ADPKD
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Recommendations for the use of tolvaptan in ADPKD: a proposal to update the ERA-EDTA decision algorithm

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Unpublished
Chapter 10

ABSTRACT

In 2016, the ERA-EDTA Working Groups of Inherited Kidney Disorders and European Renal Best Practice provided a series of recommendations which ADPKD patients to treat with tolvaptan. This resulted in a hierarchical decision algorithm. In this paper we provide an update of these recommendations now results of another large clinical trial with tolvaptan (the REPRISE study) have become available and clinical experience with tolvaptan has been acquired. Given these data, the eGFR threshold to initiate tolvaptan treatment, can be lowered to 30 ml/min/1.73m² and the age threshold increased to 55 years of age. Based on experiences from clinical care, the hierarchical decision algorithm can also be simplified. With examples from clinical care we provide evidence that selection based on eGFR and age alone is already a sensitive parameter to select patients with rapidly progressive disease. The decision algorithm may therefore be changed to an algorithm largely focused on CKD stage by age.
INTRODUCTION

In May 2015 the European Medicines Agency (EMA) approved the use of the vasopressin V2 receptor antagonist tolvaptan to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD). This approval was based on the results of TEMPO 3:4 trial, a randomized controlled clinical trial, in which the efficacy of tolvaptan was tested in 1445 ADPKD patients with relatively early stage disease (estimated creatinine clearance (Cockroft-Gault) ≥60 ml/min). This study showed that tolvaptan slowed the rate of TKV growth by 49%, from 5.5 to 2.8% per year, and the rate of estimated GFR (eGFR) loss on treatment by 26%, from 3.70 to 2.72 ml/min/1.73 m² per year, during the median observation period of 3 years. Provided that this effect is maintained, it would translate into every 4 years of treatment delaying the incidence of end stage kidney disease by approximately one additional year.

According to the EMA label, tolvaptan ‘is indicated to slow the progression of cyst development and renal insufficiency of ADPKD in adults with CKD stages 1-3 at initiation of treatment with evidence of rapidly progressing disease’. This indication needed clarification at which CKD stage and age patients were qualified for treatment and how ‘evidence of rapidly progressing disease’ is defined. Therefore the ERA-EDTA working groups on inherited kidney disorders (WGIKD) and European renal best practice (ERBP) provided a recommendation on how to use tolvaptan for ADPKD in clinical care. Partly based on these recommendations, tolvaptan has now been incorporated in clinical care by regulatory authorities of several countries in Europe.

Recently, the results of another large clinical trial with tolvaptan have become available (the REPRISE study), which included patients with later stage ADPKD (eGFR (CKD-EPI) 25-65 ml/min/1.73m²). With these new results, and now clinical experience with tolvaptan has been acquired, the position statement by the WGIKD and ERBP needs to be updated. In this paper we provide an updated recommendation for the use of tolvaptan in clinical care and show what the consequences of this update are in terms of number of patients eligible for tolvaptan treatment.
INITIAL POSITION STATEMENT BY THE WGIKD AND ERBP

As previously stated, tolvaptan is indicated by the EMA in patients with ADPKD with CKD stages 1-3 (i.e. eGFR>30 ml/min/1.73m²). However, the WGIKD and ERBP recommended to only prescribe tolvaptan in patients with CKD stages 1-3a (i.e. eGFR>45 ml/min/1.73m²), because information on the benefit-to-risk ratio of tolvaptan in patients with CKD stage 3b (i.e. eGFR 30-45 ml/min/1.73m²) was too limited to warrant treatment. The TEMPO 3:4 trial included patients with an estimated creatinine clearance (Cockroft-Gault) ≥60 ml/min/1.73m². Due to tubular creatinine secretion, creatinine clearance overestimates GFR⁴ and consequently, the TEMPO 3:4 trial did include a considerable number of ADPKD patients with an eGFR (CKD-EPI equation) of <60 ml/min/1.73m² (n=247; 17%). Yet, the number of patients with CKD stage 3b (i.e. eGFR 30-45 ml/min/1.73m²) was small (n=42, 3%). With the recent publication of the REPRISE study, more information has become available on the benefit-to-risk ratio of tolvaptan in patients with CKD stage 3b.

RESULTS OF THE REPRISE STUDY

In November 2017, the results of the REPRISE study have become available⁵. In this double blinded trial, 1370 patients with ADPKD, who tolerated tolvaptan at daily morning/afternoon doses of 60/30 mg, or 90/30 mg, respectively, were randomly assigned in a 1:1 ratio, to receive tolvaptan or matching placebo for 12 months. Down-titration of the dose to morning/afternoon doses of 45/15 mg, or of 30/15 mg, respectively, was permitted during the trial period. Inclusion criteria were age 18-55 years and eGFR (CKD-EPI equation) 25-65 ml/min/1.73m² or age 56-65 years, eGFR 25-44 ml/min/1.73m² and historical rate of eGFR loss of ≥ 2.5 ml/min/year. This study showed that tolvaptan decreased eGFR loss (primary endpoint), by 35% from 3.61 to 2.34 ml/min/1.73m² at 1 year and slowed the rate of eGFR loss, with adjustment for the acute effect of tolvaptan (secondary endpoint), by 24% from 4.17 to 3.16 ml/min/1.73m². Prespecified subgroup analyses showed a beneficial effect of tolvaptan in patients with CKD stage 3b (mean change in eGFR in 432 patients receiving tolvaptan versus 423 patients receiving placebo, -3.20 versus -3.99 ml/min/1.73m², difference 20%, p<0.001). Of note, a beneficial effect was also seen in patients with CKD stage 2, 3a and 4. No beneficial effect of tolvaptan was seen in patients who were older.
than 55 years with an eGFR between 25-44 ml/min/1.73m², because these patients had slowly progressive disease.

Although the REPRISE study included patients with more advanced ADPKD, the observed safety profile of tolvaptan was comparable to that observed in the TEMPO 3:4 trial. Elevations in liver-enzyme levels were, as in the TEMPO 3:4 trial, seen between 60 and 240 days after initiation of tolvaptan and became less frequent thereafter. No new cases of elevations in liver enzymes and bilirubin levels were identified that met Hy’s law criteria (serum alanine aminotransferase level >3 and bilirubin level >2 times the upper limit of the normal range)⁵.

CURRENT RECOMMENDATION AND ADJUSTMENTS BASED ON RESULTS OF THE REPRISE STUDY

Because the REPRISE study showed a beneficial effect of tolvaptan in patients with later stage ADPKD and showed a comparable safety profile of this drug as seen in the TEMPO 3:4 trial, the recommendation to prescribe tolvaptan can be extended to patients with CKD stage 3b (i.e. eGFR 30-45 ml/min/1.73m²). The REPRISE study also showed a statistical significant beneficial effect of tolvaptan in CKD stage 4. One might therefore argue to extend the recommendation even further. In this respect, the EMA very recently adopted an extension to the existing indication to initiate tolvaptan treatment in patients with CKD stages 4. In our opinion, it is, however, debatable if tolvaptan will have a beneficial effect in patients with CKD stage 4. First, in the REPRISE study, no patients were included with CKD stage 4 with a kidney function <25 ml/min/1.73m², so the effect of tolvaptan below this kidney function remains unknown. Second, tolvaptan has an effect on renal hemodynamics which results in a reversible drop in kidney function shortly after treatment is started. Its chronic structural renoprotective effect will only become apparent after months of treatment. Initiating tolvaptan treatment in a patient with CKD stage 4 may therefore delay end stage kidney disease for a very limited period of time. Keeping the risk-to-benefit ratio of tolvaptan in mind, starting tolvaptan in patients with CKD stage 4 will, for this reason, probably not lead to a clinical relevant benefit. This emphasizes that tolvaptan treatment should be initiated as early as possible in the disease course. However, many other factors than eligibility play a role in the decision to initiate
tolvaptan treatment, like patients motivation. And therefore, the decision to initiate tolvaptan treatment requires shared-decision making with the patient.

According to the EMA label, tolvaptan is indicated in patients with evidence of rapidly progressive disease. As there is no generally accepted definition of rapidly progressive ADPKD, the WGKID and the ERBP provided a series of recommendations resulting in a hierarchical decision algorithm that encompasses a sequence of risk-factor assessments for rapid disease progression in a descending order of reliability. Because ADPKD progresses steadily over time, markers of disease severity and prognosis must be interpreted in conjunction with age. For instance, ADPKD patients with a relatively high eGFR for their age are unlikely to show rapid disease progression in the future. There is no generally accepted definition at which age and what eGFR a patient has slowly or rapidly progressive disease. As the main renal outcome of ADPKD is end stage kidney disease, it seems logical to define rapidly progressive disease as the occurrence of end stage kidney disease (eGFR ≤ 15 ml/min/1.73m²) before the average age for initiation of kidney replacement therapy, which in Europe is around 58 years of age. This resulted in the first step of the hierarchical decision algorithm, which recommends not to not start tolvaptan in patients aged >50 years who still have an eGFR >45 ml/min/1.73m² (CKD stage 1-3a), because these patients have a high probability of slowly progressive disease. Likewise, this recommendation states not to treat patients aged 40–50 years who have an eGFR >60 ml/min/1.73m² (CKD stages 1 and 2), or patients 30–40 years who have an eGFR >90 ml/min/1.73m² (CKD stage 1). By extending the recommendation to start tolvaptan in patients with CKD stage 3b and taking the previous recommendations into account, the age threshold may now be extended to patients aged 55 years. The recommendation not to treat patients aged >55 years with an eGFR >30 ml/min/1.73m² seems to be valid as tolvaptan was not effective in patients >55 years with an eGFR of 25-44 ml/min/1.73m² in the REPRISE study because, as expected, these patients had slowly progressive disease with an average eGFR decline in the placebo group of 2.34 ml/min/1.73m².

To demonstrate what the current update means for clinical care, in terms of increase in number of patients eligible for tolvaptan treatment, we applied the hierarchical decision algorithm to all adult ADPKD patients from the University Medical Center of Groningen (UMCG), the Netherlands (n=386). We first applied the decision algorithm according to the initial recommendations of the WGIKD and ERBP (Figure 1, upper panel). A priori we predicted that a quarter of patients would be eligible for tolvaptan treatment, like patients motivation. And therefore, the decision to initiate tolvaptan treatment requires shared-decision making with the patient.
by reasoning that approximately half of patients would not meet the eGFR and/or age criteria and of the patients who did meet these criteria, approximately half would not show signs of rapid disease progression. When we applied the decision algorithm to our patient population, 76 patients of 386 were eligible for tolvaptan, which is approximately 20%. By lowering the eGFR threshold to 30 ml/min/1.73m² and age threshold to 55 years (Figure 1, lower panel), 30 additional patients became eligible for tolvaptan (27% of total patient cohort). Table 1 represents characteristics of patients according to the outcome of the decision algorithm with the updated criteria. Patients with fast progression had lower eGFR and higher htTKV compared to patients with likely slow progression. Patients with predicted fast progression were in general younger and had a higher eGFR compared to patients with fast progression, but had a lower eGFR and higher htTKV compared to patients with likely slow progression.
Figure 1. Algorithm to assess indications for tolvaptan treatment in ADPKD with lower eGFR threshold of 45 ml/min/1.73m² and upper age threshold of 50 years (upper panel), or lower eGFR threshold of 30 ml/min/1.73m² and upper age threshold of 55 years (lower panel) with results for adult patients from the University Medical Center Groningen, the Netherlands (n=386).
### Table 3. Baseline characteristics of adults ADPKD patients from the University Medical Center Groningen overall and according to outcome in the flowchart.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=386)</th>
<th>Fast progression (n=18)</th>
<th>Predicted fast progression (n=88)</th>
<th>Likely slow progression (n=129)</th>
<th>eGFR ≤ 30 and age &lt;55 (n=54)</th>
<th>eGFR ≤ 30 and age ≥ 55 (n=36)</th>
<th>eGFR &gt; 30 and age ≥ 55 (n=59)</th>
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<tbody>
<tr>
<td>Female, n (%)</td>
<td>198 (51.3)</td>
<td>12 (66.7)</td>
<td>45 (51.1)</td>
<td>77 (59.7)</td>
<td>18 (33.3)</td>
<td>17 (47.2)</td>
<td>27 (45.8)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46.4 ± 11.3</td>
<td>42.1 ± 6.3</td>
<td>36.7 ± 9.4</td>
<td>44.7 ± 7.5</td>
<td>44.4 ± 6.5</td>
<td>60.8 ± 4.9</td>
<td>60.2 ± 4.3</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>178 ± 10</td>
<td>177 ± 9</td>
<td>179 ± 10</td>
<td>177 ± 9.7</td>
<td>180 ± 10</td>
<td>177 ± 11</td>
<td>177 ± 9</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m2)</td>
<td>55.0 ± 30.4</td>
<td>53.2 ± 17.2</td>
<td>68.6 ± 29.3</td>
<td>74.2 ± 21.7</td>
<td>17.8 ± 7.7</td>
<td>15.9 ± 7.6</td>
<td>53.2 ± 15.9</td>
</tr>
<tr>
<td>htTKV (ml/m)</td>
<td>1055 (594-1367)</td>
<td>1062 (555-1212)</td>
<td>1051 (597-1423)</td>
<td>639 (424-1003)</td>
<td>1408 (955-2217)</td>
<td>1340 (921-1855)</td>
<td>765 (485-1215)</td>
</tr>
<tr>
<td>CKD stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 1</td>
<td>52 (13.5)</td>
<td>0 (0.0)</td>
<td>21 (23.9)</td>
<td>30 (23.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.7)</td>
</tr>
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<td>- 2</td>
<td>111 (28.2)</td>
<td>6 (33.3)</td>
<td>21 (23.9)</td>
<td>64 (49.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>20 (33.9)</td>
</tr>
<tr>
<td>- 3a</td>
<td>73 (18.9)</td>
<td>5 (27.8)</td>
<td>23 (26.1)</td>
<td>29 (22.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>15 (25.4)</td>
</tr>
<tr>
<td>- 3b</td>
<td>60 (15.5)</td>
<td>7 (38.9)</td>
<td>23 (26.1)</td>
<td>6 (4.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>23 (39.0)</td>
</tr>
<tr>
<td>- 4</td>
<td>52 (13.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>34 (63.0)</td>
<td>18 (50.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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<tr>
<td>- 5</td>
<td>38 (9.8)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>20 (37.0)</td>
<td>18 (50.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Mayo htTKV class, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>- 1A</td>
<td>12 (3.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>9 (7.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (5.1)</td>
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<tr>
<td>- 1B</td>
<td>51 (13.1)</td>
<td>1 (5.6)</td>
<td>0 (0.0)</td>
<td>30 (23.3)</td>
<td>0 (0.0)</td>
<td>7 (19.4)</td>
<td>13 (22.0)</td>
</tr>
<tr>
<td>- 1C</td>
<td>100 (26.8)</td>
<td>5 (27.8)</td>
<td>25 (28.4)</td>
<td>27 (20.9)</td>
<td>11 (20.4)</td>
<td>16 (44.4)</td>
<td>16 (27.1)</td>
</tr>
<tr>
<td>- 1D</td>
<td>74 (19.1)</td>
<td>8 (44.4)</td>
<td>33 (37.5)</td>
<td>14 (10.9)</td>
<td>15 (27.8)</td>
<td>4 (11.1)</td>
<td>0 (0.0)</td>
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<tr>
<td>- 1E</td>
<td>49 (12.6)</td>
<td>2 (11.1)</td>
<td>26 (29.5)</td>
<td>4 (3.1)</td>
<td>15 (27.8)</td>
<td>2 (5.6)</td>
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</tr>
<tr>
<td>- 2</td>
<td>16 (4.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>8 (6.2)</td>
<td>1 (1.9)</td>
<td>1 (2.8)</td>
<td>6 (10.2)</td>
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<tr>
<td>- Missing</td>
<td>84 (21.8)</td>
<td>2 (11.1)</td>
<td>4 (4.5)</td>
<td>37 (28.7)</td>
<td>12 (22.2)</td>
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<td>- PKD mutation</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>- PKD-1 truncating</td>
<td>99 (25.5)</td>
<td>9 (50.0)</td>
<td>30 (34.1)</td>
<td>26 (20.2)</td>
<td>19 (35.2)</td>
<td>8 (22.2)</td>
<td>8 (13.6)</td>
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<tr>
<td>- PKD-1 non-truncating</td>
<td>73 (18.8)</td>
<td>5 (27.8)</td>
<td>13 (14.8)</td>
<td>29 (22.5)</td>
<td>9 (16.7)</td>
<td>11 (30.6)</td>
<td>6 (10.2)</td>
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<tr>
<td>- PKD-2</td>
<td>42 (10.8)</td>
<td>0 (0.0)</td>
<td>6 (6.8)</td>
<td>13 (10.1)</td>
<td>3 (5.6)</td>
<td>4 (11.1)</td>
<td>15 (25.4)</td>
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<tr>
<td>- PKD-1 unknown*</td>
<td>5 (1.3)</td>
<td>1 (5.6)</td>
<td>1 (1.1)</td>
<td>3 (2.3)</td>
<td>0 (0.0)</td>
<td>1 (2.8)</td>
<td>0 (0.0)</td>
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<tr>
<td>- No mutation detected</td>
<td>8 (2.1)</td>
<td>0 (0.0)</td>
<td>2 (2.3)</td>
<td>3 (2.3)</td>
<td>1 (1.9)</td>
<td>0 (0.0)</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>- Missing</td>
<td>159 (41.2)</td>
<td>3 (16.7)</td>
<td>36 (40.9)</td>
<td>55 (42.6)</td>
<td>22 (40.7)</td>
<td>12 (33.4)</td>
<td>28 (47.5)</td>
</tr>
</tbody>
</table>

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.
Chapter 10

A SIMPLIFIED DECISION ALGORITHM BASED ON EXPERIENCE FROM CLINICAL CARE AND NEW INSIGHTS FROM OTHER CLINICAL STUDIES

Besides the adjustment of the eGFR and age thresholds to initiate tolvaptan treatment, the hierarchical decision algorithm may need more adjustments now clinical experience with tolvaptan has been acquired.

When working with the hierarchical decision algorithm from Figure 1, it was noticed that the algorithm was quite extensive and sometimes difficult to use. In routine clinical care, often only age and one GFR value is available to complete the first step of the algorithm. When patients have more historical GFR data available for the second step in the algorithm, it was noticed that the criterion of an eGFR decline of ≥ 5 ml/min/1.73m² in one year in the second step of the algorithm was of little value. This criterion was sometimes easily met, while a patient had a rather stable kidney function when more data over a longer time was taken into account. The second definition of rapidly progressive disease based on historical eGFR decline was an average eGFR decline of ≥ 2.5 ml/min/1.73m² over a period of 5 years. All large clinical trials that have been published have, so far, reported a more rapid eGFR decline in patients with ADPKD. Therefore there may be a reasonable chance that with this definition, patients with slowly progressive disease are selected for tolvaptan treatment. For example, the average eGFR decline in the placebo group of the TEMPO 3:4¹ (n=484) and REPRISE study² (n=687) were 3.70 and 3.61 ml/min/1.73m² per year respectively. However, these clinical trials were enriched for patients with rapidly progressive disease. A less selective observational cohort form our center (n=104), for example, had an average eGFR decline of 3.22 ml/min/1.73m². We would therefore like to propose adjustment of this criterion to an eGFR decline > 3.0 ml/min/1.73m² over a period of 5 years to select patients for tolvaptan treatment. When patients do not have historical eGFR data available, patients end up in the third step op of the algorithm: historical kidney growth. However, most patients do not have historical data available on kidney growth and therefore end up in the fourth step of the algorithm: prediction of disease progression. When no imaging or genetic data are available at the moment of screening to assess eligibility for tolvaptan treatment, the patient ends up in the fifth step: predicted progression by family history. Although family history can easily be obtained at the outpatient clinic, it is of little value compared to the other parameters. Moreover, in these cases, imaging can easily be performed to
predict disease progression and is a faster and cheaper option compared to genetic testing. Keeping this clinical experience in mind, the algorithm may be simplified as presented in Figure 2.

**Figure 2.** Simplified algorithm to assess indication for tolvaptan treatment in ADPKD with eGFR threshold of 30 ml/min/1.73m², age criteria <55 years, and results for adult patients from the University Medical Center Groningen (n=386).

**A SIMPLIFIED DECISION ALGORITHM LARGELY FOCUSED ON CKD STAGE BY AGE; EXAMPLES FROM CLINICAL CARE**

The hierarchical decision algorithm is based on the assumption that patients with rapidly progressive disease will benefit the most from tolvaptan treatment and that GFR for age, or historical changes in GFR, provide more information on rate of disease progression than (change in) TKV or PKD gene mutation analysis. It can be even reasoned that one might even need no other parameters than just one GFR and age value to assess evidence of rapidly progressive disease for treatment selection. As data was available for multiple steps in the algorithm for 386 patients with ADPKD from the University Medical Center Groningen, we investigated if we could provide evidence to support this hypothesis.

**CKD stage by age**

The first step of the decision algorithm is based on CKD stage by age. When strictly following this algorithm, patients who are 50 or 40 years of age with a GFR of 60 ml/min/1.73m² will both be eligible for tolvaptan treatment. In this example, the patient of 50 years of age is probably a slower progressor and of 40 years of age a faster progressor. Although the ERA-EDTA algorithm denotes age classes, it is better
to keep a continuous scale of GFR by age in mind in the decision to start tolvaptan treatment. In Figure 3, the eGFR of all 386 patients from the UMCG are plotted against age. In this figure a theoretical line is plotted: Patients below this line are defined as fast progressors and eligible for tolvaptan and patients above this line are defined as slow progressors and ineligible for tolvaptan. Of note, patients younger than 30 years were not taken into account, since in young patients with CKD stage 1, kidney function may be less sensitive for assessment of disease severity, progression and prognosis (as discussed later).

**Figure 3.** Estimated GFR according to age for adult patients from the University Medical Center Groningen (n=386). The dotted line represents threshold for rapidly progressive disease based on eGFR by age and was calculated with the following data points: 35 years of age with an eGFR of 90 ml/min/1.73m², 45 years of age with an eGFR of 60 ml/min/1.73m² and 60 years of age with an eGFR of 15 ml/min/1.73m² (eGFR=195 – 3*age). Grey areas are sections outside the indication for tolvaptan; old situation (upper panel, eGFR<45 ml/min/1.73m² or age>50 years), new situation (lower panel, eGFR<30 ml/min/1.73m² or age>55 years).
**Historical eGFR decline**

In Figure 4 the eGFR of all 386 patients from the UMCG are again plotted against age including the theoretical threshold line. In this figure patients are marked according to a confirmed eGFR decline ≥ or < 3.0 ml/min/1.73m² over a period of five years. Table 2 represents a cross tabulation of patients with ‘likely’ rapidly or slowly progressive disease according to eGFR by age versus ‘proven’ rapidly or slowly progressive disease according to eGFR decline for patients within the age and eGFR criteria of tolvaptan. Overall, concordance between eGFR by age and eGFR decline was 76% ((11+17)/37*100%). When only patients with low eGFR for age are taken into consideration, concordance with rapidly progressive disease as determined by eGFR decline was 81% (17/21*100%).

![Figure 4](image)

**Figure 4.** Rapidly or slowly progressive ADPKD based on eGFR decline versus eGFR by age. The dotted line represents threshold for rapidly progressive disease based on eGFR by age and was calculated with the following data points: 35 years of age with an eGFR of 90 ml/min/1.73m², 45 years of age with an eGFR of 60 ml/min/1.73m² and 60 years of age with an eGFR of 15 ml/min/1.73m² (eGFR=195 - 3*age). Grey areas are sections outside the indication for tolvaptan (eGFR<30 ml/min/1.73m² or age>55 years).
Table 2. Proven slow or fast progressor versus predicted slow or fast progressor according to eGFR by age.

<table>
<thead>
<tr>
<th>Only patients with eGFR&gt;30 and age&lt;55</th>
<th>eGFR decline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proven slow progressor (&lt; 3.0 ml/min/1.73m²)</td>
</tr>
<tr>
<td>Likely slow progressor</td>
<td>11</td>
</tr>
<tr>
<td>Likely fast progressor</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
</tr>
</tbody>
</table>

Predicted progression by baseline htTKV indexed for age

In Figure 5, all 386 patients were again plotted according to eGFR by age with the theoretical threshold line and patients were marked according to rapidly or slowly progressive disease as predicted by the Mayo htTKV classification (i.e. Mayo class 1C-E or 1A-B and 2 respectively). Table 3 represents a cross tabulation of patients with ‘likely’ rapidly or slowly progressive disease according to eGFR by age versus ‘predicted’ rapidly or slowly progressive disease according to the Mayo htTKV classification for patients within the age and eGFR criteria of tolvaptan. Overall, concordance between eGFR by age and the Mayo htTKV classification was 64% ((33+75)/168*100%). When only patients with low eGFR for age are taken into consideration, concordance with rapidly progressive disease as predicted by the Mayo htTKV classification was 86% (75/87*100%).
Figure 5. Rapidly or slowly progressive ADPKD based on Mayo htTKV class versus eGFR by age. The dotted line represents threshold for rapidly progressive disease based on eGFR by age and was calculated with the following data points: 35 years of age with an eGFR of 90 ml/min/1.73m², 45 years of age with an eGFR of 60 ml/min/1.73m² and 60 years of age with an eGFR of 15 ml/min/1.73m² (eGFR=195 – 3*age). Grey areas are sections outside the indication for tolvaptan (eGFR<30 ml/min/1.73m² or age>55 years).

Table 3. Predicted slow or fast progressor according to Mayo htTKV class versus eGFR by age.

<table>
<thead>
<tr>
<th>Mayo htTKV class</th>
<th>Predicted slow progressor (Mayo htTKV class 1A, 1B, 2)</th>
<th>Predicted fast progressor (Mayo htTKV class 1C, 1D, 1E)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely slow progressor</td>
<td>33</td>
<td>48</td>
<td>81</td>
</tr>
<tr>
<td>Likely fast progressor</td>
<td>12</td>
<td>75</td>
<td>87</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>123</td>
<td>168</td>
</tr>
</tbody>
</table>

Predicted progression by genotype

When imaging is not available, ADPKD genotype can also provide information on prognosis. A cross-sectional study of 1341 patients from the Genkyst cohort has been used to establish the ‘PRO-PKD’ risk-scoring system on the basis of PKD mutation as
well as clinical parameters\textsuperscript{9}. When clinical parameters are not available, the ‘Genetic Risk Score’ can be used, which is a score based on sex and genotype only. A genetic score $\geq 2$ points, which incorporates the presence of a truncating $PKD1$ mutation, predicted end stage kidney disease onset before age 65 years with a sensitivity of 73.8%, a specificity of 74.3%, a positive predictive value of 80.4%, and an negative predictive value of 66.6%. In Figure 6 patients are plotted according to eGFR by age with the theoretical threshold line and marked as slowly or rapidly progressive disease predicted by the Genetic Risk Score (i.e. $<2$ or $\geq 2$ respectively). Table 4 represents a cross tabulation of patients with ‘likely’ rapidly or slowly progressive disease according to eGFR by age versus ‘predicted’ rapidly or slowly progressive disease according to the Genetic Risk Score for patients within the age and eGFR criteria of tolvaptan. Overall, concordance between eGFR by age and the Genetic Risk Score was 60% ($\frac{(40+36)}{126}\times100\%$). When only patients with low eGFR for age are taken into consideration, concordance with rapidly progressive disease as predicted by the Genetic Risk Score was 57% ($\frac{36}{63}\times100\%$).

**Figure 6.** Rapidly or slowly progressive ADPKD based on Genetic Risk Score compared to eGFR by age. The dotted line represents threshold for rapidly progressive disease based on eGFR by age and was calculated with the following data points: 35 years of age with an eGFR of 90 ml/min/1.73m$^2$, 45 years of age with an eGFR of 60 ml/min/1.73m$^2$ and 60 years of age with an eGFR of 15 ml/min/1.73m$^2$ (eGFR=195 - $3\times$age). Grey areas are sections outside the indication for tolvaptan (eGFR<30 ml/min/1.73m$^2$ or age>55 years).
Table 4. Predicted slow or fast progressor according to Genetic Risk score versus eGFR by age

<table>
<thead>
<tr>
<th>Genetic Risk Score</th>
<th>Predicted slow progressor (≤ 2 points)</th>
<th>Predicted fast progressor (&gt; 2 points)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely slow progressor</td>
<td>40</td>
<td>23</td>
<td>63</td>
</tr>
<tr>
<td>Likely fast progressor</td>
<td>27</td>
<td>36</td>
<td>63</td>
</tr>
<tr>
<td>Total</td>
<td>67</td>
<td>59</td>
<td>126</td>
</tr>
</tbody>
</table>

Patients <30 years of age with CKD stage 1

As described earlier, young patients (<30 years of age) were not taken into account in the above calculation. In such patients, with CKD stage 1 (eGFR > 90 ml/min/1.73m²), kidney function is less sensitive for assessment of disease severity, progression and prognosis, since eGFR can remain fairly stable during a prolonged period of time due to compensatory hyperfiltration of remnant nephrons that are yet not lost due to disease progression. We would therefore recommend to perform risk prediction in these patients, for instance by imaging and measuring TKV.

A new and more simple decision algorithm

In conclusion, almost all patients that were classified as having rapidly progressive disease according to eGFR by age were also classified as having rapidly progressive disease according to their historical eGFR decline or their Mayo hTKV class. Therefore historical eGFR decline or imaging may not be necessary to assess that a patient has rapidly progressive disease. eGFR by age alone can be used for this purpose. Of note, only half of patients that were classified as having rapidly progressive disease according to eGFR by age were classified as fast progressors according to their Genetic Risk Score (57%). This may be explained because the Genetic Risk Score has a relatively low sensitivity and specificity and is less accurate than the PROPKD score. Unfortunately, clinical parameters were not readily available in a large part of our study population to allow assessment of the PROPKD score.

Remarkably, only 69% of patients classified as having slowly progressive disease according to eGFR by age were classified as having slowly progressive disease according to
to their historical eGFR decline and 41% of these patients had slowly progressive
disease according to their Mayo htTKV classification. This would imply when patients
are selected for tolvaptan treatment by eGFR and age only, some patients with rapidly
progressive disease are ‘misclassified’ and will not receive treatment. However, it
is reasonable to assume that a patient of 55 years of age with an eGFR of 70 ml/
min/1.73m² had slowly progressive disease throughout his lifetime, even though
this patient had a historical eGFR decline of >3.0 ml/min/1.73m² over 5 years, or a
Mayo classification of 1C or higher. When investigating these ‘misclassified’ patients
closer, their average eGFR decline was less than that of patients that were ‘correctly
classified’ with rapidly progressive disease (3.2 ± 0.1 versus 5.0 ± 1.3 ml/min/1.73m²
per year, p<0.001). Furthermore, most of the patients that were ‘misclassified’ based
on imaging, had Mayo class 1C (1C: 54.2%, 1D: 33.3% and 1E: 12.5%) whereas most of
the patients that were ‘correctly classified’ had Mayo class 1D (1C: 28%, 1D: 47% and
1E: 25%). Therefore, we believe that most of these patients are correctly classified
as having slowly progressive disease. However, in case a patient has an eGFR value
just below or above the threshold for eGFR by age, or when eGFR is not reliable (for
example in patients with increased or decreased muscle mass), we would recommend
to use historical eGFR decline, or when not available or reliable, to perform imaging for
risk prediction to assess whether a patient has slowly or rapidly progressive disease.

Taken all above into account, we may simplify the ERA-EDTA decision algorithm into
an algorithm focusing more on CKD stage by age for the decision to initiate tolvaptan
treatment. Other parameters to provide evidence of rapidly progressive disease may
only be necessary if it is not clear whether a patient has rapidly or slowly progressive
disease based on eGFR by age or in in case a patient is young and has CKD stage 1.
This results in the algorithm as presented in Figure 7.
**Recommendation for the use of tolvaptan in ADPKD**

**CONCLUSION**

Now clinical experience with tolvaptan as treatment of ADPKD has been acquired, and with the results of a recent large clinical trial, the recommendations when to initiate tolvaptan treatment need to be updated. We reason that the eGFR threshold can be lowered from 45 to 30 ml/min/1.73m², and that the age threshold can be increased from 50 to 55 years. In addition, we provided an updated and simplified decision algorithm to assess whether tolvaptan treatment is warranted in patients with ADPKD. It is important to emphasize that these are only recommendations to help caregivers in the decision to initiate tolvaptan treatment and not rules that are set in stone. The previous recommendations by the ERA-EDTA unfortunately have led to exclusion of patients from reimbursement of tolvaptan from health care insurances because they were not officially eligible for treatment. The decision to initiate treatment requires the consideration of many factors besides eligibility, like patients motivation and requires shared decision-making with the patient.

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**Figure 7.** Simplified algorithm focused on CKD stage by age to assess indication for tolvaptan treatment in ADPKD with eGFR threshold of 30 ml/min/1.73m² and age criteria <55 years.
REFERENCES

Recommendation for the use of tolvaptan in ADPKD