An update on the use of tolvaptan for autosomal dominant polycystic kidney disease: consensus statement on behalf of the ERA Working Group on Inherited Kidney Disorders, the European Rare Kidney Disease Reference Network and Polycystic Kidney Disease International

Roman-Ulrich Müller 1,2, A. Lianne Messchendorp 3, Henrik Birn 4,5, Giovambattista Capasso 6,7, Emilie CorneC-Le Gall 8, Olivier Devuyst 9,10, Albertien van Eerde 11, Patrick Guirchoun 12, Tess Harris 13, Ewout J. Hoorn 14, Nine V.A.M. Knoers 15, Uwe Korst 16, Djalila Mekahli 17,18, Yannick Le Meur 19, Tom Nijenhuis 20, Albert C.M. Ong 21,22, John A. Sayer 23, Franz Schaefer 24, Aude Servais 25, Vladimir Tesar 26, Roser Torra 27,28, Stephen B. Walsh 29 and Ron T. Gansevoort 3

1Department II of Internal Medicine and Center for Molecular Medicine, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany, 2CECAD, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany, 3Department of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, 4Department of Renal Medicine, Aarhus University Hospital, Aarhus, Denmark, 5Department of Clinical Medicine and Biomedicine, Aarhus University, Aarhus, Denmark, 6Department of Translational Medical Sciences, Vanvitelli University, Naples, Italy, 7Biogem Institute for Molecular Biology and Genetics, Ariano Irpino, Italy, 8University Brest, Inserm, UMR 1078, GGB, CHU Brest, Brest, France, 9Institute of Physiology, University of Zurich, Zurich, Switzerland, 10Division of Nephrology, UCL Medical School, Brussels, Belgium, 11Department of Genetics, University Medical Center Utrecht, Utrecht, The Netherlands, 12Association PolyKystose France (PKD France), Saclay, France, 13PKD International, Geneva, Switzerland, 14Department of Internal Medicine, Division of Nephrology and Transplantation, Erasmus Medical Center, University Medical Center Rotterdam, Rotterdam, The Netherlands, 15Department Genetics, University Medical Centre Groningen, Groningen, The Netherlands, 16PKD Familiäre Zystennieren e.V., Bensheim, Germany, 17PKD Research Group, Laboratory of Pediatrics, Department of Development and Regeneration, KU Leuven, Leuven, Belgium, 18Department of Pediatric Nephrology and Organ Transplantation, University Hospitals Leuven, Leuven, Belgium, 19Department of Nephrology, Hémofiltration and Renal Transplantation, CHU and University of Brest, Brest, France, 20Department of Nephrology, Radboud Institute for Molecular Life Sciences, Radboudumc Center of Expertise for Rare Kidney Disorders, Radboud University Medical Center, Nijmegen, The Netherlands, 21Academic Nephrology Unit, Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield Medical School, Sheffield, UK, 22Sheffield Kidney Institute, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK, 23Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle Upon Tyne, UK, 24Division of Pediatric Nephrology, Center for Pediatrics and Adolescent Medicine, Heidelberg University Hospital, Heidelberg, Germany, 25Nephrology and Transplantation Department, Necker University Hospital, APHP, Paris, France, 26Department of Nephrology, 1st Faculty of Medicine, General University Hospital, Prague, Czech Republic, 27Inherited Kidney Diseases Nephrology Department, Fundació Puigvert Instituto de Investigaciones Biomédicas Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain, 28REDINREN, Barcelona, Spain and 29Department of Renal Medicine, University College London, London, UK

Correspondence to: Roman-Ulrich Müller; E-mail: roman-ulrich.mueller@uk-koeln.de

Watch the video of this contribution at https://academic.oup.com/ndt/pages/author_videos

ABSTRACT

Approval of the vasopressin V2 receptor antagonist tolvaptan—based on the landmark TEMPO 3:4 trial—marked a transformation in the management of autosomal dominant polycystic kidney disease...
polycystic kidney disease (ADPKD). This development has advanced patient care in ADPKD from general measures to prevent progression of chronic kidney disease to targeting disease-specific mechanisms. However, considering the long-term nature of this treatment, as well as potential side effects, evidence-based approaches to initiate treatment only in patients with rapidly progressing disease are crucial. In 2016, the position statement issued by the European Renal Association (ERA) was the first society-based recommendation on the use of tolvaptan and has served as a widely used decision-making tool for nephrologists. Since then, considerable practical experience regarding the use of tolvaptan in ADPKD has accumulated. More importantly, additional data from REPRISE, a second randomized clinical trial (RCT) examining the use of tolvaptan in later-stage disease, have added important evidence to the field, as have post hoc studies of these RCTs. To incorporate this new knowledge, we provide an updated algorithm to guide patient selection for treatment with tolvaptan and add practical advice for its use.

**Keywords:** ADPKD, polycystic kidney disease, position statement, tolvaptan, vasopressin V2 receptor antagonist

**INTRODUCTION**

In the past 5 years the vasopressin V2 receptor (V2R) antagonist tolvaptan has become an important treatment option in the management of patients with autosomal dominant polycystic kidney disease (ADPKD) [1–3]. Two randomized clinical trials (RCTs) have shown a beneficial effect of tolvaptan regarding the ADPKD-associated estimated glomerular filtration rate (eGFR) decline in patients with rapid disease progression. Considering the potential drawbacks—including its side effects and cost—associated with this treatment, the selection of patients who are most likely to show a positive benefit-risk ratio regarding this therapy—i.e. individuals showing rapid disease progression—is important and required.

Tolvaptan is a V2R antagonist that blocks vasopressin signaling, a key driver of cyst growth in ADPKD due to the resulting intracellular increase in cyclic adenosine monophosphate [4]. Polyuria is the logical consequence of V2R blockade and as such is expected to occur in every patient on treatment. Nonetheless, adherence to tolvaptan appears to be well-feasible in the majority of patients [5–7]. Importantly, only a subset of ADPKD patients suffers from rapid disease progression and will reach early kidney failure due to ADPKD, resulting in the need for guidance regarding patient selection. Following the Working Group on Inherited Kidney Disease (WGIKD) 2016 position statement [8], several treatment decision algorithms have been published for different countries [9] in order to identify ADPKD patients with rapid disease progression. Most of these recommendations mainly rely on predictors of rapid disease progression, with a central role for total kidney volume (TKV) [2]. In contrast, the original WGIKD position statement put the most weight on measured rapid progression based on the historical decline in eGFR. This resulted in a more conservative algorithm that primarily recommended treatment for patients showing rapid loss of kidney function in the past—the only real evidence of actual rapid progression. However, since cyst formation precedes the decline in eGFR, ADPKD may be progressing rapidly in young patients despite a normal eGFR, and such patients should not be excluded by a very restrictive algorithm. Furthermore, pivotal information obtained from the REPRISE (Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD) trial [10] in 2018 has allowed for an extension of eligibility criteria to older patients and later-stage ADPKD [11]. Consequently, an update of the position statement based on these data as well as accumulating real-world experience with tolvaptan is timely and required. This update was developed by a panel of experts and endorsed by the boards of the European Renal Association (ERA) WGIKD and the European Rare Kidney disease reference NETwork (ERKNet).

All recommendations are based on the following simple notion: patients expected to reach kidney failure due to ADPKD before the average age at which ADPKD leads to the need for renal replacement therapy (RRT) are by definition subjects with rapid disease progression and thus candidates for this therapy. The following sections present and rationalize the updated recommendations for the clinical parameters allowing the actual selection of patients who should be offered treatment with tolvaptan. Specific changes in the recommendations compared with the original position statement are highlighted in Supplementary data, Table S1.

**An update on the efficacy of tolvaptan in ADPKD**

While TKV increase is a surrogate marker of disease progression in ADPKD, the actual aim of medical treatment is to slow the loss of kidney function in order to delay the onset of kidney failure. In the TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes) 3:4 study, tolvaptan reduced eGFR decline by ~1 mL/min/1.73 m²/year (from −3.70 to −2.72 mL/min/1.73 m²) in early-stage ADPKD (18–50 years of age, estimated creatinine clearance >60 mL/min) [12] over a period of 3 years. The effect size of tolvaptan is comparable to other agents considered the gold standard for prevention of kidney function loss in CKD, e.g. renin-angiotensin-aldosterone system blockade in diabetic kidney disease [13–15]. In 2017, data from the open-label extension study TEMPO 4:4 showed that the eGFR benefit accumulated in TEMPO 3:4 was maintained over 2 additional years, while the effect on TKV appeared not to be sustained [16]. However, the interpretation of these findings was limited by the non-randomized design, resulting in imbalances in baseline characteristics, including gender. TKV and eGFR, which may at least explain in part the loss of sustained effect on TKV. Later, the randomized controlled REPRISE trial added substantial evidence to the use of tolvaptan in ADPKD [10]. REPRISE examined tolvaptan in later-stage ADPKD (eGFR 25–65 mL/min/1.73 m² in subjects 18–55 years of age and eGFR 25–45 mL/min/1.73 m² in subjects 55–65 years of age). Here, tolvaptan slowed the decrease in eGFR by 1.27 mL/min/1.73 m²/year (from −3.61 to −2.34 mL/min/1.73 m²)—an
An update on the use of tolvaptan for ADPKD

The TEMPO 3:4 trial—the basis for the approval of tolvaptan for ADPKD by the European Medicines Agency (EMA)—enrolled patients 18–50 years of age [12]. Therefore, most previous recommendations limited the use of tolvaptan to this age group. The succeeding REPRISE trial included individuals in later-stage ADPKD up to the age of 65 years [10] showing a similar and significant reduction in eGFR decline. However, a subgroup analysis suggested that this was not the case for patients >55 years of age, implying that tolvaptan should only be offered up to this age. Nonetheless, it is important to recognize that the group of patients in REPRISE who were 56–65 years of age comprised only 190 individuals in total (<15% of the study population). Also, despite the fact that only individuals with an eGFR <45 mL/min/1.73 m² were enrolled in this age group, these patients showed a slower decline of kidney function—both on placebo (−2.34 mL/min/1.73 m²/year) and on tolvaptan (−2.54 mL/min/1.73 m²/year)—compared with participants <55 years of age. Thus this group of patients would usually not be considered rapidly progressing. This finding highlighted two key aspects when evaluating patients for tolvaptan. First, only patients with rapid disease progression should be treated. Second, when applying an algorithm similar to the inclusion criteria in the REPRISE study (solely based on age-adjusted eGFR cut-offs), patients >55 years of age with an eGFR ≥25 mL/min/1.73 m², are likely to have slowly progressing disease. Most patients with rapidly progressing disease will have reached kidney failure before the age of 55 years, given that the average age of kidney failure requiring RRT is 58 years for patients with ADPKD [21].

When current eGFR loss points towards rapid disease progression in elderly subjects, it is extremely important to identify whether this decline is indeed due to ADPKD or rather the consequence of other causes. Notably, in young patients, reduced kidney function is very likely to be the result of ADPKD itself and to reflect rapid disease progression (e.g. in a 30-year-old with an eGFR of 50 mL/min/1.73 m² and no comorbidities). With increasing age, additional comorbidities—such as vascular/hypertensive nephropathy or diabetes mellitus—become more important and may contribute to or govern the eGFR loss recorded. It is not expected that V2R blockers will have a beneficial impact on these comorbidities. Based on this, the proposed new algorithm recommends evaluation of patients up to the age of 55 years and emphasizes the need to consider other, non-ADPKD-related causes for eGFR decline in elderly subjects. Since the indication by the EMA does not specify an upper age limit for treatment initiation, such a limit cannot be definitive and—in the context of individualized decisions (e.g. in a highly motivated 56-year-old patient)—we do not necessarily exclude treatment with tolvaptan based on this age limit.

Taken together, eGFR indexed for age should not be higher than expected in individuals assessed for tolvaptan (see recommendation below). This entry criterion remains very important to exclude individuals who clearly do not have rapid disease progression at an early stage in the decision-making process. In retrospect, the thresholds defined in the original WGIKD algorithm were rather conservative, potentially excluding patients who could have been eligible for therapy [9, 22]. Based on the additional evidence and increased experience in real-life settings, these limits are revised in the updated version to allow more patients to benefit from treatment. The alleviation of age-adjusted eGFR cut-offs comes at the risk of including more patients with slow disease progression. However, this aspect is addressed by the additional steps in the algorithm regarding, for example, past eGFR loss (see section ‘Evidence of rapid disease progression’ below). Taken together, age-adjusted eGFR cut-offs should exclude individuals with a clearly high eGFR for their age, include those with a clearly low age-adjusted eGFR and allow for further assessment using additional criteria for all others.

Based on the REPRISE trial, we suggest that the lower eGFR threshold for treatment initiation should be lowered to 25 mL/min/1.73 m², as subgroup analyses show efficacy also at this late stage. As there are no data from RCTs regarding patients with an eGFR <25 mL/min/1.73 m², our algorithm adopts this lower eGFR limit. Even if the effect of tolvaptan can be extrapolated to patients with an eGFR <25 mL/min/1.73 m², the potential delay in the time of RRT as a consequence of treatment would only be a few months to 1 year [2].
Extrapolations from the results of the (A) TEMPO 3:4 and (B) REPRISE trials allow estimations of the potential benefit of tolvaptan treatment in delaying the need for RRT (adapted from Chebib et al. [2]).

**Recommendation 1.1:** We suggest that treatment with tolvaptan can be initiated in adult ADPKD patients ≤55 years of age with an eGFR ≥25 mL/min/1.73 m² who have demonstrated or who are likely to have rapidly progressive disease based on a hierarchical decision algorithm (see Recommendation 6).

**Recommendation 1.2:** We recommend not to start tolvaptan in patients with an eGFR indexed for age suggesting slowly progressive disease (<40 years, no eGFR limit; 40–44 years, ≥90 mL/min/1.73 m²; 45–49 years, ≥75 mL/min/1.73 m²; 50–55 years, ≥60 mL/min/1.73 m²).

At what ages should tolvaptan be started? When should it be stopped?

To date, no data from RCTs regarding the efficacy and safety of tolvaptan in children and adolescents are available and the drug has not been approved for this age group. The results of an ongoing pediatric study are expected soon but have not been published to date [23]. Consequently, we currently do not recommend initiating tolvaptan before the age of 18 years. The optimal time point for initiating tolvaptan in an adult patient with ADPKD has not been fully established. The fact that REPRISE showed a beneficial effect of tolvaptan even in older age groups may lead to the misunderstanding that therapy should generally be delayed until sufficient data are available to prove rapid disease progression based on eGFR decline. While both the TEMPO 3:4 and REPRISE trials showed a reduction in the rate of eGFR loss in patients with an eGFR <90 mL/min/1.73 m² (Figure 1), a subgroup analysis of TEMPO 3:4 suggested that the effect on eGFR in patients with an eGFR >90 mL/min/1.73 m² (CKD stage 1) was minor and non-significant [10, 12]. It is important to recognize, however, that ADPKD progresses even before GFR is declining and that the effect on kidney growth was comparable among patients across CKD stages. Young patients with preserved kidney function will still have kidney function reserve capacity, which is used to compensate for a loss in kidney function. Therefore a decrease in eGFR will become apparent only at an older age [24]. Thus the apparent non-significant effect in young patients with an eGFR >90 mL/min/1.73 m² does not exclude a beneficial effect of tolvaptan on kidney function with a resulting delay of kidney failure, as kidney size and prognosis are closely associated. In this context, it is also important to point out the limitations of eGFR calculations in patients with (near-to) normal kidney function [25]. Also, a potential effect on structural changes in the kidney of any treatment in ADPKD is expected to benefit from an early start. Since tolvaptan slows disease progression rather than bringing it to a halt or reversing the disease, the absolute effect of this therapy, i.e. years with maintained kidney function before reaching kidney failure, is expected to correlate with the duration of treatment. Consequently, the full benefit of treatment is likely to be missed if tolvaptan is withheld until a decline in GFR is apparent. As a result, young patients with normal GFR should not be excluded from treatment if other markers, such as TKV, suggest rapid disease progression. We therefore recommend starting treatment in an adult patient with ADPKD when rapid disease progression has been established by a decline in GFR or by accepted predictors of progression, such as TKV (see below). Since young patients fulfilling these criteria are likely to be on treatment for many years, it is particularly important to discuss side effects and potential impacts on lifestyle with these patients before starting treatment (see below).

The REPRISE trial showed tolvaptan to be effective when commenced in patients with an eGFR down to 25 mL/min/1.73 m². No data have been published to suggest that the effect is reduced or abolished if eGFR declines below 25 mL/min/1.73 m² during treatment. Consequently we recommend not to stop tolvaptan before kidney failure has been reached. Notably, tolvaptan has been shown to cause an initial 3–9% decrease in measured GFR, probably due to treatment-associated haemodynamic effects, which is reversible upon withdrawal [10, 12, 16]. Thus it seems reasonable to stop tolvaptan in patients approaching the start of RRT (e.g. reaching an eGFR <15 mL/min/1.73 m²), since they may benefit from this predicted small increase in GFR. At this time point, the very limited expected remaining time on tolvaptan, even if still effective, would not allow for any major benefits.
**Recommendation 2.1:** We recommend tolvaptan treatment be started as soon as rapid disease progression can be determined in patients $\geq 18$ years of age.

**Recommendation 2.2:** We suggest tolvaptan treatment be discontinued when patients approach kidney failure (i.e. the need for RRT).

Although this prediction model is simplistic as it assumes that all patients progress linearly at the same slope to kidney failure, it allows for visualization of the benefit gained by patients if treated with tolvaptan early in their disease state.

**Evidence of rapid disease progression**

**Markers of rapid disease progression.** When assessing disease progression, it is important to distinguish markers that prove rapid disease progression from predictors of outcome. A historic fast decline in eGFR as well as rapid TKV growth can indeed be regarded as actual evidence of rapid disease progression. In contrast to eGFR, which can easily be measured in clinical practice, changes in TKV are difficult to assess using reliable methods in routine clinical practice and thus have been excluded from the updated algorithm (see section ‘The holistic approach’ below). Other markers, like the disease-causing genetic variant or age-related TKV, predict disease progression. To allow for quantifiable use of these markers, scoring systems have been established that use height-adjusted TKV (htTKV) in combination with age (Mayo Classification [26]) or mutation analysis in combination with clinical factors to classify ADPKD patients by risk of disease progression. These tools are particularly useful regarding patients in CKD stages G1 and 2, when there may be insufficient data on past eGFR to assess a reliable slope of eGFR decline and to assess if the observed eGFR loss is indeed due to ADPKD or a consequence of other comorbidities.

In general, the predictive power of each individual marker depends on the amount of information on disease progression this marker incorporates. In ADPKD, different progression markers represent different stages in the pathophysiological cascade (Figure 2). The disease-causing genetic variant acts far upstream in its pathogenesis and drives downstream mechanisms, which eventually lead to kidney failure. However, while the genetic mutation can be measured with high precision, it is also quite distant from the actual endpoint, kidney failure, which is the treatment target. During this process, downstream measures of the disease may be influenced by other factors, e.g. environmental factors, comorbidities and treatment, which will be incorporated in the information provided by these measures [27, 28]. TKV reflects the severity of the genetic variant, but it also integrates additional disease modifiers such as intra-uterine programming or environmental factors (e.g. salt intake, obesity). Only eGFR loss—as the last step in this cascade—incorporates all factors related to kidney disease progression. As a caveat regarding eGFR, comorbidities that are completely independent from ADPKD may contribute to the loss of kidney function. While such comorbidities do not prohibit the use of tolvaptan per se, loss of kidney function should be primarily attributable to ADPKD when considering eGFR loss as an indicator to select patients for treatment with tolvaptan.

**Kidney function.** When historic eGFR data are available, rapid disease progression can be identified by the rate of decline in eGFR. Kidney Disease: Improving Global Outcomes defines rapidly progressive CKD as an annual decline in GFR $\geq 5$ mL/min/1.73 m$^2$. However, observations suggest that in ADPKD, an annual eGFR decline less than that may be associated with kidney failure before the age of 58 years and is associated with other markers of rapidly progressive disease. An annual loss of $\geq 2.5$ mL/min/1.73 m$^2$ over a period of $>5$ years was chosen as a cut-off in the previous...
FIGURE 3: Updated algorithm to assess (likely) fast disease progression as an indication for initiation of tolvaptan in ADPKD. This algorithm is only valid for individuals ≤ 55 years of age with an eGFR ≥ 25 mL/min/1.73m² and a confirmed diagnosis of ADPKD. We do not recommend treatment in patients who do not fulfill these criteria. If alternative explanations for eGFR loss are likely (e.g. vascular disease, diabetic nephropathy), initiation of treatment should be reconsidered even in the presence of rapid eGFR decline. The following indicators point towards potential alternative explanations: proteinuria ≥ 1 g/day, signs for vascular disease (e.g. coronary heart disease, stroke), uncontrolled severe arterial hypertension and diabetes mellitus. In these cases, additional information (including MRI (CT) imaging if not performed before) should be acquired to ensure ADPKD as the primary reason for eGFR loss (see also Table 1): Mayo Class 1 C–E, PROPKD score >6, early hypertension/urological manifestations, truncating PKD1 mutation, family history (onset kidney replacement therapy <60 years in two or more first-line family members). Mayo Class 1 C can be found in individuals without rapid disease progression. Consequently, we recommend obtaining additional information in these patients to confirm the prediction (e.g. observe patients to see whether they actually lose eGFR compatible with rapid disease progression) and/or obtain additional arguments for an initiation of treatment such as (see also Table 1): a PROPKD score >6, early hypertension/urological manifestations, truncating PKD1 mutation, family history (onset dialysis <60 years in two or more first-line family members).

version of the WGIKD algorithm. According to the Mayo Imaging Classification system to assess the risk of progression in patients with morphologically typical ADPKD, the annual decline in eGFR in Mayo Class 1 C was 2.63 mL/min/1.73 m² for men and 2.43 mL/min/1.73 m² for women [26] (see Mayo Classification below). While Mayo Class 1 C was associated with a significantly greater risk of kidney failure when applied to two different ADPKD cohorts, it may include a significant proportion of individuals considered to have slow disease progression, especially in elderly individuals. Also, the placebo groups of the two large RCTs showing the efficacy of tolvaptan (REPRISE, TEMPO 3:4) revealed an average decline of ~3.5 mL/min/1.73 m²/year. It should be noted, however, that these RCTs were enriched for subjects with rapid disease progression. Consequently, we recommend that rapidly progressive disease may be defined by a yearly decline in GFR of ≥ 3.0 mL/min/1.73 m² when this decline can be attributed primarily to ADPKD (Figure 3). However, considering day-to-day fluctuations in eGFR, especially in the higher range, this criterion needs to be based on a sufficient number of measurements over a sufficient duration of follow-up. Also, non-linearity of eGFR loss in a subgroup of patients needs to be taken into consideration [29, 30]. Based on these points, we suggest obtaining at least five serum creatinine values over a period of ≥4 years when using the eGFR slope as the criterion to define rapid progression. This criterion depends on the availability of sufficient values and standardization of creatinine measurements. However, both are required by most European healthcare systems, making this approach feasible. In ADPKD, GFR has been shown to be adequately reflected by the Chronic Kidney Disease Epidemiology Collaboration equation for eGFR [31–33] and thus we suggest that this equation should be used. However, even if historical eGFR data are limited, the present eGFR provides a lot of information about the past. As an example, a normal eGFR in an individual > 50 years of age clearly indicates slow disease progression, while impaired kidney function in a patient below <30 years of age is very likely the result of rapid disease progression (see age-adjusted eGFR cut-offs in Recommendation 1.2).

Recommendation 3.1: A confirmed annual eGFR decline ≥ 3 mL/min/1.73 m² defines rapid disease progression. The estimation of eGFR loss should be reliable and based on at least five measurements over a period of ≥4 years. Recommendation 3.2: We recommend that other causes for eGFR decline should be assessed and excluded as major contributing factors, especially in case of non-linear eGFR decline, in older patients and/or patients with multiple comorbidities that can have an impact on eGFR.

Risk prediction: Mayo Classification and Predicting Renal Outcomes in ADPKD (PROPKD) score. A number of markers have been associated with a more severe disease
An update on the use of tolvaptan for ADPKD

A number of these have been incorporated into different prediction models based on age, sex, hTKV, mutation type and clinical complications. Such models include the Mayo Classification, which integrates hTKV with age and sex and is now widely used in the clinical setting [26]. The performance of the Mayo Classification has been validated in independent cohorts and compared favorably to models based on genetic information [27]. The PROPKD score is an alternative model established in the large Analysis of Clinical and Molecular Genetic Data Influencing the Evolution and Response to Therapy of ADPKD Patients (GENKYST) cohort and uses a combination of genetics and clinical parameters—specifically early onset of arterial hypertension and urological symptoms [36]. Since the effect of the disease-causing gene variant has been shown to be reflected in TKV [31], we suggest that the Mayo Classification should be used as the standard model to predict kidney outcome for a decision to recommend the start of tolvaptan in ADPKD with a typical kidney morphology as reflected by the updated algorithm (Figure 3). Importantly, since measurement of kidney size along the three axes and calculation of kidney volume by the ellipsoid equation has been shown to be sufficient for a reliable estimate in the clinical setting [26, 37], this appears feasible. However, real volumetry by segmentation remains the most accurate approach and should thus be favored if available [38]. In any case, it is important to recognize that these measurements depend on an experienced examiner skilled in the use of the size estimation tool and able to distinguish between typical and atypical morphology. In some cases, the inclusion of a second exam if available, or the use of a segmentation-based quantification of TKV may improve the precision of the TKV estimate. Particular caution is warranted when distinguishing between Mayo Classes 1B and 1C, where a misclassification could have a major impact on therapeutic decisions. Also, while Classes 1A/1B and 1D/1E are clearly separated from each other regarding the rate of eGFR loss, Class 1C includes both rapidly and slowly progressive disease with respect to the rate of eGFR decline [26, 31, 37]. Patients with atypical morphology, also known as Mayo Class 2 patients, must be recognized since the TKV-based model has not been validated in these patients [26]. In fact, Class 2 patients generally show a mild disease course. Consequently, imaging data [magnetic resonance imaging (MRI) or computed tomography (CT)] should be reviewed by an ADPKD expert (usually a radiologist or a nephrologist) at least once and should be—if available—complemented by other indicators of rapid disease progression to increase confidence. Regarding the imaging modality, TKV has primarily been validated using MRI scans. However, the alternative use of CT scans is acceptable for this purpose.

**Recommendation 4.1:** We recommend the use of the Mayo Classification as the primary method for risk prediction in routine clinical care. MRI (or CT) scans should be reviewed by radiologists/nephrologists experienced in ADPKD to ensure correct classification and exclude atypical cases (Class 2, see Recommendation 4.3).

**Table 1. Core set of clinical parameters for the assessment of rapid disease progression**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Assessment of rapid progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-adjusted assessment of eGFR</td>
<td>Is eGFR unexpectedly low (or high) for the age of the patient?</td>
</tr>
<tr>
<td>Kidney volume/Mayo Classification</td>
<td>Class 1D/1E: rapid progression</td>
</tr>
<tr>
<td>If not possible, kidney length by ultrasound</td>
<td>Class 1C: individual assessment</td>
</tr>
<tr>
<td>PROPKD score</td>
<td>&gt;6: rapid progression</td>
</tr>
<tr>
<td>Genetics</td>
<td>Truncating PKD1 mutation: rapid progression</td>
</tr>
<tr>
<td>Early onset of urological symptoms</td>
<td>Macrohematuria, cyst hemorrhage, flank pain, cyst infection before the age of 35 years</td>
</tr>
<tr>
<td>Early onset of arterial hypertension</td>
<td>Before the age of 35 years</td>
</tr>
<tr>
<td>Family history</td>
<td>Did most affected family members reach kidney failure? At an age &lt; 58 years?</td>
</tr>
</tbody>
</table>

**Recommendation 4.2:** Mayo Classes 1D and 1E indicate rapid disease progression. Mayo Class 1C patients should be carefully considered due to the overlap with slowly progressive disease and additional evidence for rapid disease progression should be sought in these patients.

**Recommendation 4.3:** We suggest that rapid disease progression is unlikely in patients with atypical morphology of ADPKD, as described in the Mayo Classification (or with Mayo Classes 1A and 1B).

**Adding information when initial assessment is inconclusive (a holistic approach).** Due to the individual variability associated with all prediction models, it is important to include all available clinical, genetic and imaging data to assess the ADPKD-associated renal progression risk when considering treatment with tolvaptan. A list of such parameters—most of which are easily accessible—is shown in Table 1. In cases with availability of genetic data and an age ≥35 years (also possible in younger patients if clinical complications have already occurred), the PROPKD score may be applied [39]. Even if a full PROPKD score cannot be calculated, each of the individual parameters contained in the score (onset of arterial hypertension or urological complications before the age of 35 years, type of mutation and male sex) has been shown to be significantly associated with kidney survival on its own and should be considered individually [39]. Regarding genetics, patients with PKD2 mutations, on average, reach kidney failure ~20 years later than patients with truncating PKD1 mutations, making PKD2 an important marker of slow disease progression [27, 39]. Although genotype is reflected by TKV, adding genotype information has been shown to improve the predictive power of the Mayo Classification regarding time to kidney failure [27]. If genetic data are missing, family history can be used to obtain insights regarding the genetic component. However, based on the considerable potential for intrafamilial variability, this criterion must be interpreted with caution [28]. In general, confirmation of kidney enlargement as a central aspect in ADPKD remains important in all patients even if treatment decisions are based on other criteria. Taken
together, a combination of all clinical, imaging and genetic information can assist the decision-making process and should be included in cases where historical eGFR decline and/or Mayo Classification are inconclusive.

Including all available information also helps to ascertain that eGFR decline is actually due to ADPKD and not explained by other causes. Comorbidities such as vascular disease, uncontrolled hypertension, diabetes mellitus as well as the presence of severe proteinuria (>1 g/day) point towards additional factors that can explain the rate of eGFR decline. As mentioned above, imaging of the kidneys (preferably by MRI) should be performed in all patients and the resulting Mayo Class is especially helpful in these cases. Also, serial measurements of TKV have previously been proposed as a method to assess progression. An increase in TKV ≥5% per year was also included as a marker indicating rapid disease progression in the original ERA position statement. However, such an approach would require at least three serial MRI or CT scans that are usually not available in clinical practice. Furthermore, variance of volume determination between different timepoints is a concern. In routine clinical care—and in contrast to clinical trials averaging measurements from large cohorts—the involvement of different scanners, protocols and radiologists add to this variability. Furthermore, cysts may rupture, which makes the use of serial volumetry to assess the rate of disease progression impossible. While these factors may indeed influence the results of single measurements that are used for the Mayo Classification, their impact is much larger regarding small relative changes over time. Thus the assessment of progression by consecutive estimates of TKV is not generally recommended. We suggest using a one-time MRI-based volume determination evaluated using the Mayo Classification. Measurement of kidney length by ultrasound is an alternative to MRI and may theoretically be used by experienced examiners in individuals up to 46 years of age. However, we suggest using this criterion only in patients with typical ADPKD and to take into account that it may underestimate the risk of progression (especially in young patients with short stature). We therefore do not include this approach in the updated algorithm (Figure 3), given the lack of an age-adjusted ultrasound-based approach and the greater precision as well as validation of MRI-based (or alternatively CT scan) TKV estimates in relation to prognosis.

**Recommendation 5.1:** When the initial assessment whether or not to treat with tolvaptan is inconclusive, we recommend that a full clinical picture should be obtained to allow for optimal counseling and decision-making.

**Recommendation 5.2:** In this regard, we suggest that the PROPKD score should be used in cases in which the eGFR and/or Mayo Classification estimates are inconclusive or contradictory. A score >6 is an indicator of rapid disease progression.

**Recommendation 5.3:** We recommend not to use TKV changes over time as a marker of progression in individual patients.

If alternative explanations for eGFR loss are likely (e.g., vascular disease, diabetic nephropathy), initiation of treatment should be reconsidered even in the presence of rapid eGFR decline. The following indicators point towards potential alternative explanations: proteinuria ≥1 g/day, signs of vascular disease (e.g., coronary heart disease, stroke), uncontrolled severe arterial hypertension and diabetes mellitus. In these cases, additional information [including MRI (CT) imaging if not performed before] should be acquired to ensure ADPKD as the primary reason for eGFR loss (see also Table 1): Mayo Class 1C–1E, PROPKD score >6, early hypertension/urological manifestations, truncating PKD1 mutation, family history (onset of RRT at <60 years in two or more first-line family members)?

Mayo Class 1C can be found in individuals without rapid disease progression. Consequently, we recommend obtaining additional information in these patients to confirm the prediction (e.g. observe patients to see whether they actually lose eGFR compatible with rapid disease progression) and/or obtain additional arguments for an initiation of treatment, such as (see also Table 1) a PROPKD score >6, early hypertension/urological manifestations, truncating PKD1 mutation, family history (onset of RRT at <60 years of age in two or more first-line family members).

**Recommendation 6:** We suggest using a hierarchical decision algorithm to assess whether ADPKD patients are rapid progressors or likely rapid progressors and accordingly may qualify for treatment.

**Applying the algorithm in the real-life setting**

The proposed algorithm was applied to a cohort of 878 ADPKD patients managed by the Expertise Center for Polycystic Kidney Diseases at the University Medical Center Groningen, Groningen, The Netherlands to assess the proportion of patients qualifying for tolvaptan treatment (Table 2). A total of 415 (47%) were excluded from treatment due to an eGFR <25 mL/min/1.73 m² or an age >55 years. Of the remaining 463 patients, 248 (53.6%) were eligible for treatment based on documented rapid disease progression (19.7%) or predicted rapid disease progression (33.9%). Of the 215 (48.4%) who did not qualify for treatment, 11.0% revealed documented slowly progressive disease and 17.1% had an eGFR that was too high for their age, while 18.4% showed other evidence predicting slowly progressive disease.

Nearly all patients with Mayo Class 1E would qualify for treatment, while 94.8% of the subjects with Mayo Class 1B and approximately half of the subjects with Mayo Class 1C would not. Patients with an indication for treatment are also enriched for the presence of a PKD1 truncating mutation, albeit slightly less clear than for Mayo Class 1E and 1D. Patients with an indication for treatment according to the algorithm had an average annual rate of eGFR decline of 4.12 mL/min/1.73 m² versus 2.12 mL/min/1.73 m² with no indication for treatment (Table 3). Obviously all possible progression criteria harbor a potential risk for misclassification, explaining the lack of complete concordance between eGFR decline and Mayo Class. Nonetheless, eGFR loss is downstream to TKV in the pathogenesis of ADPKD (see Figure 2) and as such shows the true velocity of disease progression, while TKV/Mayo Class predicts disease progression
Table 2. Baseline characteristics of adult ADPKD patients from the UMCG overall (N = 878) and according to outcome in the updated flowchart

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (N = 878)</th>
<th>eGFR or age outside indication</th>
<th>Indication for treatment</th>
<th>No treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>eGFR too low (&lt; 25 mL/min/1.73 m²) (n = 196)</td>
<td>Age too high (≥ 55 years) (n = 219)</td>
<td>Rapid progression (n = 91)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>507 (57.7)</td>
<td>89 (45.4)</td>
<td>128 (58.4)</td>
<td>49 (52.7)</td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
<td>49.9 ± 11.1</td>
<td>54.2 ± 9.32</td>
<td>61.4 ± 5.17</td>
<td>44.7 ± 7.25</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²), mean ± SD</td>
<td>50.5 ± 28.8</td>
<td>16.4 ± 5.13</td>
<td>47.9 ± 17.4</td>
<td>48.5 ± 17.7</td>
</tr>
<tr>
<td>hTmTKV (mL/m), median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD stage, n (%)</td>
<td></td>
<td></td>
<td>8 (3.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>1</td>
<td>91 (10.4)</td>
<td>0 (0.0)</td>
<td>8 (3.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>2</td>
<td>207 (23.6)</td>
<td>0 (0.0)</td>
<td>43 (19.6)</td>
<td>25 (26.9)</td>
</tr>
<tr>
<td>3a</td>
<td>144 (16.4)</td>
<td>0 (0.0)</td>
<td>55 (25.1)</td>
<td>22 (23.7)</td>
</tr>
<tr>
<td>3b</td>
<td>172 (19.6)</td>
<td>0 (0.0)</td>
<td>81 (37.0)</td>
<td>30 (32.3)</td>
</tr>
<tr>
<td>4</td>
<td>212 (24.1)</td>
<td>144 (73.5)</td>
<td>32 (14.6)</td>
<td>16 (17.2)</td>
</tr>
<tr>
<td>5</td>
<td>52 (5.9)</td>
<td>52 (26.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Mayo hTmTKV Class, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1E</td>
<td>116 (13.2)</td>
<td>33 (16.8)</td>
<td>1 (0.5)</td>
<td>25 (26.9)</td>
</tr>
<tr>
<td>1D</td>
<td>185 (21.1)</td>
<td>53 (27.0)</td>
<td>26 (11.9)</td>
<td>28 (30.1)</td>
</tr>
<tr>
<td>1C</td>
<td>271 (30.9)</td>
<td>73 (37.2)</td>
<td>64 (29.2)</td>
<td>26 (28.0)</td>
</tr>
<tr>
<td>1B</td>
<td>151 (17.2)</td>
<td>11 (5.6)</td>
<td>59 (26.9)</td>
<td>9 (9.7)</td>
</tr>
<tr>
<td>1A</td>
<td>36 (4.1)</td>
<td>1 (0.5)</td>
<td>18 (8.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>2</td>
<td>25 (2.8)</td>
<td>4 (2.0)</td>
<td>14 (6.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>94 (10.7)</td>
<td>21 (10.7)</td>
<td>37 (16.9)</td>
<td>5 (5.4)</td>
</tr>
<tr>
<td>PKD mutation, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PKD1 truncating</td>
<td>345 (39.3)</td>
<td>86 (43.9)</td>
<td>38 (17.4)</td>
<td>54 (58.1)</td>
</tr>
<tr>
<td>PKD1</td>
<td>200 (22.8)</td>
<td>47 (24.0)</td>
<td>46 (21.0)</td>
<td>25 (26.9)</td>
</tr>
<tr>
<td>Non-truncating , n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PKD2</td>
<td>174 (19.9)</td>
<td>27 (13.8)</td>
<td>73 (33.3)</td>
<td>7 (7.5)</td>
</tr>
<tr>
<td>PKD1 unknowna</td>
<td>11 (1.3)</td>
<td>3 (1.5)</td>
<td>12 (5.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other (e.g. GANAB)</td>
<td>2 (0.2)</td>
<td>0 (0.0)</td>
<td>2 (0.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>No mutation detected</td>
<td>38 (4.3)</td>
<td>5 (2.6)</td>
<td>18 (8.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Missing</td>
<td>108 (12.3)</td>
<td>28 (14.2)</td>
<td>30 (13.7)</td>
<td>7 (7.5)</td>
</tr>
</tbody>
</table>

*Not possible to decide truncating/non-truncating.
or allows attributing eGFR loss to ADPKD. Taken together, as indicated above, a holistic approach is indeed required in all cases of doubt. Supplementary data, Figures S1 and S2 underline the group separation achieved using the age/eGFR thresholds of the algorithm based on individual patient data plotting age versus eGFR, with patients categorized according to rate of eGFR decline before presentation (Supplementary data, Figure S1) or Mayo hTKV Class (Supplementary data, Figure S2). The findings show that, based on a cohort of ADPKD patients followed at an expert center, ~28% of all patient would qualify for treatment with tolvaptan using the proposed algorithm. Furthermore, the algorithm identified approximately half of the ADPKD patients with an age and eGFR within the range of the indication as having (likely) rapid disease progression, and these patients indeed have a rate of eGFR loss that is compatible with such qualification.

**New parameters to simplify the assessment of rapid progression?**

Currently risk prediction in ADPKD mainly relies on TKV and is complemented by genetic information and clinical complications [42, 43]. Easily measurable blood or urine markers that provide reliable predictive information are lacking. So far, no studies have identified markers that are sufficiently validated for routine clinical use. Proposed biomarkers include serum levels of the soluble urokinase plasminogen activator receptor (suPAR) [44] and copeptin [45]—serving as a surrogate parameter for arginine vasopressin (AVP) levels—as well as urinary monocyte chemoattractant protein-1 [46] and β2-microglobulin [47]. In general, blood-derived marker discovery is hampered by renal clearance, making serum levels dependent on GFR, which has been established for several of the candidates examined. ADPKD-associated proteinuria may complicate marker identification in urine due to the resulting contribution of serum-derived proteins to the peptides measured. In this regard, the quantification of microRNAs and proteins in urinary extracellular vesicles opens up an entirely new opportunity for biomarker discovery in kidney disease [48–51] and would also be applicable to ADPKD. In addition to biochemical markers, novel imaging-based predictors are actively being explored. MRIs are an extremely rich source of data that provide information on tissue composition beyond mere kidney volume. This source can be mined using novel approaches such as texture analyses or T2 mapping [52, 53]. In conclusion, despite promising first results, there are currently no newly established biomarkers that can be used on a routine basis to improve selection algorithms for targeted treatment.

**Recommendation 7:** We encourage further studies examining novel imaging and molecular biomarker candidates as easy to measure, inexpensive tools for risk prediction, but currently available evidence is not sufficient to support their use in clinical routine.

**Monitoring of the response to tolvaptan and its therapeutic efficacy**

There are currently no validated markers that allow for monitoring or predicting the effect of tolvaptan on TKV or GFR in an individual patient on treatment. Effective blockade of the V2 receptor (the target of tolvaptan) may be assessed by measuring urine osmolality [54]. Lowering of urine osmolality and increased aquaretics/nocturia does indeed reflect adherence to treatment; however, there is insufficient evidence for this to be a marker of treatment efficacy and these parameters are also subject in tolvaptan-independent changes of fluid intake. A post hoc analysis of TEMPO 3:4 suggested that suppression of urine osmolality in morning spot urine samples <250 mOsm/L was not associated with an added benefit [54]. However, patients with ADPKD show a baseline defect in concentrating urine [55] and are often encouraged to drink more water. Consequently, in the individual patient, this does not allow the use of this threshold to predict the impact of tolvaptan on future GFR loss (see also section on ‘Dose selection and titration of tolvaptan’ below). The relative increase in serum copeptin levels associated with tolvaptan has been shown to predict outcome in patients on tolvaptan [45]. While this may suggest copeptin is a potential biomarker to monitor the response to tolvaptan and identify individuals that benefit most from this therapy, there are currently no sufficient data to recommend this for routine clinical practice. Changes in eGFR and TKV on tolvaptan treatment may be compared with trends in pretreatment data or with predictions based on the Mayo Classification, but the validity and sensitivity of such an approach has not been established and is likely to be hampered by individual fluctuations and non-linear

---

Table 3. Annual change in eGFR of adult ADPKD patients from the UMCG overall (N = 878) and according to outcome in the updated flowchart

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>eGFR or age outside indication</th>
<th>Indication for treatment</th>
<th>No treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>eGFR too low (&lt;25 mL/min/1.73 m²) (n = 196)</td>
<td>Age too high (≥55 years) (n = 219)</td>
<td>Rapid progression (n = 91)</td>
</tr>
<tr>
<td>Period of historical measurements (years), mean ± SD</td>
<td>4.15 ± 3.10</td>
<td>4.43 ± 3.25</td>
<td>4.00 ± 2.86</td>
</tr>
<tr>
<td>Number of measurements, median (IQR)</td>
<td>8 (5–19)</td>
<td>18 (7–21)</td>
<td>7 (5–19)</td>
</tr>
<tr>
<td>Annual change in eGFR (mL/min/1.73 m²), mean ± SD</td>
<td>−3.41 ± 2.19</td>
<td>−4.69 ± 1.53</td>
<td>−2.76 ± 1.44</td>
</tr>
</tbody>
</table>
An update on the use of tolvaptan for ADPKD

Courses of eGFR changes, lack of serial MRIs and variability in TKV estimates as previously discussed. Consequently, even though these approaches may be useful in large cohorts, they should not be used in individual patients [13, 14]. Thus we do not recommend monitoring treatment efficacy outside clinical trials. Nonetheless, considering the interest in characteristics that identify patients who will benefit from tolvaptan, future research in this field should be encouraged. Notably, in this regard, tolvaptan is no exception, since monitoring of direct treatment efficacy—e.g. regarding eGFR loss—in individual patients is not possible for the vast majority of available drugs, e.g. sodium–glucose cotransporter-2 inhibitors for diabetic nephropathy [56]. Nonetheless, determining urine volume, osmolality and body weight are helpful tools to monitor adherence to and the feasibility of tolvaptan therapy (see section on ‘Management of side effects of tolvaptan’ below). A more detailed discussion of potential markers to guide dose selection is provided in the section ‘Dose selection and titration of tolvaptan’.

Recommendation 8: We suggest that monitoring tolvaptan treatment efficacy has currently limited value in individual patients in routine care.

Dose selection and titration of tolvaptan

Tolvaptan for ADPKD comes in three different dose regimens (45/15, 60/30, 90/30 mg), all to be taken twice daily, with the first dose taken early in the morning and the second dose 8 h later based on the pharmacokinetic profile of tolvaptan [57]. In the TEMPO 3:4 trial the drug was titrated weekly to a target dose of 90/30 mg based on pharmacokinetic data showing that suppression of urine osmolality <300 mOsmol/L was achieved in more subjects on higher doses, with 90/30 mg being the highest tolerated dose [57]. Since tolerability may be dose dependent, an initial titration was included allowing patients to slowly adjust to the effects of the drug or to continue at a lower dose depending on tolerability. Importantly, in TEMPO 3:4, 77% in the tolvaptan group completed the trial and 55% of these patients reached 90/30 mg. As previously described, urine osmolality likely reflects the degree of V2R blockade and has been discussed as a marker to guide dosing of tolvaptan based on the finding that as a group, a urine osmolality <250 mOsmol/L was not associated with greater benefit in a post hoc analysis of TEMPO 3:4 [54]. However, the minimum level of blockade required to provide treatment benefits in individual patients is not known. Furthermore, urine concentrating capacity is impaired in ADPKD, especially in later-stage patients [58], which may result in a urine osmolality below serum osmolality even before starting tolvaptan.

Importantly, dosing by urine osmolality or by changes in urine osmolality after starting tolvaptan has not been validated in clinical trials. Efficacy has been proven in RCTs only if aiming for a daily dose of 90/30 mg, which was achieved in most patients in these trials. Furthermore, considering that, from a pharmacodynamic point of view, maximal and 24-h blockade of V2R should be attempted to also overcome the compensatory increase in vasopressin levels after starting tolvaptan, a maximal dose of 90/30 mg should be pursued independent of spot urine osmolality measurements. In case of drug interactions, mainly due to indispensable, concomitant treatment with inhibitors or inducers of CYP3A, a tolvaptan dose adjustment may be required. While we do not recommend the determination of urine osmolality to guide dosing, it may be useful to assist in the assessment of treatment adherence. In cases in which titration to higher doses limits tolerability, suppressed urine osmolality may indicate V2R blockade already at lower doses. However, for these patients, treatment decisions will probably be guided by feasibility and quality of life rather than urine osmolality.

It is currently unknown if a specific titration regimen, e.g. weekly or monthly, is associated with better tolerability, dose maximization and/or adherence, although current package sizing (with 28 daily doses) favors a monthly rather than weekly schedule. We suggest that the specific titration scheme adopted should be determined based on patient and/or physician preferences as well as site-specific features of patient care, including the possibilities for and frequency of outpatient visits, taking into account that monthly liver function testing will need to be performed anyway.

Recommendation 9.1: We recommend tolvaptan treatment be started with a dose of 45 mg in the morning and 15 mg in the afternoon.

Recommendation 9.2: We recommend that a target dose of 90/30 mg/day should generally be aimed for in all patients unless this becomes intolerable or is contraindicated by drug interactions.

Recommendation 9.3: We suggest that titration to the target dose should be performed directly after initiation of treatment. Both a weekly and a monthly dose escalation scheme are appropriate.

Management of side effects of tolvaptan

Polyuria and the risk of hepatotoxicity are the two most notable adverse effects of tolvaptan identified in all clinical trials of tolvaptan in ADPKD [10, 12, 59]. Polyuria is the natural consequence of V2R blockade and is to be expected in every patient on treatment. This is especially a problem in young patients with preserved kidney function. In later-stage disease—due to impaired urine concentrating capacity—patients in general already have polyuria before treatment is started. Since tolvaptan leads to a maximally diluted urine, the reduced number of nephrons in later-stage disease will also lead to a lower 24-h urine volume on treatment when compared to early-stage disease. It was shown that in younger ADPKD patients with near-normal GFR, urine volume increases from 2 L in the untreated situation to 7 L on tolvaptan (an increase of 5 L), whereas in later-stage disease urine volume starts at 3 L in the untreated situation and increases to 5 L on tolvaptan, an increase of only 2 L [60]. This phenomenon is likely to be the reason why a greater number of younger subjects stop treatment [5]. This is indeed a relevant problem in clinical practice because, as reasoned above, starting treatment at a young age would yield the greatest absolute benefit with respect to delaying the onset of kidney failure. Carefully counselling younger patients and
providing practical suggestions on how to minimize problems with polyuria (see section 'Practical considerations regarding polyuria' below) and how to deal with polyuria in daily life are therefore essential.

Hepatotoxicity is rare and the underlying mechanism is still poorly understood [59]. An increase of transaminases more than 3-fold the upper limit of normal (ULN) is observed in ~5% of patients in clinical trials and appears to be idiosyncratic. This increase is generally reversible following cessation of tolvaptan. Rare severe cases fulfilling the Hy law criteria, which implies a significant risk of acute liver failure, have been described and led to the introduction of a risk management plan and the requirement for blood testing of hepatic transaminases and bilirubin. Liver function tests are required prior to the initiation of treatment and monthly for 18 months and at 3-month intervals thereafter [59, 61]. This approach was based on the finding that nearly all cases of treatment-associated liver abnormalities in clinical trials occurred within the first 18 months and was included in the REPRISE trial, in which no more cases fulfilling Hy law criteria were detected [10].

A recent publication provides an updated and well-structured algorithm to guide the need for pausing or stopping tolvaptan depending on the pattern of liver function test abnormalities [2]. Besides monitoring liver enzymes, the risk management plan implemented by the EMA includes education of both prescribing physicians and patients, and the manufacturer of tolvaptan (Otsuka Pharmaceutical, Tokyo, Japan) has also issued information [62].

Additional changes in serum electrolytes (e.g. a slight increase in sodium) and urate may be observed after starting tolvaptan. However, this rarely becomes clinically significant, although stopping tolvaptan should be considered in the rare cases of recurrent gout after initiation. In any case, both parameters—alongside body weight and serum creatinine/blood urea nitrogen (BUN)—provide information regarding water–salt balance and volume status in patients on tolvaptan.

Recommendation 10.1: We recommend discussing adverse effects and impacts on lifestyle with patients when considering starting tolvaptan. Treating physicians need to be aware of the adverse effects, contraindications and drug interactions of tolvaptan.

Recommendation 10.2: We recommend measuring liver function monthly during the first 18 months of treatment and every 3 months thereafter.

Recommendation 10.3: Patients showing signs of relevant liver toxicity upon exposure to tolvaptan should not be re-exposed. Alternative causes of liver damage should be excluded.

Recommendation 10.4: We recommend that plasma sodium levels as well as serum creatinine/BUN and body weight should be checked regularly in patients on tolvaptan.

Practical considerations regarding polyuria

It is essential that patients are informed of polyuria as the most common adverse effect of tolvaptan before treatment initiation and that—unlike common side effects of most other drugs—polyuria is expected in almost all cases due to the mode of action of tolvaptan. Urine volume reaches ∼5–8 L/day on average and patients should be informed that this volume increase results in the likely need to go the bathroom hourly during daytime and two to three times per night. Importantly, as explained above, the increase in urine volume is expected to be most pronounced in individuals with a higher GFR. Simple measures such as starting treatment on a weekend rather than on a working day or avoiding taking the second pill too late in the afternoon to prevent excessive nocturia may be helpful advice. In our experience, nocturia is indeed an issue that may limit tolerability. Nonetheless, tolvaptan has been surprisingly well-tolerated by the majority of patients, both in clinical trials and in real-life settings [5, 7]. If polyuria becomes a major issue that may limit drug adherence, additional measures may be recommended. Lowering dietary sodium intake may reduce urine output by reducing the amount of osmotically active solutes to be excreted [63]. Sodium intake can be assessed using repetitive 24-h urine collections in order to quantitate this problem and to increase patient adherence to dietary advice. In addition, lowering dietary sodium intake may have protective effects by improving blood pressure control and kidney outcome in ADPKD [64]. If nocturia remains a significant problem, decreasing the (second) dose may be an option; however, as previously discussed, dose reduction may affect treatment efficacy. The use of thiazide diuretics to reduce urinary output similar to their use in nephrogenic diabetes insipidus has been discussed in a recent case report [65]. However, published experiences regarding the combination of diuretics and tolvaptan are limited [66]. Hence additional studies are required, considering that in the clinical trials of tolvaptan for ADPKD, concomitant treatment with diuretics was discouraged because of theoretical concern for electrolyte disturbances and volume contraction. An additional point that needs to be discussed with all patients before initiating treatment is the advice that tolvaptan has to be stopped in situations that are associated with a risk of dehydration, e.g. diarrhea, vomiting or limited access to water. Furthermore, ADPKD patients can—in addition to counselling by their nephrologists—access information on practical aspects regarding tolvaptan provided by (inter)national patient organizations, which is freely offered through brochures, symposia and social media groups.

Recommendation 11.1: Polyuria and its practical consequences should be addressed specifically with all patients before starting tolvaptan.

Recommendation 11.2: Counseling should be provided to patients starting tolvaptan regarding measures that can decrease polyuria, with a focus on reducing sodium intake.

Recommendation 11.3: Potential situations in which tolvaptan should be temporarily stopped due to the risk of dehydration should be discussed with all patients before initiation.

Increasing fluid intake as an alternative to tolvaptan treatment?

Increased fluid intake is one of the supportive measures commonly recommended to ADPKD patients based on its
suppression of vasopressin secretion and the consequent potential to ameliorate the rate of disease progression [67–69]. It is important to note that this specifically refers to water intake since other fluids, like sodas, come at added health risks when consumed in large volumes. Compared with the impact of increased fluid intake, tolvaptan treatment leads to a strong increase of vasopressin levels (AVP) [45]. While V2R signaling in tubular epithelial cells is blocked by tolvaptan, the increase in AVP may have an impact on other vasopressin receptor subtypes, e.g. V1a receptors in the renal vasculature [70]. An ongoing multicenter randomized clinical trial is currently investigating the effect of increased fluid intake in ADPKD on TKV, vasopressin activity and eGFR [71]; however, to date there are no data available showing a benefit of this approach, and a tolvaptan group was not included in the cited study for comparison. Importantly, all participants in TEMPO 3:4 were advised to increase fluid intake and this advice was indeed followed by the placebo patients, as evidenced by a significant decrease in urine osmolality [54]. Despite this, tolvaptan was superior in reducing a TKV increase and eGFR decline, as described above. When comparing the potential benefit of increased fluid intake with tolvaptan treatment, it should be considered that the twice-daily dosing strategy and pharmacokinetic profile of tolvaptan results in efficient, 24-h V2R blockade [57, 72]. This is likely difficult to replicate by lowering vasopressin levels through high fluid intake, especially at night. Also, excessive fluid intake involves a risk of hyponatremia, which may increase as the capacity for urine dilution is reduced upon a loss of kidney function [73]. Thus, while ample fluid intake remains an important supportive measure, there is currently no evidence supporting its use as an equally effective alternative to tolvaptan.

**Recommendation 12:** We suggest that increased fluid intake should not be recommended as an alternative equal to tolvaptan. This notwithstanding, although formal evidence is lacking, it seems prudent to advise ADPKD patients not treated with a V2R blocker to adhere to a low-salt diet (3–5 g/day) and high water (3–4 L/day) intake to improve the rate of disease progression.

**CONCLUSION**

Since its approval for ADPKD by the EMA in 2015, tolvaptan has become an important component in the management of ADPKD patients. Based on the EMA ruling, patient selection for this treatment was perceived as a challenge by many nephrologists, leading to the issue of the first ERA position statement in 2016 to provide practical guidance for tolvaptan prescribing in clinical care. Since then, the REPRISE trial has provided additional evidence and allows for the extension of tolvaptan to later-stage ADPKD patients. This fact, as well as the increased clinical experience in real-world settings, are the basis for these updated recommendations and the modified selection algorithm. Finally, it is likely that the selection algorithm will be applicable to other emerging treatments besides tolvaptan in coming years.

**SUPPLEMENTARY DATA**

Supplementary data are available at *ndt* online.

**ACKNOWLEDGEMENTS**


**CONFLICT OF INTEREST STATEMENT**

Department 2 of Internal Medicine received grants from Otsuka (manufacturer of tolvaptan) and Thermo Fisher Scientific (manufacturer of assays to determine copeptin). R.-U.M. received remuneration as an advisor and lecturer from the same companies. R.T.G. was a member of the Steering Committee of the TEMPO 3:4 and REPRISE trials and received grants and/or remuneration from Otsuka, Ipsen, Sanofi-Genzyme and Galapagos (manufacturers of tolvaptan, lanreotide, venglustat and GLP2737, respectively; agents used or in development as disease-modifying agents in ADPKD). R.T. was a member of the Independent Data Monitoring Committee for the TEMPO 3:4 study and received grants and/or remuneration from Otsuka, Ipsen, Sanofi-Genzyme, Galapagos...
and Reata (manufacturers of tolvaptan, lanreotide, venglustat, GLP2737 and bardoxolone, respectively, agents used or in development as disease-modifying agents in ADPKD). D.M. reports research grants and/or remunerations paid to her institutions (KU Leuven/ULeuvén) from Otsuka, Galapagos and Sanofi-Genzyme. E.S. is the chair of the pediatric tolvaptan trial program and has received remunerations from Otsuka for this and other consulting activities. A.C.M.O. reports having received grants and/or consultancy fees from Otsuka, ONO, Sanofi-Genzyme, Galapagos and Mirionid, companies working in the field of ADPKD. All money is paid to his employing institution. H.B. reports speaker and/or consultancy remuneration from Otsuka and Galapagos (manufacturers of tolvaptan and GLP2737, respectively, agents used or in development as disease-modifying agents in ADPKD).

REFERENCES

11. Ong ACM. Tolvaptan slows disease progression in late-stage ADPKD. Nat Rev Nephrol 2018; 14: 146–8
27. Lavu S, Vaughan LE, Senum SR et al. The value of genotypic and imaging information to predict functional and structural outcomes in ADPKD. JCI Insight 2020; 5: e138724
An update on the use of tolvaptan for ADPKD

57. Meijer E, Heida JE, Gansevoort RT. No change in nocturia after NOCTURNE. Kidney Int Rep 2020; 5: 762–5
69. Wong ATY, Mannix C, Grantham JJ et al. Randomised controlled trial to determine the efficacy and safety of prescribed water intake to prevent kidney failure due to autosomal dominant polycystic kidney disease (PREVENT-ADPKD). BMJ Open 2018; 8: e018794

Received: 8.7.2021; Editorial decision: 30.9.2021