eGFR falls below 90ml/min/1.73m^2. The frequency of future re-evaluation for eligibility for treatment will depend on the individual and the presence or absence of other known risk factors (as detailed above) but is normally expected to be yearly.

2. Monitoring Tolvaptan therapy

2.1 An acute decline in eGFR may occur following initiation of Tolvaptan therapy (22, 23). This acute decline varies depending on baseline renal function and is reversible on cessation of treatment. This is comparable to the frequent acute decline in eGFR observed on starting renin angiotensin aldosterone system inhibitors. It is recommended that Tolvaptan therapy is discontinued as patients approach ESRF and when eGFR is less than 15ml/min/1.73m^2 (Stage 5 CKD).

2.2 Mandatory monitoring of liver function tests is required monthly for the first 18 months and then 3 monthly subsequently if Tolvaptan therapy continues. In TEMPO3/4, 4.9% of patients on Tolvaptan had a 2.5 fold elevation in ALT with 2 cases fulfilling Hy's Law (predictive of liver failure) (1). All resolved with discontinuation of treatment.

2.3 Recommendations of information to discuss with patients prior to prescribing Tolvaptan (JINARC®) and a checklist of contraindications (pregnancy, breastfeeding) and precautions associated with comorbidities have been prepared by Otsuka (Appendix 5)

3. Additional Recommendations when evaluating or managing patients on Tolvaptan

3.1 We recommend that all patients should be offered initial assessment and follow-up in dedicated renal clinics based in secondary or tertiary centres, under the supervision of nephrologists with a specialist interest in the condition ideally with multidisciplinary input (10).

3.2 We recommend that all patients commenced on treatment with Tolvaptan should be registered and monitored though the ADPKD RaDaR Registry under the overall sponsorship of the Renal Association.

3.3 We recommend that a Working Group be established to monitor uptake and outcomes nationally, ideally in coordination with the other nations.

3.4 We recommend that discussions with radiology societies be initiated to agree national standards for reporting kidney lengths and to establish national protocols for measuring kidney volumes.

3.5 We recommend that a national review be initiated by the Renal Association of what should constitute standard care for patients and to agree a new patient pathway.

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Appendix 1 Unified ultrasound age related modified Pei-Ravine imaging criteria (4)

Age (yrs)	Diagnostic crieria	PPV	Sensitivity
15-29	≥3 cysts (total)	100%	81.7%
30-39	≥3 cysts (total)	100%	95.5%
40-59	≥2 cysts (each kidney)	100%	90%
>60	≥4 cysts (each kidney)	100%	100%

These diagnostic criteria are only valid in patients with a positive family history and are specific for ultrasound imaging only.

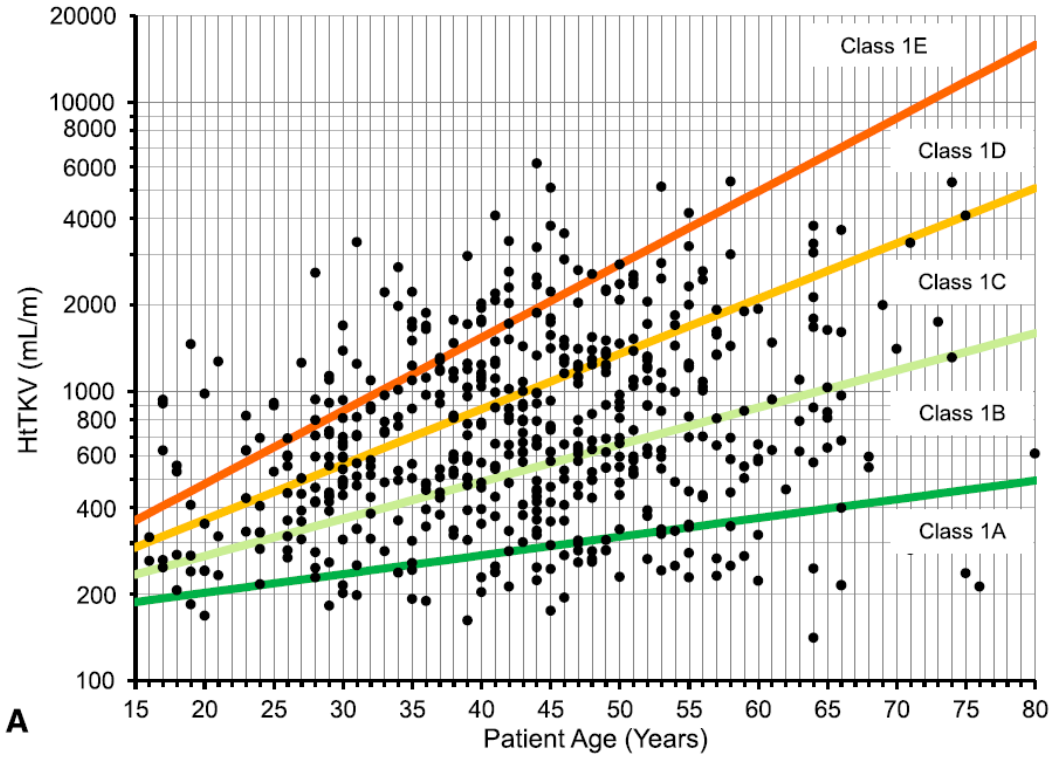
Appendix 2 The CKD-EPI Equation

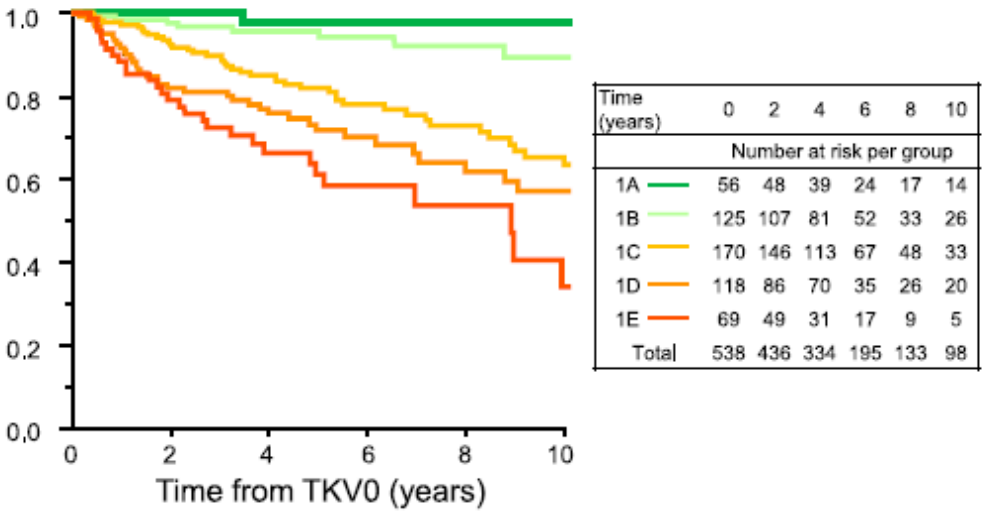
The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation estimates glomerular filtration rate (GFR) from serum creatinine (μmol/l), age, gender and race of adults ≥ 18 years (24). This equation is recommended for use in current Renal Association guidelines for the detection and monitoring of CKD. This table is modified from (24).

Race	Gender	Serum Creatinine, S_{cr} μmol/L	Equation (age in years)
Black	Female	≤ 61.9	$GFR = 166 \times (S_{cr}/61.9)^{-0.329} \times (0.993)^{Age}$
Black	Female	> 61.9	$GFR = 166 \times (S_{cr}/61.9)^{-1.209} \times (0.993)^{Age}$
Black	Male	≤ 79.6	$GFR = 163 \times (S_{cr}/79.6)^{-0.411} \times (0.993)^{Age}$
Black	Male	> 79.6	$GFR = 163 \times (S_{cr}/79.6)^{-1.209} \times (0.993)^{Age}$
White or other	Female	≤ 61.9	$GFR = 144 \times (S_{cr}/61.9)^{-0.329} \times (0.993)^{Age}$
White or other	Female	> 61.9	$GFR = 144 \times (S_{cr}/61.9)^{-1.209} \times (0.993)^{Age}$
White or other	Male	≤ 79.6	$GFR = 141 \times (S_{cr}/79.6)^{-0.411} \times (0.993)^{Age}$
White or other	Male	> 79.6	$GFR = 141 \times (S_{cr}/79.6)^{-1.209} \times (0.993)^{Age}$

Appendix 3 Mayo Imaging Classification of risk of disease progression in ADPKD

Imaging classification of patients with typical (Class 1) ADPKD based on height adjusted TKV measured on MRI [from Figure 3 (11)]. The Kaplan-Meier survival plot of renal survival at follow up following the MRI measurement of TKV in the Mayo patients shows the increased risk of ESRF in patients with Class 1C-1E.





Time (years)	0	2	4	6	8	10
	Number at risk per group					
1A	56	48	39	24	17	14
1B	125	107	81	52	33	26
1C	170	146	113	67	48	33
1D	118	86	70	35	26	20
1E	69	49	31	17	9	5
Total	538	436	334	195	133	98

Appendix 4 PROPKD Score

The points allocated to each variable in the PROPKD score was determined using hazard ratios. A PROPKD score of greater than 6 was associated with a significantly high risk of decline in renal function (mean rate of eGFR decline 4.4ml/min/year) (13). Table modified from (13). A urological event is defined as either frank haematuria, cyst infection or flank pain related to cysts.

Variable	Points for PROPKD Score
Sex	
Female	0
Male	1
Hypertension before age 35 yr	
No	0
Yes	2
≥1 urologic event before age 35 yr	
No	0
Yes	2
Mutation	
PKD2	0
PKD1 nontruncating	2
PKD1 truncating	4

Appendix 5 Checklist of contraindications and precautions associated with comorbidities prior to prescribing (Tolvaptan) JINARC (Ref/version: OPUK/0315/JIN/1091b June 2015)

JINARC® ▼ (tolvaptan) prescribing checklist for treatment initiation

Patient name		Patient hospital number	

JINARC (tolvaptan) is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease. The following checklists are provided as items that can help you before you initiate patients on JINARC (Section A) and to assist you with assessing patients for ongoing treatment with JINARC (Section B). It may be useful to use these checklists in patient records or notes to assist in the documentation of prescribing decisions. For full information on JINARC please consult the Summary of Product Characteristics. If you require further information on JINARC please contact Otsuka UK Medical Information via medinfo@otsuka.co.uk or call **0808 168 6726**.

Section A: Checklist for patient assessment prior to initiation of JINARC treatment

CONTRAINDICATIONS – if any of the following apply to the patient then they should **not** be treated with JINARC	Yes	No
Elevated liver enzymes as follows: • ALT or AST >8 x upper limit of normal (ULN) • ALT or AST >5 x ULN for more than 2 weeks • ALT or AST >3 x ULN and BT >2 x ULN or international normalized ratio (INR) >1.5 and/or signs or symptoms of liver injury (fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice)		
Hypersensitivity to the active substance or any of its excipients (e.g. lactose or galactose intolerance)		
Volume depletion		
Hypernatraemia		
Inability to perceive or respond to thirst		
Pregnancy or breastfeeding		
PRECAUTIONARY CONDITIONS – if any of the following apply to the patient, JINARC may be prescribed with caution along with appropriate monitoring	Yes	No
Raised liver enzymes, AST and/or ALT stabilised at no greater than 3 x ULN **In case of abnormal baseline levels below the limits for permanent discontinuation, treatment can only be initiated if the potential benefits of treatment outweigh the potential risks, and liver function testing must continue at increased time frequency. The advice of a hepatologist is recommended.**		
Severe hepatic impairment (Child-Pugh class C)		
Cirrhosis (if benefits outweigh the risks)		
Limited access to water		
Dehydration		
Partial obstruction of urinary outflow (e.g. prostatic hypertrophy)		
Fluid and electrolyte imbalance		
Serum sodium abnormalities		
Anaphylaxis		
Lactose and galactose intolerance		
Diabetes mellitus		
Elevated uric acid concentration		
Use of medicines likely to interact with JINARC such as CYP3A inhibitors (e.g. ketoconazole), CYP3A inducers (e.g. rifampicin), CYP3A substrates (warfarin/amiodarone), digoxin, drugs increasing serum sodium concentration and vasopressin analogues. JINARC is to be administered in daily doses of 15 mg or 30 mg in patients taking drugs that are moderate or strong CYP3A inhibitors, as concomitant use of these drugs increases JINARC exposure.		

PRESCRIBING DECISION (initiation)

I intend to initiate treatment with JINARC at the following dose (enter dosing):

Clinician name		Date	

If you have decided to prescribe JINARC the patient should be informed of the following points:
• There is a need for monthly blood tests for liver function during the first 18 months of therapy
• The patient needs to be vigilant for signs and symptoms of hepatic injury
• The patient needs to drink adequate fluids ahead of thirst and to drink 1-2 glasses of fluid before bedtime
• If the patient is a female of childbearing potential, she will need to use adequate contraception and to report pregnancy if it occurs
• You will provide them with a patient/carer education brochure and patient alert card

JINARC® ▼ (tolvaptan) prescribing checklist for patient monitoring

Patient name		Patient hospital number	

Section B: Checklist for patient assessment for ongoing eligibility for JINARC treatment
It is suggested that the following checklist is completed monthly for JINARC patients who are being treated for ADPKD for the first 18 months, and then every 3 months thereafter.

All adverse events should be reported to the MHRA and Otsuka UK as described in the box below.

HEPATIC INJURY	Yes	No
Is the patient showing any signs or symptoms of liver injury? (fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) **If the answer is Yes, treatment with JINARC should be interrupted, the cause investigated and the occurrence reported using the reporting mechanism below**		

Liver function test results	Recommended action
ALT or AST abnormal	**Interrupt JINARC treatment and investigate the cause of the raised liver enzyme(s) including repeat tests as soon as possible (ideally within 48–72 hours). Report decision to Otsuka UK using the reporting mechanism below. Continue monitoring.**
Liver function results stabilise If ALT and AST levels remain below 3 x ULN	**Restart JINARC treatment at same or lower dose with frequent monitoring and report decision to Otsuka UK using the reporting mechanism below.**
ALT or AST >8 x ULN	**Permanently discontinue and report decision to Otsuka UK using the reporting mechanism below.**
ALT or AST >5 x ULN for more than 2 weeks	
ALT or AST >3 x ULN and (BT >2 x ULN or International Normalized Ratio (INR) >1.5)	

PRESCRIBING DECISION (ongoing treatment) Titrate dose upward, if tolerated, with at least weekly intervals between up-titrations.	Tick box
Based on tolerability and other tests performed on this patient (select one option below)	
• **I intend to continue JINARC at the following dose (enter dosing)**	
• **I have decided to interrupt treatment with JINARC**	
• **I have decided to permanently discontinue treatment with JINARC**	

Clinician name		Date	

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Otsuka UK at opuksafety@otsuka.co.uk or call 07795426048.

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