An update on the use of tolvaptan for ADPKD: Consensus statement on behalf of the ERA Working Group on Inherited Kidney Disorders (WG IKD), the European Rare Kidney Disease Reference Network (ERK Net) and Polycystic Kidney Disease International (PKD-International)

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ABSTRACT
The approval of the vasopressin V2-receptor antagonist tolvaptan – based on the landmark TEMPO 3:4 trial – has marked a transformation in the management of autosomal dominant 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 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 has 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

ADDITIONAL CONTENT
An author video to accompany this article is available at: https://academic.oup.com/ndt/pages/author_videos.

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) 

Two randomized clinical trials have shown a beneficial effect of tolvaptan regarding the ADPKD-associated eGFR decline in patients with rapid disease progression. Considering the potential drawbacks – including its side effects and costs – associated with this treatment, the selection of patients that are most likely to show a positive benefit to risk ratio regarding this therapy – i.e. individuals showing rapid disease progression - is important and required.

Tolvaptan is a V2 receptor (V2R) antagonist that blocks vasopressin signaling, a key driver of cyst growth in ADPKD due to the resulting intracellular increase in cAMP. Polyuria is the logical consequence of V2R-blockade and as such expected to occur in every patient on treatment. Nonetheless, adherence to tolvaptan appears to be well-feasible in the majority of patients. 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 WGIKD 2016 position statement several treatment decision algorithms have been published for different countries 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). In contrast, the original WGIKD position statement put most weight on measured rapid progression based on the historical decline in estimated glomerular filtration rate (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 trial in 2018 has allowed for an extension of
eligibility criteria to older patients and later-stage ADPKD. 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 has been developed by a panel of experts, and endorsed by the boards of the ERA Working Group on Inherited Kidney Disease (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 of kidney replacement therapy 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 to the original position statement are highlighted in Suppl. Table 1.

An update on the efficacy of tolvaptan in ADPKD

Whilst 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 onset of kidney failure. In TEMPO 3:4 tolvaptan reduced eGFR decline by ~ 1 ml/min/1.73 m² per 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) 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. RAAS-blockade in diabetic kidney disease. 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. The interpretation of these findings, however, was limited by the non-randomization design resulting in imbalances in baseline characteristics, including gender, TKV and eGFR, which may at least in part explain the loss of sustained effect on TKV. Later, the randomized controlled REPRISE trial added substantial evidence to the use of tolvaptan in ADPKD. REPRISE examined tolvaptan in later-stage ADPKD (eGFR 25–65 ml/min/1.73 m² in subjects with age 18-55 and eGFR 25 – 45 ml/min/1.73 m² in subjects with age 55-65 years). Here, tolvaptan slowed the decrease in eGFR by 1.27 mL/min/1.73m² per year (from −3.61 to −2.34 ml/min/1.73 m²) – an effect size comparable to TEMPO 3:4. REPRISE and several subgroup analyses of this trial have added much to our current knowledge on the use of tolvaptan in ADPKD and will be discussed in more detail below in the context of the updated recommendations. While neither TEMPO 3:4 nor REPRISE provide data on long-term outcome, a more recent study addressed this issue based on a retrospective analysis of 97 patients that had been treated with tolvaptan for up to 11 years (median 4.0, range 1.1 – 11.2 years). A comparison with both matched controls from several ADPKD studies and with predicted eGFR decline again revealed an effect size similar to the two randomized trials. In addition to the reported effects on eGFR loss and TKV increase, TEMPO 3:4 also showed a tolvaptan-associated reduction in kidney pain and urinary tract infections. It should be noted that, in general, currently available data for tolvaptan in ADPKD are derived from clinical trials that primarily recruited people from European descent and to lesser extent Asians and people from African background and therefore may not account for ethnic differences.

Importantly, before starting the evaluation of a patient for treatment with tolvaptan, the diagnosis of ADPKD needs to be confirmed. The diagnostic approach to ADPKD is not the focus of this consensus statement. Nonetheless, this is a point that needs increasing attention when targeted treatments become available for polycystic kidney disease. Briefly, in the presence of a positive family history, classical ADPKD can be diagnosed using imaging criteria. Consequently, kidney imaging (preferably by MRI) is a prerequisite before
evaluation of patients for tolvaptan. Cases with atypical clinical presentation or kidney morphology, usually require confirmation by genetic testing.\textsuperscript{20}

**Thresholds for treatment initiation – outer eGFR and age limits**

The TEMPO 3:4 trial - the basis to the approval of tolvaptan for ADPKD by the European Medicines Agency (EMA) - enrolled patients 18 to 50 years of age.\textsuperscript{12} Most previous recommendations had thus 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\textsuperscript{10} showing a similar and significant reduction in eGFR decline. However, a subgroup analysis suggested that this was not the case for patients above 55 years implicating that tolvaptan should only be offered up to this age. Nonetheless, it is important to recognize that the group of patients in REPRISE aged 56 to 65 years comprised only 190 individuals in total (less than 15\% of the study population). Besides, and despite the fact that only individuals with an eGFR of below 45 ml/min/1.73m\textsuperscript{2} were enrolled in this age group, these patients showed a slower decline of kidney function – both on placebo (-2.34 ml/min/1.73 m\textsuperscript{2} per year) and on tolvaptan (-2.54 ml/min/1.73 m\textsuperscript{2} per year) – compared to participants below the age of 55. Thus, this group of patients would usually not be considered rapidly progressing. This finding highlighted two key aspects when evaluating patients for tolvaptan. Firstly, only patients with rapid disease progression should be treated. Secondly, when applying an algorithm similar to the inclusion criteria in the REPRISE study (solely based on age-adjusted eGFR cutoffs), patients above the age of 55 with an eGFR \(\geq 25\) ml/min/1.73m\textsuperscript{2} are likely to have slowly progressive disease. Most patients with rapidly progressive disease will have reached kidney failure before the age of 55, given that the average age of kidney failure requiring kidney replacement therapy is 58 years of age for patients with ADPKD.\textsuperscript{21}

When current eGFR loss may point 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 a 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/1.73m\textsuperscript{2} 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 to be 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 and emphasizes the need to consider other, non-ADPKD related causes for eGFR decline in elderly subjects. Since the indication by 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 that clearly do not have rapid disease progression at an early step in the decision-making process. In retrospect the thresholds defined in the original WGIKD algorithm were rather conservative, potentially excluding patients that could have been eligible for therapy.\textsuperscript{9,22} Based on the additional evidence and the increased experience in the real-life setting, these limits are revised in the updated version to allow more patients to benefit from treatment. The alleviation of age-adjusted eGFR cutoffs 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 e.g. past-time eGFR loss (see section on Evidence of rapid disease progression below). Taken together, age-adjusted eGFR cutoffs should exclude individuals with a clearly high eGFR for 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/1.73m² as subgroup analyses show efficacy also at this late stage. As there is no data from RCTs regarding patients with an eGFR < 25 ml/min/1.73m², our algorithm adopts this lower eGFR limit. Even if the effect of tolvaptan may be extrapolated to patients with an eGFR < 25 ml/min/1.73m² the potential delay in the time of kidney replacement therapy as a consequence of treatment would only be a few months to 1 year.

**Recommendation 1.1:** We suggest that treatment with tolvaptan can be initiated in adult ADPKD patients aged ≤ 55 years 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 upper eGFR limit, 40-44 years ≥ 90 ml/min/1.73m², 45-49 years ≥ 75 ml/min/1.73m², 50-55 years ≥ 60 ml/min/1.73m²).

**At what age 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. Consequently, we currently do not recommend initiating tolvaptan before the age of 18. 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 past-time 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 of <90 ml/min/1.73m² (Fig. 1), a subgroup analysis of TEMPO 3:4 suggested that the effect on eGFR in patients with an eGFR of >90 ml/min/1.73m² (CKD stage 1) was minor and non-significant. 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. A loss in eGFR therefore will become apparent only at an older age. Thus, the apparent non-significant effect in young patients with an eGFR of >90 ml/min/1.73m² 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 calculation in patients with a (near-to) normal kidney function. Besides, 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 impact on lifestyle with such 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/1.73m². No data have been published to suggest that the effect is reduced or abolished if eGFR declines below 25 ml/min/1.73m² 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 mGFR, probably due to treatment-associated hemodynamic effects, which is reversible upon withdrawal. Thus, it seems reasonable to stop tolvaptan in patients approaching the start of kidney function replacement therapy (e.g. reaching an eGFR < 15 ml/min/1.73m²), 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 to be started as soon as rapid disease progression can be determined in patients at the age ≥ 18 years.

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

**FIGURE 1:** Extrapolations from the results of the TEMPO 3:4 (left panel A) and REPRISE (right panel B) trials allow estimations of the potential benefit of tolvaptan treatment in delaying the need of kidney function replacement therapy (adapted from Chebib et al. JASN 2018²) 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 historical 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, that can easily be measured in clinical practice, past-time 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 instead, like the disease-causing genetic variant or age-related TKV, predict disease progression. To allow for a quantifiable use of these markers, scoring systems have been established that use height adjusted TKV (htTKV) in combination with age (Mayo
Classification\textsuperscript{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-time 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 co-morbidities.

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 (Fig. 2). The disease-causing genetic variant acts far upstream in its pathogenesis and drives downstream mechanisms, which eventually lead to kidney failure. However, whilst 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.\textsuperscript{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, co-morbidities which are completely independent from ADPKD may contribute to the loss of kidney function. Whilst such co-morbidities 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.

![Diagram of disease progression and markers contributing to information contained in these markers](https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfab312/6431643)

**FIGURE 2:** Markers of disease progression and factors contributing to the information contained in these markers

**Kidney function**

When historic eGFR data are available, rapid disease progression can be identified by the rate of decline in eGFR. KDIGO defines rapidly progressive CKD by an annual decline in GFR of \( \geq 5 \text{ ml/min}/1.73 \text{ m}^2 \). However, observations suggest that in ADPKD an annual eGFR decline less than that may be associated with kidney failure before the age of 58 and is associated with other markers of rapidly progressive disease. An annual loss of \( \geq 2.5 \text{ ml/min}/1.73 \text{ m}^2 \) over a period of more than 5 years was chosen as cutoff in the previous 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 1C was 2.63 ml/min/1.73m² for men and 2.43 ml/min/1.73 m² for women²⁶ (see Mayo Classification below). While Mayo Class 1C was associated with a significant 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. Besides, the placebo groups of the two large RCTs showing efficacy of tolvaptan (REPRISE, TEMPO 3:4) revealed an average decline of ~ 3.5 ml/min/1.73m² per 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/1.73m² or more when this decline can be attributed primarily to the ADPKD (Fig. 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. Besides, non-linearity of eGFR loss in a subgroup of patients needs to be taken into consideration²⁹,³⁰. Based on these points, we suggest to obtain at least 5 serum creatinine values over a period of ≥ 4 years when using the eGFR slope as the criterion to define rapid progression. This criterion indeed depends on availability of sufficient values and standardization of creatinine measurements. However, both is warranted by most European healthcare systems making this approach feasible. In ADPKD, GFR has been shown to be adequately reflected by the CKD-EPI equation for eGFR³¹–³³ and thus we suggest that this equation is 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 of > 50 years clearly indicates slow disease progression, whilst an impaired kidney function in a patient below 30 years is very likely the result of rapid disease progression (see age-adjusted eGFR cutoffs in recommendation 1.2).

**Recommendation 3.1:** A confirmed annual eGFR decline ≥ 3 ml/min/1.73m² defines rapid disease progression. The estimation of eGFR loss should be reliable and based on at least 5 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 PROPKD score

A number of markers have been associated with a more severe disease course in ADPKD and thus, may serve as predictors of kidney outcome even before any decline in eGFR has occurred. These have been reviewed extensively before.³⁴,³⁵ A number of these have been incorporated into different prediction models based on age, sex, htTKV, mutation type and clinical complications. Such models include the Mayo Classification, which integrates htTKV with age and sex and which 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 information²⁷. The PROPKD score is an alternative model established in the large GENKYST cohort and uses the 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 TKV³¹, we suggest that the Mayo Classification is used as the standard model to predict kidney outcome for a decision to recommend start of tolvaptan in ADPKD with a typical kidney morphology as reflected by the updated algorithm (Fig. 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 setting²⁶,³⁷, this appears
feasible. However, real volumetry by segmentation remains the most accurate approach and should thus be favored if available\textsuperscript{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 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. Besides, whilst classes 1A/B and 1D/E are clearly separated from each other regarding the rate of eGFR loss, class 1C includes both rapidly and slowly progressive disease with respect to rate of eGFR decline\textsuperscript{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\textsuperscript{26}. In fact, Class 2 patients generally show a mild disease course. Consequently, imaging data (MRI or 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).

**Recommendation 4.2:** Mayo Classes 1D and E 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 B).

Adding information when initial assessment is inconclusive (a holistic approach)
Due 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 \( \geq 35 \) years (also possible in younger patients if clinical complications have already occurred), the PROPKD score may be applied\textsuperscript{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\textsuperscript{39}. Regarding genetics, patients with \( PKD2 \) mutations, on average, reach kidney failure approximately 20 years later than patients with truncating \( PKD1 \) mutations, making \( PKD2 \) an important marker of slow disease progression\textsuperscript{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\textsuperscript{27}. If genetic data is missing, family history can be used to obtain an insight regarding the genetic component. However, based on the considerable potential for intrafamilial variability, this criterion must be interpreted with caution\textsuperscript{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 (> 1g/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. Besides, 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 which 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 use of serial volumetry to assess the rate of disease progression impossible. Whilst these factors may indeed also 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 merely 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. However, we suggest to use this criterion only in patients with typical ADPKD and to take into account that it may underestimate risk of progression (esp. in young patients with short stature). We therefore do not include this approach in the updated algorithm (Fig. 3) given the lack of an age-adjusted ultrasound-based approach and the greater precision as well as validation of MRI (or alternatively CT-scan) based 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 based 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.
| parameter                        | assessment of rapid progression                                                                 |
|---------------------------------|--------------------------------------------------------------------------------------------------|
| age-adjusted assessment of eGFR | Is eGFR unexpectedly low (or high) for the age of the patient?                                      |
| kidney volume / Mayo Classification | Class 1D/E: rapid progression  <br> Class 1C: individual assessment  <br> > 16.5 cm ≤ 46 years of age  <br> > 6: rapid progression |
| PROPKD score                    | Truncating PKD1 mutation: rapid progression                                                       |
| genetics                        | macrohematuria, cyst hemorrhage, flank pain, cyst infection before the age of 35 years             |
| early onset of urological symptoms | before the age of 35 years                                                                        |
| early onset of arterial hypertension | Did most affected family members reach kidney failure? At an age < 58 years?                     |
| family history                  |                                                                                                  |

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

**ERA WGIKD / ERKNet Position Statement 2021**

Indication to prescribe the vasopressin V2 receptor antagonist tolvaptan:
1. eGFR ≥ 25 ml/min/1.73m²
2. Age ≤ 55 years
3. ( Likely) fast disease progression, as defined in the algorithm below

**EgFR indexed for age is compatible with (likely) fast disease progression**

- 18 - 39 yr: any eGFR
- 40 - 44 yr: eGFR < 90 ml/min/1.73m²
- 45 - 49 yr: eGFR < 75 ml/min/1.73m²
- 50 - 55 yr: eGFR < 60 ml/min/1.73m²

**Historical fast eGFR decline, with no other confounding cause than ADPKD?**

- Reliability eGFR decline ≥ 3.0 ml/min/1.73 m² per year over a period of ≥ 4 years?
- Not available or not reliable (e.g. CKD1)

**Predicted progression by baseline hTKV indexed for age and additional evidence:**
1. hTKV compatible with Mayo class 1D or 1E
2. In case of Mayo class 1C look for additional evidence for rapid progression

**Figure 3: Updated algorithm to assess (likely) fast disease progression as 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 that 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 ≥ 1g/d, signs for vascular disease (e.g. CHD, 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, PRO-PKD score > 6, early hypertension / urological manifestations, truncating PKD1 mutation, family history (onset kidney replacement therapy < 60 years in ≥ 2 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 PRO-PKD score > 6, early hypertension / urological manifestations, truncating PKD1 mutation, family history (onset dialysis < 60 years in ≥ 2 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, 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/1.73m2 or an age >55 years. Of the remaining 463 patients, 248 (53.6%) would be 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 age while 18.4% showed other evidence predicting slowly progressive disease.

Nearly all patients with Mayo class 1E would qualify for treatment, whilst by far the majority of 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 PKD 1 truncating mutation, albeit slightly less clear than for Mayo class 1E and D. Patients with an indication for treatment according to the algorithm had an average annual rate of eGFR decline of 4.12 ml/min/1.73m2 versus 2.12 ml/min/1.73m2 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 Fig. 2) and as such shows the true velocity of disease progression, whilst TKV /Mayo Class rather predicts disease progression or allows to attribute eGFR loss to ADPKD. Taken together, as indicated above, a holistic approach is indeed required in all cases of doubt.

**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. 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) and copeptin – serving as a surrogate parameter for AVP levels – as well as urinary MCP-1 and B2MG.
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 and would also be applicable to ADPKD. In addition to biochemical markers, novel imaging-based predictors are actively being explored. MRI images are an extremely rich source of data that provides information on tissue composition beyond mere kidney volume. This source can be mined using novel approaches such as texture analyses or T2-mapping. In conclusion, despite promising first results, there are currently no newly established biomarkers that can be used on a routine base 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. Lowering of urine osmolality and increased aquaresis/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 posthoc analysis of TEMPO 3:4 suggested that suppression of urine osmolality in morning spot urine samples below 250 mOsmol/l was not associated with an added benefit. However, patients with ADPKD show a baseline defect in concentrating urine 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 below). The relative increase in serum copeptin levels associated with tolvaptan has been shown to predict outcome in patients on tolvaptan. While this may suggest copeptin to be a potential biomarker to monitor the response to tolvaptan and identify individuals that benefit most from this therapy, there is currently not sufficient data to recommend this for routine clinical practice. Changes in eGFR and TKV on tolvaptan treatment may be compared with trends in pre-treatment 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 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. 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. SGLT-2 inhibitors for diabetic nephropathy. Nonetheless, determining urine volume, osmolality, and body weight are helpful tools to monitor adherence and feasibility of the therapy with tolvaptan (see section on management of side effects below). A more detailed discussion of potential markers to guide dose selection is provided in the next section.
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 mg, 60/30 mg, 90/30 mg), all to be taken twice daily with the first dose taken early in the morning and the second dose 8 hours later based on the pharmacokinetic profile of tolvaptan. 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 below 300 mOsmol/l was achieved in more subjects on higher doses with 90/30 mg being the highest tolerated dose. 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 below 250 mOsmol/l was not associated with greater benefit in a posthoc analysis of TEMPO 3:4. However, it is not known what is the minimum level of blockade required to provide treatment benefits in individual patients. Furthermore, urine concentrating capacity is impaired in ADPKD, especially in later-stage patients, 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-hour blockade of the 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 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 rather be guided by feasibility and quality of life 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 to 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 per 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 on tolvaptan in ADPKD. 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-hour 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 liters in the untreated situation to 7 liters on tolvaptan (an increase of 5 liters), whereas in later stage disease urine volume starts at 3 liters in the untreated situation and rises to 5 liters on tolvaptan, an increase of only 2 liters. This phenomenon is likely to be the reason, why a greater number of younger subjects stop treatment. This is indeed a relevant problem in clinical practice because, as reasoned above, start of treatment at a young age would yield the greatest absolute benefit with respect to delaying the onset of kidney failure. Carefully counselling younger subjects and providing practical suggestions how to minimize problems with polyuria (see section on practical considerations below) and how to deal with polyuria in daily life are therefore essential.

Hepatotoxicity is rare and the underlying mechanism is still poorly understood. An increase of transaminases above 3-fold the upper limit of normal (ULN) is observed in approximately 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’s law criteria, which imply 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 10 months and at 3-monthly intervals thereafter. 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’s law criteria were detected.

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. 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) has also issued according information material.

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 / BUN – provide information regarding water / salt balance and volume status in patients on tolvaptan.

**Recommendation 10.1:** We recommend discussing adverse effects and impact 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 three 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 approximately 5-8 liters per 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 2-3x/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 the second pill too late in the afternoon to prevent excessive nocturia may be helpful advice. In our experience, especially 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 the real-life setting.\(^5,7\) 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. Sodium intake can be assessed using repetitive 24-hour 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. 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. However, published experiences regarding the combination of diuretics and tolvaptan are limited.\(^6\) 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 (international 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.\(^7,8\) It is important to note, that this specifically refers to water intake since other fluids, like sodas, come at added health risks when consumed at high volumes. Compared to the impact of increased fluid intake, tolvaptan treatment leads to a strong increase of vasopressin levels (AVP).\(^45\) Whilst 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.\(^30\) An ongoing
multicenter randomized clinical trial is currently investigating the effect of increased fluid intake in ADPKD on TKV, vasopressin activity and eGFR\textsuperscript{31}; however, to date there is 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\textsuperscript{54}. Despite this, tolvaptan was superior in reducing 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-hour V2R blockade\textsuperscript{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 loss of kidney function\textsuperscript{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. 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 to 5 gram per day) and a high water (3 to 4 liters per day) intake to improve the rate of disease progression.

"The need for expertise regarding the decision-making and counselling process"

According to the provisions set by the EMA, tolvaptan treatment must be initiated and monitored under the supervision of physicians with expertise in managing ADPKD and a full understanding of the risks of tolvaptan therapy including hepatotoxicity and monitoring requirements. The proposed algorithm provides guidance to assist general nephrologists in the selection and management of ADPKD patients on tolvaptan treatment. However, it is advisable that small centers with only a few ADPKD patients that are potentially eligible for tolvaptan treatment take the opportunity to consult an experienced center regarding the selection of individual patients, including evaluation of MRIs, patient counseling and the management of side effects. This algorithm aims to provide an evidence-based medical guidance consensus. Prescribing physicians should also be aware of national reimbursement criteria that may differ from the updated algorithm.

**Recommendation 13:** We suggest that the initial treatment decision and patient counseling regarding this treatment option should be performed by a nephrologist experienced in the use of tolvaptan for ADPKD.

**CONCLUSIONS**

Since its approval for ADPKD by the European Medicines Agency 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 the real-world setting 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 over the next years.
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CONFLICT OF INTEREST STATEMENT
The Dept. 2 of Internal Medicine received grants from Otsuka (manufacturer of tolvaptan) and Thermo Fisher Scientific (manufacturer of assays to determine copeptin). RUM received remuneration as an advisor and lecturer from the same companies.
RTG 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).
RT was a member of the Independent data Monitoring Committee for the TEMPO 3:4 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).
DM reports research grants and/or remunerations paid to her institutions (KU Leuven/ UZleuven) from Otsuka, Galapagos and Sanofi-Genzyme.
FS is the chair of the pediatric Tolvaptan trial program and has received remunerations from Otsuka for this and other consulting activities.
Table 2. Baseline characteristics of adult ADPKD patients from the UMCG overall (n=878) and according to outcome in the updated flowchart.

|                        | All (n=878) | eGFR or age outside indication (n=196) | Age too high (≥ 55 years) (n=219) | Indication for treatment | Rapid progression | Likely rapid progression | eGFR indexed for age too high | No treatment | Likely slow progression |
|------------------------|------------|--------------------------------------|-----------------------------------|--------------------------|-------------------|--------------------------|----------------------------|--------------|------------------------|
| **Female, n (%)**      | 507 (57.7%)| 89 (45.4%)                           | 128 (58.4%)                       | (n=91)                   | 49 (52.7)         | 91 (58.0)                | (n=79)                     | (n=51)      | (n=85)                 |
| **Age (years)**        | 49.9 ± 11.1| 54.2 ± 9.3                            | 61.4 ± 5.17                       | 4.7 ± 7.25               | 40.0 ± 8.89       |                           | 48.7 ± 4.32               | 44.3 ± 6.10 | 41.2 ± 9.69            |
| **eGFR (mL/min/1.73m²)** | 50.5 ± 28.8| 16.4 ± 5.13                           | 47.9 ± 17.4                       | 48.5 ± 17.7              | 62.2 ± 28.6       |                           | 83.4 ± 16.5               | 62.2 ± 19.2 | 75.5 ± 29.5            |
| **htTKV (mL/m²)**      | 92.0 (571-1422) | 1313 (963-1855)                     | 837 (546-1351)                    | 948 (699-1552)           | 1062 (740-1538)   |                           | 580 (374-936)             | 647 (430-968) | 430 (326-639)          |
| **CKD stage**          |            |                                      |                                   |                          |                   |                          |                           |             |                        |
| - 1                    | 91 (10.4%) | 0 (0.0%)                             | 8 (3.7)                           | 0 (0.0)                  | 33 (21.0)         | 22 (27.8)                | 0 (0.0)                   | 28 (32.9)   |                        |
| - 2                    | 207 (23.6%)| 0 (0.0%)                             | 43 (19.6)                         | 25 (26.9)                | 28 (17.8)         | 57 (72.2)                | 32 (60.4)                | 24 (28.2)   |                        |
| - 3a                   | 144 (16.4%)| 0 (0.0%)                             | 55 (25.1)                         | 22 (23.7)                | 39 (24.8)         | 0 (0.0)                  | 9 (17.0)                 | 19 (22.4)   |                        |
| - 3b                   | 172 (19.6%)| 0 (0.0%)                             | 81 (37.0)                         | 30 (32.3)                | 45 (28.7)         | 0 (0.0)                  | 8 (15.1)                 | 10 (11.8)   |                        |
| - 4                    | 212 (24.1%)| 344 (73.5)                           | 32 (14.6)                         | 16 (17.2)                | 12 (7.6)          | 0 (0.0)                  | 4 (7.5)                  | 4 (4.7)     |                        |
| - 5                    | 52 (5.9%)  | 52 (26.5)                            | 0 (0.0)                           | 0 (0.0)                  | 0 (0.0)           | 0 (0.0)                  | 0 (0.0)                  | 0 (0.0)     |                        |
| **Mayo htTKV class, n (%)** |            |                                      |                                   |                          |                   |                          |                           |             |                        |
| - 1E                   | 116 (13.2%)| 33 (16.8)                            | 1 (0.5)                           | 25 (26.9)                | 51 (27.5)         | 2 (2.5)                  | 4 (7.5)                  | 0 (0.0)     |                        |
| - 1D                   | 185 (21.1%)| 53 (27.0)                            | 26 (11.9)                         | 28 (30.3)                | 37 (19.7)         | 10 (12.7)                | 9 (17.0)                 | 0 (0.0)     |                        |
| - 1C                   | 271 (30.9%)| 73 (37.2)                            | 64 (29.2)                         | 26 (28.0)                | 41 (21.6)         | 16 (20.3)                | 19 (35.8)                | 32 (37.6)   |                        |
| - 1B                   | 151 (17.2%)| 11 (5.6)                             | 59 (26.9)                         | 9 (9.7)                  | 0 (0.0)           | 22 (27.8)                | 11 (20.8)                | 39 (45.9)   |                        |
| - 1A                   | 36 (4.1%)  | 1 (0.5)                              | 18 (8.2)                          | 0 (0.0)                  | 0 (0.0)           | 8 (10.1)                 | 4 (7.5)                  | 5 (5.9)     |                        |
| - 2                    | 25 (2.8%)  | 4 (2.0)                              | 14 (6.4)                          | 0 (0.0)                  | 0 (0.0)           | 2 (2.5)                  | 1 (1.9)                  | 4 (4.7)     |                        |
| - Missing              | 94 (10.7%) | 21 (10.7)                            | 37 (16.9)                         | 5 (5.4)                  | 6 (3.8)           | 19 (24.1)                | 5 (9.4)                  | 5 (5.9)     |                        |
| **PKD mutation**       |            |                                      |                                   |                          |                   |                          |                           |             |                        |
| - PKD-1 truncating      | 345 (39.3%)| 86 (43.9)                            | 38 (17.4)                         | 54 (58.1)                | 106 (67.5)        | 22 (27.8)                | 23 (43.4)                | 16 (18.8)   |                        |
| - PKD-1 non-truncating | 200 (22.8%)| 47 (24.0)                            | 46 (21.0)                         | 25 (26.9)                | 21 (13.4)         | 17 (21.5)                | 14 (26.4)                | 30 (35.3)   |                        |
| - PKD-2                 | 174 (19.9%)| 27 (13.8)                            | 73 (33.3)                         | 7 (7.5)                  | 5 (3.2)           | 23 (29.1)                | 6 (11.3)                 | 4 (4.7)     |                        |
| - PKD-1 unknown*       | 11 (1.3%)  | 3 (1.5)                              | 12 (5.5)                          | 0 (0.0)                  | 2 (1.3)           | 1 (1.3)                  | 1 (1.9)                  | 0 (0.0)     |                        |
| - Other (e.g. GANAB)    | 2 (0.2%)   | 0 (0.0)                              | 2 (0.9)                           | 0 (0.0)                  | 0 (0.0)           | 1 (1.3)                  | 0 (0.0)                  | 1 (1.2)     |                        |
| - No mutation detected | 38 (4.3%)  | 5 (2.6)                              | 18 (8.2)                          | 0 (0.0)                  | 3 (1.9)           | 3 (3.8)                  | 5 (9.4)                  | 4 (4.7)     |                        |
| - Missing              | 108 (12.3%)| 28 (14.2)                            | 30 (13.7)                         | 7 (7.5)                  | 20 (12.7)         | 12 (15.2)                | 4 (7.6)                  | 11 (13.0)   |                        |

Variables are presented as mean ± SD, or as median (IQR) in case of non-normal distribution. Abbreviations are: n, number; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; htTKV, height adjusted total kidney volume; PKD, polycystic kidney disease. * Not possible to decide truncating/non-truncating
Table 3. Annual change in eGFR of adult ADPKD patients from the UMCG overall (n=878) and according to outcome in the updated flowchart.

|                         | All                  | eGFR or age outside indication | Indication for treatment | No treatment                  |
|-------------------------|----------------------|--------------------------------|--------------------------|------------------------------|
|                         | (n=878)              | (n=196)                        | (n=219)                  | (n=79)                       |
| Period of historical measurements (years) | 4.15 ± 3.10         | 4.43 ± 3.25                    | 4.00 ± 2.86              | 4.09 ± 3.29                  |
| Number of measurements  | 8 (5-19)             | 18 (7-21)                      | 7 (5-19)                 | 6 (4-7)                      |
| Annual change in eGFR  | -3.41 ± 2.19         | -4.69 ± 1.53                   | -2.76 ± 1.44             | -1.94 ± 3.89                 |

Variables are presented as mean ± SD, or as median (IQR) in case of non-normal distribution.
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