ABSTRACT

Autosomal-dominant polycystic kidney disease (ADPKD) is the most frequent genetic cause of end-stage renal disease in adults. Affected individuals and families face a significant medical and psychosocial burden due to both renal and extrarenal manifestations. Consequently, interventions that ameliorate the course of the disease and specifically slow down the loss of kidney function are of special interest. Major research efforts in both the clinical and pre-clinical setting in the last two decades resulted in a number of pivotal clinical trials aimed to ameliorate the disease. These studies have underlined the important role of specific supportive measures and provided the basis for first targeted pharmacological therapies. Very recently, the concept of repurposing drugs approved for other conditions for a use in ADPKD has gained increasing attention. Here, we review the current best-practice management of ADPKD patients with a focus on interventions that have reached clinical use to maintain kidney function and give an outlook on future trials and potential novel treatment strategies.

Keywords: ADPKD, clinical trials, management, tolvaptan

INTRODUCTION

Cystic kidney diseases are caused by mutations in genes encoding proteins that are important for the function of primary cilia—a fact that led to the classification of these diseases as ciliopathies [1, 2]. Defective biogenesis or impaired function of primary cilia impacts proliferation, cell survival, polarity and secretion of renal epithelial cells [3]. These cell biological phenotypes are then the basis of cyst formation and progressive loss of kidney function. In the clinical setting, cystic kidney diseases can be separated into several groups of disorders based on age of onset, kidney morphology and extrarenal findings [4, 5]. Primarily, disorders of the nephronophthisis spectrum are distinguished from autosomal-recessive and autosomal-dominant polycystic kidney disease (ADPKD). Furthermore, there is also a significant phenotype–genotype overlap with other entities such as HNF1ß-associated nephropathy [6], autosomal-dominant tubulointerstitial kidney disease [7] and familial tumour syndromes (namely tuberous sclerosis, von-Hippel-Lindau, Birt-Hogg-Dubé and renal coloboma syndromes) [8]. Differential diagnosis of cystic kidney diseases relies primarily on clinical criteria based on kidney morphology and specific extrarenal findings. ADPKD is characterized by bilateral large kidneys showing a distribution of cysts throughout the entire parenchyma (Figure 1). The disorder may cause flank pain, cyst haemorrhage, nephrolithiasis and progressive loss of kidney function. However, cysts do also occur in other organs (e.g. liver,
pancreas, spleen). Moreover, additional extrarenal complications may be observed in ADPKD patients including intracranial aneurysms (ICA), biliary tract disease, intestinal diverticulosis and cardiac valve defects [8, 9] (Figure 1). Primarily, two genes are involved in the pathogenesis of ADPKD—PKD1 and PKD2. Other genes have been implicated in cases in which no mutation could be detected; however, these novel genes (DNAJH1, GANAB) play a minor role taking into account the low frequency in ADPKD patients [10]. Importantly, truncating PKD1 mutations leadson average—to end-stage renal disease (ESRD) ~20 years earlier than PKD2 mutations [11]. Molecular genetics are rarely needed for making a diagnosis in ADPKD patients with a positive family history based on clear imaging criteria [12]. However, the genetic lesion may play a more prominent role in the future to predict the course of the disease and allow for counselling regarding therapeutic options [13]. Furthermore, a molecular genetic diagnosis should be obtained if the clinical presentation does not allow for a clear diagnosis and in cases in which one of the tumour syndromes is suspected to allow for early prognostic testing of other family members [4].

In the past, the only therapeutic options available were supportive measures largely extrapolated from other chronic kidney diseases (CKDs) (Table 1). This has changed tremendously in the last years. On one hand, general interventions such as blood pressure control have been emphasized in ADPKD by randomized trials [14]. On the other hand, the Tolvaptan Phase 3 Efficacy and Safety Study in ADPKD (TEMPO) 3:4 trial has led to the approval of the first targeted therapy for this disease with the Genetic Testing of Other Family Members 

**Renal and extrarenal manifestations in ADPKD**

- **Renal manifestations**: nephrolithiasis, flank pain, hematuria, cyst infection
- **Imaging of differential diagnoses of ADPKD**: imaging of differential diagnoses of ADPKD
- **Extrarenal manifestations of ADPKD**: extrarenal cysts (liver, pancreas, spleen, seminal vesicles, arachnoid...), biliary disease, cardiac valve defects, vascular dissections/aneurysms, pericardial effusion, intracranial aneurysms, hernia, diverticulosis

**STATE-OF-THE-ART: SUPPORTIVE MEASURES**

**Blood pressure control**

Elevated blood pressure occurs early in the course of ADPKD [11]: treating arterial hypertension is one of the cornerstones in the management of ADPKD. The increase in blood pressure—also in other CKDs—contributes to cardiovascular morbidity on one hand. On the other hand, onset of arterial hypertension before the age of 35 years has been shown to be a strong clinical indicator of rapid progression of ADPKD [11]. However, specific blood pressure targets and the impact of blood pressure control on progression of the disease had been unclear for a long time. This problem was addressed in 2014 in an important double-blind placebo-controlled trial—study arm A of HALT-PKD—which compared strict blood pressure control (<110/75 mmHg) with a standard regimen (<130/80 mmHg) in early ADPKD (age <50 years, eGFR >60 mL/min/1.73 m²; Table 2) [14]. Rigorous blood pressure control was well-tolerated and induced a slower increase in TKV indicating a disease-modifying effect. In the primary publication, no significant effect on eGFR loss could be demonstrated. This may be a consequence of the fact that many participants were still in CKD Stage 1 and did not lose kidney function during the period of the trial. A recent post hoc analysis of HALT-PKD could show that eGFR loss was significantly attenuated in patients with indicators of rapid progression (Mayo Classes 1D–E) [17]. It is important to recognize—when transferring the findings to the real-life setting—that blood pressure values in this trial were obtained by home blood pressure measures. Importantly, as seen in previous trials, dual renin–angiotensin system (RAS)-blockade did not improve the outcome (compared with the use of an angiotensin-converting enzyme inhibitor or AT1-antagonist alone). This was also confirmed again by the study arm B of HALT-PKD, which primarily...
compared dual with single RAS-blockade in late ADPKD (age <65 years, eGFR 20–60 mL/min/1.73 m²; Table 2) showing that there is no role for this strategy in ADPKD [18].

Although conclusive data on the choice of specific antihypertensive drugs is not available [19], the strong increase in RAAS activity in ADPKD [20] and the fact that HALT-PKD primarily employed RAS-inhibitors justifies a preference for these agents in ADPKD. However, blood pressure control itself appears to be more important than the choice of the agent used [21].

**Fluid intake**

Whilst avoiding hypovolaemia and dehydration is important in any case of CKD, fluid intake plays a particular role in ADPKD [22]. Vasopressin-receptor signalling is central to disease progression due to its impact on increasing cAMP levels—a key driver of cyst growth. This concept was translated into the clinics and resulted in a clinical trial to test the V2 receptor blocker tolvaptan in ADPKD (see the section on the rationale of V2R blockade). Vasopressin secretion is primarily regulated by serum osmolality and consequently water intake. Consequently, increasing water intake can decrease vasopressin levels [23]. Daily fluid intake leading to an increase of the urine volume to ~3 L/day has been shown to be sufficient to decrease urine osmolality to levels below the serum osmolality that indicates suppression of vasopressin secretion [24, 25]. Consequently, a fluid intake of ~3–3.5 L/day is commonly recommended. However, there are no data from randomized trials regarding clinically relevant endpoints (e.g. eGFR loss or TKV increase) for this measure. A recently launched trial will hopefully close this gap in the future [ACTRN12614001216606; [23]].

**Sodium chloride consumption**

Limiting sodium chloride intake is generally recommended to patients suffering from CKD based on the role of sodium chloride in volume retention and arterial hypertension [26]. As to ADPKD this approach has recently been strengthened by a post hoc analysis of the HALT-PKD trial [27]. In study arm A, urinary sodium excretion was significantly associated with kidney growth. Furthermore, this was also the case for eGFR loss in study arm B (but not in study arm A, again potentially due to the lack of any eGFR loss in a significant proportion of CKD1 patients) [27]. Consequently, limiting sodium chloride intake (e.g. to a range of 5–7 g/day) is a rational choice in ADPKD.

**Healthy diet**

There are no randomized trials regarding dietary interventions in ADPKD, so current recommendations either result from post hoc analyses or must be extrapolated from trials in non-ADPKD patients [28]. In the Modification of Diet in Renal Disease trial low protein intake—which showed some promise in a PKD1 mouse model [29, 30]—was only associated with a marginal benefit regarding GFR decline whilst no effect was observed in earlier disease (i.e. eGFR >25 mL/min/1.73 m²) [31]. A keto acid-amino acid supplement did not show any effect at all [31].

However, taking into account the increased cardiovascular risk in CKD, data from other trials can be extrapolated to prevent cardiovascular morbidity. In this context, primarily two dietary regimens are supported by evidence. On one hand, the Dietary Approaches to Stop Hypertension (DASH) diet—a regimen high in fruits and vegetables and low in fat—was shown to reduce blood pressure [32]. Furthermore, the DASH-sodium study again supports lowering sodium intake in this context [33]. On the other hand, the PREDIMED trial gained a lot of attention comparing a Mediterranean diet—low in red meat, soda drinks and commercial bakery products, and high in fish, vegetables and white meat combined with a supplementation of olive oil or nuts—to a low-fat diet in primary prevention of cardiovascular disease in patients at risk [34]. Here, the Mediterranean diet showed a major benefit in the primary composite endpoint of myocardial infarction, stroke and death from cardiovascular causes. The difference was remarkable, leading to premature termination of the trial after 4.8 years. In our view, these results warrant the recommendation for a healthy diet in ADPKD patients. Whether any of these or other dietary regimens can modify the course of renal disease remains unclear at this point. However, studies in rodent models of ADPKD using caloric restriction yielded interesting results with a significant impact on both TKV increase and eGFR loss [35, 36]. Whether these results can be translated to the clinical setting remains to be elucidated by clinical trials that will require more targeted approaches than a mere reduction in calories. Currently, a trial with 40 participants is starting to compare caloric restriction and intermittent fasting focusing on feasibility (NCT03342742). In any case, maintaining a normal weight is clearly beneficial in ADPKD with recent data confirming the association between overweight/obesity [i.e. body mass index (BMI) ≥25.0] and both a greater eGFR decline and a greater annual percent change in TKV [37].

In addition to these findings, nutritional supplements—similar to nut and olive oil in the PREDIMED trial—are gaining increasing attention in ADPKD. In this context, curcumin has been shown to have beneficial effects on cyst formation and loss of kidney function in a PKD1 knockout mouse model—presumably due to its effects on Wnt and mammalian target of rapamycin (mTOR) signalling [38]. There is no clinical trial registered as of
Table 2. Summary of key interventional trials for the treatment of ADPKD discussed in this review

| Agent/intervention examined | Trial | Key inclusion criteria | Status / key findings |
|----------------------------|-------|------------------------|-----------------------|
| mTOR inhibitors            | Walz et al. [121], 433 patients, 24 months, double-blind placebo-controlled RCT | eGFR >30–89 or 90 mL/min/1.73 m² and TKV > 1000 mL | Data published; TKV growth significantly slower in everolimus group; no benefit regarding eGFR loss |
|                           | Serra et al. [120], 100 patients, 18 months, open-label placebo-controlled RCT | Age 18–40 years and eCrCl ≥70 mL/min; No TKV criterion | Data published; no benefit regarding TKV increase and eGFR loss |
| Tolvaptan                  | TEMPO 3:4 Torres et al. [15], 1445 patients, 36 months, double-blind placebo-controlled RCT | Age 18–50 years and eCrCl >60 mL/min and TKV >750 mL | Data published; TKV growth and eGFR loss significantly slower in tolvaptan group; lower rates in kidney pain episodes |
|                           | TEMPO 4:4 Torres et al. [90], 871 patients, 24 months, open-label extension trial of TEMPO 3:4 | Patients from TEMPO 3:4 (non-Japanese centers); imbalances at inclusion due to trial design | Data published; no sustained effect on TKV between the groups; significant benefit of early treatment regarding eGFR |
|                           | REPRISE Torres et al. [91], 1370 patients, 12 months, double-blind placebo-controlled randomized withdrawal trial | Age 18–55 years and eGFR 25–65 mL/min/1.73 m² or Age 56–65 years and eGFR 25–44 mL/min/1.73 m²; No TKV criterion | Data published; significant benefit regarding eGFR loss (not in group >55 years of age) |
| Somatostatin analogues     | ALADIN Caroli et al. [102], 79 patients, 36 months, single-blind placebo-controlled RCT; octreotide-LAR | Age >18 years AND eGFR >40 mL/min/1.73 m²; No TKV criterion | Data published; significant benefit regarding eTKV increase at 1 year; trend at 3 years; explorative analysis indicates benefit regarding eGFR loss |
|                           | ALADIN2 NCT01377246 100 patients, 36 months, double-blind placebo-controlled RCT; octreotide-LAR | Age >18 years and eGFR 15–40 mL/min/1.73 m²; No TKV criterion | Completed; unpublished primary outcome TKV change after 1 year and GFR decline after 3 years |
|                           | DIPAK 1 NCT01616927 300 patients, 30 months, open-label RCT; lanreotide versus standard care | Age 18–60 years and eGFR 30–60 mL/min/1.73 m²; No TKV criterion | Completed; unpublished; data presented at ERA-EDTA 2018: no benefit regarding eGFR loss, TKV increase significantly lower |
|                           | LIPS NCT02127437 156 patients, 36 months, double-blind placebo-controlled RCT; lanreotide | Age >18 years and mGFR 30–89 mL/min/1.73 m²; No TKV criterion | Active, not recruiting; unpublished |
| Tyrosine kinase inhibitors | Tesar et al. [123], 172 patients, 24 months, double-blind placebo-controlled RCT; bosutinib | Age 18–50 years and eGFR >60 mL/min/1.73 m²; TKV >750 mL | Data published; significantly slower TKV growth; no benefit regarding eGFR loss |
|                           | NCT03203642 100 patients, 24 months, double-blind placebo-controlled RCT; tesevatinib | Age 18–60 years and eGFR 30–80 mL/min/1.73 m² TKV ≥900 mL | Recruiting; primary outcome TKV increase |
| Glucosylceramide synthase inhibitor | NCT03523728 560 patients, 24 months, double-blind placebo-controlled RCT; venglustat | Age 18–50 years and eGFR 45–90 mL/min/1.73 m²; Mayo classes 1G–E | Recruitment not started yet; primary outcome TKV increase and eGFR loss |

(continued)
now primarily examining its role in preventing renal disease progression; however, there is one trial looking at vascular dysfunction in ADPKD (NCT02494141). For niacinamide—a form of Vitamin B3—the situation is similar with interesting data from a mouse model and two active small clinical trials looking at renal outcomes among other endpoints (NCT02558595; NCT03493802). The results of a small pilot trial in only 10 patients that primarily examined Sirtuin (the target of niacinamide) deacetylase activity are awaiting publication (NCT02140814).

Taken together, dietary interventions hold the promise to be one major field of novel interventions to treat ADPKD in the future.

### Caffeine consumption

Based on the consideration that caffeine inhibits phosphodiesterases (PDEs), which could lead to an increase of cAMP in epithelial cells of the renal tubules [39], ADPKD patients were often

| Agent/intervention examined | Trial | Key inclusion criteria | Status /key findings |
|-----------------------------|-------|------------------------|---------------------|
| **Statins**                 |       |                        |                     |
| NCT03273413                 |       | 200 patients, 24 months, double-blind placebo-controlled RCT; pravastatin | Recruiting; primary outcome TKV increase$^a$ |
| Cadnapaphornchai et al. [112], |       | 110 paediatric patients, 36 months; double-blind placebo-controlled RCT; pravastatin | Data published; significantly slower TKV growth$^a$; no benefit regarding UAE$^a$ and LVMI$^a$ (composite endpoint) |
| **Metformin**               |       |                        |                     |
| NCT02656017 (TAME)         |       | Age 18–60 years; No TKV or GFR criterion | Recruiting; primary outcome: tolerability/safety eGFR and TKV change among secondary endpoints |
| NCT02903511                |       | Age 30–60 years; eGFR 50–80 mL/min/1.73 m$^2$; No TKV criterion | Recruiting; primary outcome: tolerability/safety eGFR and TKV change among secondary endpoints |
| **Water intake**            |       |                        |                     |
| PREVENT-ADPKD               |       | Age ≤65 years AND eGFR ≥30 mL/min/1.73 m$^2$; No TKV criterion | Recruiting; primary outcome TKV increase$^a$ |
| **Blood pressure control** |       |                        |                     |
| HALT-PKD A                  |       | Age 15–49 years and Hypertensive and eGFR ≥60 mL/min/1.73 m$^2$ | Data published; significant benefit of low blood pressure group regarding TKV growth$^a$; no significant benefit for eGFR loss in primary analysis |
| HALT-PKD B                  |       | Age 18–64 years and Hypertensive and eGFR 25–80 mL/min/1.73 m$^2$ | Data published; no difference regarding primary composite endpoint (time to death, end-stage renal disease, or a 50% reduction from the baseline estimated GFR)$^a$ |
| **Niacinamide**             |       | Age 18–40 years and eGFR ≥60 mL/min/1.73 m$^2$ | Recruiting; TKV and GFR change among primary outcome measures$^a$ |
| NCT03493802                 |       | And Mayo Class 1B–D    |                     |
| NCT02558595 (NIAC-PKD2)     |       | Age 18–60 years and eGFR 50–80 mL/min/1.73 m$^2$; No TKV criterion | Active, not recruiting; primary outcome: acetylated p53$^a$; TKV and eGFR change among secondary endpoints |
| **Caloric restriction/weight loss** |       | Age 18–65 years and eGFR ≥45 mL/min/1.73 m$^2$ and BMI 25–45 kg/m$^2$; No TKV criterion | Recruiting; primary outcome: feasibility$^a$ and weight loss$^a$; TKV change among secondary endpoints |

*eCrCl, estimated creatinine clearance; UAE, urinary albumin excretion; LVMI, left ventricular mass index.

$^a$Primary endpoint.

### Table 2. Continued

| Agent/intervention examined | Trial | Key inclusion criteria | Status /key findings |
|-----------------------------|-------|------------------------|---------------------|
| Statins                     |       |                        |                     |
| NCT03273413                 |       | 200 patients, 24 months, double-blind placebo-controlled RCT; pravastatin | Recruiting; primary outcome TKV increase$^a$ |
| Cadnapaphornchai et al. [112], |       | 110 paediatric patients, 36 months; double-blind placebo-controlled RCT; pravastatin | Data published; significantly slower TKV growth$^a$; no benefit regarding UAE$^a$ and LVMI$^a$ (composite endpoint) |
| **Metformin**               |       | Age 18–60 years; No TKV or GFR criterion | Recruiting; primary outcome: tolerability/safety eGFR and TKV change among secondary endpoints |
| NCT02656017 (TAME)         |       | Age 30–60 years; eGFR 50–80 mL/min/1.73 m$^2$; No TKV criterion | Recruiting; primary outcome: tolerability/safety eGFR and TKV change among secondary endpoints |
| **Water intake**            |       | Age ≤65 years AND eGFR ≥30 mL/min/1.73 m$^2$; No TKV criterion | Recruiting; primary outcome TKV increase$^a$ |
| **Blood pressure control** |       | Age 15–49 years and Hypertensive and eGFR ≥60 mL/min/1.73 m$^2$ | Data published; significant benefit of low blood pressure group regarding TKV growth$^a$; no significant benefit for eGFR loss in primary analysis |
| **Niacinamide**             |       | Age 18–40 years and eGFR ≥60 mL/min/1.73 m$^2$ | Recruiting; TKV and GFR change among primary outcome measures$^a$ |
| NCT03493802                 |       | And Mayo Class 1B–D    |                     |
| NCT02558595 (NIAC-PKD2)     |       | Age 18–60 years and eGFR 50–80 mL/min/1.73 m$^2$; No TKV criterion | Active, not recruiting; primary outcome: acetylated p53$^a$; TKV and eGFR change among secondary endpoints |
| **Caloric restriction/weight loss** |       | Age 18–65 years and eGFR ≥45 mL/min/1.73 m$^2$ and BMI 25–45 kg/m$^2$; No TKV criterion | Recruiting; primary outcome: feasibility$^a$ and weight loss$^a$; TKV change among secondary endpoints |

*eCrCl, estimated creatinine clearance; UAE, urinary albumin excretion; LVMI, left ventricular mass index.

$^a$Primary endpoint.
told not to consume caffeine at all in the past. However, this conclusion was primarily based on cell culture experiments [40]. In a rat model of ADPKD, caffeine intake increased arterial blood pressure but had no effect on GFR or TKV [41]. Most importantly, the data available from human cohorts do not indicate any effect on eGFR and TKV associated with caffeine consumption [42, 43]. It is assumed that—whilst it is logical that PDE inhibition can be a driver of disease progression in ADPKD—the levels of the weak PDE inhibitor caffeine reached by a normal level of e.g. coffee consumption, are far too low to cause any harm. As a consequence, in our view ADPKD patients can consume coffee, but should—as the general population—refrain from excessive amounts (e.g. >3–4 cups or 400 mg caffeine per day) [42, 44].

**Smoking**

It is undisputed that smoking has a major impact on cardiovascular and CKD as well as mortality in general [45, 46]. The impact on cardiovascular disease has been demonstrated in ADPKD patients as well [47]. Furthermore, smoking is associated with more rapid disease progression and risk of ESRD, a fact that has recently been confirmed in a PKD1 rodent model as well [48, 49]. Interestingly, smoking also increases vasopressin secretion, which may be one mechanism that leads to more rapid disease progression in ADPKD [50] and increases the risk of ICA rupture [51].

**Physical activity**

Physical activity is an important modifiable factor in the prevention of cardiovascular disease as well as cancer mortality [52–55]. Consequently, the World Health Organization recommends 150 min of moderate-intensity or 75 min of vigorous-intensity activity per week [56]. It is important to mention, when counselling patients, that activity itself is more important than the distribution over the week—that is, a higher degree on the weekend appears to be similarly effective as daily activity [52]. However, exercise intervention trials in chronic kidney disease assessing hard endpoints are still lacking. Currently, available data show feasibility and safety of increasing physical activity in CKD cohorts with the strongest evidence regarding endpoints for fitness and quality of life [57]. Furthermore, there are indications, as in the general population, that physical activity can have a positive effect on blood pressure [58, 59]—an important aspect for ADPKD patients. As a conclusion, Kidney Disease: Improving Global Outcomes recommends 30 min of moderate-intensity activity for CKD patients. However, future trials in ADPKD patients on the outcome of increasing exercise as well as the question of the optimal type of activity would be needed. Nonetheless, increasing physical activity should be a clear recommendation to ADPKD patients that can—apart from its intrinsic impact on cardiovascular disease—add to dietary interventions in maintaining a normal weight.

**STATE-OF-THE-ART: PHARMACOTHERAPY**

Antihypertensive medication has been discussed in the first section on supportive measures. Here, we will focus on pharmacological interventions that have a disease-modifying effect in ADPKD alleviating eGFR loss and TKV increase. A summary of all interventional trials discussed in this section is provided in Table 2.

**cAMP as a central player in ADPKD**

Over the last decades, groundbreaking research using both cell culture and rodent models of ADPKD have laid the foundation for a quite detailed understanding of perturbed signal transduction pathways involved in cystogenesis and cyst expansion [3, 65]. This knowledge was a prerequisite to the development of targeted pharmacological strategies. A key finding in cyst-lining epithelial cells is a decrease in intracellular calcium and a marked increase in cAMP-levels that drives primarily secretion and to a lesser extent proliferation—the hallmarks of cyst expansion [66–72]. At least in a PKD1 knockout mouse model, this increase appears to be mediated by calcium-inhibited adenylyl cyclase 6 (AC6) making AC6 a potential future therapeutic target [73]. On the other hand, PDEs are involved in reducing cellular cAMP levels and attenuating cystogenesis [39, 74].

**The rationale of V2R blockade**

The central role of cAMP raised the question of which pathways—that can be pharmacologically modulated—control cAMP generation in tubular cells. Here, V2 receptor signalling driven by vasopressin (AVP) was found to be the most potent inductor of cAMP in isolated cells of the collecting duct [75]. Based on this finding, a landmark study published in 2004 showed that treatment with a V2 receptor antagonist in an orthologous mouse model of ADPKD markedly alleviated the course of the disease [68]. This finding was corroborated later by data using the crossing of the PKC rat model with Avp knockout animals, which resulted in a nearly complete inhibition of cystogenesis [76]. Administration of a V2 receptor agonist instead recovered the phenotype and led to a significant deterioration of disease in PKC Agrp (+/-) animals, proving the central role of AVP and the V2 receptor in cyst growth. The predominance of expression of the V2 receptor in the sites of cystogenesis—collecting ducts, connecting tubules and thick ascending limbs of Henle—makes this receptor an attractive pharmacological target [77]. Despite the fact that expression has been shown in other tissues as well, human loss of function of the V2 receptor as found in congenital nephrogenic diabetes insipidus is—as to clinically relevant disease—characterized by diabetes insipidus itself making potential side effects of V2R inhibition predictable [78]. Since the concept of V2R inhibition in cystic kidney disease had been demonstrated in a number of different rodent models [68, 79–82] the design of clinical trials using such agents was a logical consequence.

**Clinical trials of V2R blockade in ADPKD**

TEMPO 3:4 was a landmark phase 3 trial that—for the first time—examined a V2R inhibitor (tolvaptan) in a double-blind randomized design, after two open-label phase 2 trials had shown safety and tolerability [15]. TKV, which—due to the lack of eGFR loss in CKD Stage 1 patients and the relatively slow loss in later stages compared with other renal diseases—is an important endpoint in ADPKD trials and has (since TEMPO 3:4) been accepted as a surrogate parameter by regulatory agencies [83, 84], was chosen as the primary endpoint. Since dosing studies had shown that administration twice a day was important to suppress urine osmolality during a full 24-h period, patients in TEMPO 3:4 received two daily split-doses starting at 45/15 mg followed by an uptitration to 90/30 mg/day [85]. Patients taking tolvaptan experienced a significantly lower rate of kidney growth by close to 50% and—even more importantly—eGFR loss was attenuated by ~26% (~3.7 versus ~2.7 mL/min/1.73 m²) [15].

TABLE 2

| Intervention | Primary Endpoint | Secondary Endpoint | Safety | Conclusion |
|--------------|------------------|--------------------|--------|------------|
| Tolvaptan    | eGFR loss        | TKV increase       |        | Reduction  |
| Tolvaptan    | TKV increase     | eGFR loss          |        | Reduction  |
| Tolvaptan    | TKV increase     | Safety             |        | Tolerability |
| Tolvaptan    | Safety           | Safety             |        | Tolerability |
Taking into account that large trials on RAAS-blockade in diabetic nephropathy have shown a similar effect size, this was a highly significant finding for ADPKD patients [86–89]. Consequently, tolvaptan was approved for the treatment of ADPKD by the European Medicines Agency (EMA), Health Canada and in Japan. As rare events of hepatotoxicity were reported—two patients in TEMPO 3:4 fulfilled the Hy’s law criteria (>3 times increase in transaminases combined with hyperbilirubinemia)—liver function tests must be performed on a regular basis. As to efficacy, two questions as to efficacy had remained unanswered after TEMPO 3:4. On one hand, it was not clear whether the beneficial effect of tolvaptan was maintained beyond the 3 years examined. TEMPO 4:4 addressed this point by comparing early treatment (starting with TEMPO 3:4) to late treatment (starting at the beginning of TEMPO 4:4) for another 2 years. Whilst design-related imbalances at the start of TEMPO 4:4 may have led to the primary endpoint of TKV increase not being significantly different at the end of the trial, the eGFR benefit was maintained indicating a disease-modifying effect of tolvaptan in ADPKD [89]. On the other hand, TEMPO 3:4 examined only patients in CKD Stages 1–3 (with very few patients in CKD Stage 3b) up to the age of 50 years, leaving the question open as to whether the treatment would continue to work in later stages. This was addressed in the recently published Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trial that enrolled patients with an eGFR between 25 and 65 mL/min/1.73 m² up to the age of 65 years. Here, the findings of TEMPO 3:4 regarding a slower loss of eGFR could be confirmed [91]. In a consecutive subgroup analysis, no benefit was observed in patients >55 years of age (containing 96 tolvaptan and 94 placebo patients). Importantly, placebo patients in this group showed a yearly eGFR loss of only –2.34 mL/min/1.73 m², which can be considered a consequence of the lenient inclusion criterion of the trial regarding past-time eGFR loss (‘historical evidence of a decline in the estimated GFR of more than 2.0 mL per minute per 1.73 m² per year’). Taking into account this rather slow loss of eGFR [92], the fact that TKV was not measured in REPRISE patients and that eGFR loss in this age group is often rather due to comorbidities such as cardiovascular disease than ADPKD itself, these patients in REPRISE were most likely not rapid progressors and would thus generally not be expected to benefit from tolvaptan. Interestingly, as to hepatotoxicity, no further case fulfilling the Hy’s law criteria occurred in REPRISE—potentially as a consequence of the lenient inclusion criterion of the trial regarding past-time eGFR loss (‘historical evidence of a decline in the estimated GFR of more than 2.0 mL per minute per 1.73 m² per year’). Taken into account this rather slow loss of eGFR [92], the fact that TKV was not measured in REPRISE patients and that eGFR loss in this age group is often rather due to comorbidities such as cardiovascular disease than ADPKD itself, these patients in REPRISE were most likely not rapid progressors and would thus generally not be expected to benefit from tolvaptan. Interestingly, as to hepatotoxicity, no further case fulfilling the Hy’s law criteria occurred in REPRISE—potentially as a consequence of the lenient inclusion criterion of the trial regarding past-time eGFR loss (‘historical evidence of a decline in the estimated GFR of more than 2.0 mL per minute per 1.73 m² per year’). Taking into account this rather slow loss of eGFR [92], the fact that TKV was not measured in REPRISE patients and that eGFR loss in this age group is often rather due to comorbidities such as cardiovascular disease than ADPKD itself, these patients in REPRISE were most likely not rapid progressors and would thus generally not be expected to benefit from tolvaptan. Interestingly, as to hepatotoxicity, no further case fulfilling the Hy’s law criteria occurred in REPRISE—potentially as a consequence of the lenient inclusion criterion of the trial regarding past-time eGFR loss (‘historical evidence of a decline in the estimated GFR of more than 2.0 mL per minute per 1.73 m² per year’).

Practical aspects in the use of tolvaptan for ADPKD

The approval of the very first targeted strategy that goes beyond general supportive measures to treat ADPKD was a milestone in the management of this disease. However, a prudent use of tolvaptan is the prerequisite for a successful implementation in the clinical setting. In Germany, it was possible to gain experience with the use of tolvaptan in ADPKD patients since 2015 and generate a large prospective cohort study [AD(H)PKD; NCT02497521], which will allow for a systematic analysis of these experiences. Due to its mode of action tolvaptan goes along with significant polyuria, which requires extensive patient counselling and knowledge about the reason for polyuria before taking the first pill. Whilst this point raised many concerns in the beginning regarding tolerability and adherence, both the trial data and the real-world experiences show that close to 80% of the patients continue the therapy in the longer term. [114, 86, 93], unpublished data from the AD(H)PKD study [94]. It is important to inform patients that—to allow for feasibility—single-doses can be skipped whenever no access to water or bathrooms is available. The German experience indicates that the vast majority of patients does not skip doses more than once or twice a month [unpublished data from the AD(H)PKD study [94]]. However, patients need to know that it is crucial to pause the treatment whenever there is a risk of dehydration—e.g. diarrhea, surgery, lacking access to water. Furthermore, it has proven to be very helpful to provide patients on tolvaptan with advice on handling the therapy in everyday life. This includes taking the first pill early in the morning to avoid peak drug levels during the night leading to nocturia, repleting the water deficit with gas-free mineral water (rather low in sodium) instead of calorie-rich drinks, reducing the amount of osmolyte intake (especially sodium chloride) and starting the treatment on a weekend rather than a working day.

As to lab parameters, potential hepatotoxicity requires a screening strategy with LFTs measured once monthly during the first 18 months of treatment (all known cases of relevant hepatotoxicity occurred during this period) and every 3 months afterwards [95]. It is important to know of the reversible hemodynamic impact of tolvaptan that leads to a slight increase in serum creatinine at the beginning of the treatment [96]. This effect is fully reversible as demonstrated in several studies [91].

Based on the data from TEMPO 3:4, regulatory agencies like the EMA have made ‘rapid disease progression’ a prerequisite for on-label use of tolvaptan in ADPKD. Consequently, the first step in making a treatment decision in an ADPKD patient is evaluation of criteria of rapid disease progression. The position statement of the WKGKD and ERBP provides both a summary of available data on this point and a useful algorithm to help physicians in gauging progression [92]. Furthermore, patient selection—which is primarily based on past-time eGFR loss, TKV as adjusted by the Mayo classification and the PROPKD score (Table 3)—has recently been reviewed extensively [5, 97, 98] and shall not be the focus of this review. Importantly, REPRISE has added more data to patient selection by showing tolvaptan to also be effective in CKD Stage 4 as well as in patients above the age of 50 years [91]. However, this does not mean that patients should be treated late when kidney function has already been lost since the assumed absolute eGFR benefit is highest when treatment is started early. Furthermore, additional weight has been added to judicious patient selection with only rapid progressors showing a benefit and the risk of choosing the wrong patients being higher in the older age group (esp. above the age of 55 years). This aspect is of high clinical relevance since patients who will not reach ESRD due to ADPKD should not be treated with tolvaptan to avoid side effects, a potential impact on quality of life and an additional economic burden. These findings will likely be a basis for future adaptations of the recommendations on the use of tolvaptan.

Somatostatin analogues in ADPKD

Since tolvaptan is the only approved pharmacological agent in ADPKD this practical review focuses on this agent. Nonetheless,
other concepts for which trial data are available shall also be discussed. Regarding the modulation of intracellular cAMP levels in tubular cells, the second important pathway is somatostatin signalling with the activation of its Gi-protein coupled receptor reducing cAMP [99]. In rodent models, somatostatin analogues showed a significant potential in reducing hepatorenal cystogenesis [100, 101]. As to the kidney involvement in ADPKD, several phase 2 trials and a small phase 3 trial (ALADIN) have shown promise for this approach in human disease as well [102, 103]. Generally, somatostatin analogues are well tolerated, but—depending on the agent used—an increased risk of disorders of glucose homeostasis and gallstone disease as well as first results from DIPAK1 suggesting an increased risk of liver cyst infections have to be taken into account [104]. Currently, the results of the follow-up study of ALADIN (ALADIN2) and two larger phase 3 trials—LIPS and DIPAK 1—are awaiting publication. In May 2018, data from the largest of these trials—DIPAK 1—was presented at the Congress of the European Renal Association [105]. In this study (including 305 later-stage ADPKD patients), a somatostatin analogue (lanreotide) did not show a beneficial effect on eGFR loss—even though slowing TKV growth—whilst increasing adverse events [104, 105]. Consequently, at the current stage somatostatin analogues will not become an agent to be used to slow down disease progression in ADPKD. However, it has to be noted that somatostatin analogues continue to play a role in the off-label treatment of ADPKD. AMPK is one of the key negative regulators of both of these central players and can be activated by metformin. Interestingly, metformin has been shown to inhibit cystogenesis in two mouse models and a zebrafish model of ADPKD [114, 115]. Two phase 2 trials have recently started to examine metformin in a placebo-controlled manner in together ~150 patients (NCT02903511; NCT02656017) [116].

Seeing the central role of the mTOR pathway in ADPKD, mTOR-inhibitors were one of the most promising options [117–119]. However, a major difference to statins and metformin may be the toxicity profile of these drugs. Unfortunately, mTOR-inhibition in ADPKD did not show any benefit regarding the loss of kidney function in two large randomized clinical trials [120, 121] and only one of them found a decrease in the rate of kidney growth [121]. Whether novel strategies targeting rapamycin to cysts will show a more advantageous profile in the clinical setting and thus lead to the design of new clinical trials in ADPKD remains to be seen [122].

Furthermore, with the overactivation of a number of kinases in ADPKD and a large number of kinase inhibitors that have been developed for clinical use in the last decade, repurposing of these drugs appears to be a promising strategy as well. Recently, a phase 2 trial examining a src/bcr-abl tyrosine kinase inhibitor, bosutinib, in ADPKD has been published. Unfortunately, despite showing an impact on kidney volume, there was no benefit regarding kidney function with a general trend towards dose-dependent worsening of kidney function. However, it is important to note that this study was not adequately powered to examine an effect on eGFR. Importantly, a high proportion of patients did not finish the trial due to treatment-associated adverse events [123]. Besides these data, tesevatinib—a multi-tyrosine kinase inhibitor targeting

Table 3. The most important parameters/predictive tools for judging rapid disease progression in ADPKD

| Parameter | Interpretation |
|----------|----------------|
| Rate of past-time eGFR decline | Evidence of established rapid progression: |
| | • Decrease in eGFR of ≥5 mL/min/1.73 m² in 1 year*
| | • Decrease in eGFR of ≥2.5 mL/min/1.73 m²/year for >5 years b |
| TKV. Mayo classification | Mayo classification: model based on one-time hTKV, sex and eGFR predicting future eGFR loss (AUC last eGFR =45 versus predicted 0.945) f |
| | • Classes 1–E predicts rapid progression with an average yearly eGFR loss of –2.63/2.43, –3.48/3.29 and –4.78/ 4.58 mL/min/1.73 m² (men/women) |
| PROPKD score | Incorporates genetics, early onset of urolological complications and hypertension, as well as gender into a model predicting disease progression d |
| | • PROPKD score of >6 predicts reaching ESRD before 60 years of age (positive predictive value 90.9%) d |

Ref. [97]; [Modified from Müller (2018)].

*Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int Suppl 2013; 3: 1-150. Doi: https://doi.org/10.1038/kisup.2012.73.

Ref. [92]; Renal Association Working Group on Tolvaptan in ADPKD. Tolvaptan for ADPKD: Interpreting the NICE decision. http://www.renal.org/docs/default-source/ default-document-library/tolvaptan-in-adpkd-nice-commentary.pdf?sfvrsn=0 (6 March 2017, date last accessed).

†trazabali MV et al. / Am Soc Nephrol 2015; 26: 160-72. Doi: 10.1681/ASN.2013101138.

‡Ref. [11]. Corner-Le Gall E et al. NDT 2017; 33: 645-652.
epidermal growth factor receptor and vascular endothelial growth factor receptor among others—is currently examined in a phase 2 trial for the treatment of ADPKD (NCT03203642).

As a last example, GZ/SAR402671, a glucosylceramide synthase inhibitor that was primarily developed for the treatment of storage disease such as Gaucher’s and Fabry’s disease (but in contrast to e.g. statins and metformin has not been approved for clinical use yet), has shown significant potential in blocking disease progression in mouse models of ADPKD and nephropathies [124]. As a result, this concept will be tested in a combined phase 2/3 trial that is going to start enrolment in 2018 (NCT03523728).

CONCLUSION

The recent years have witnessed a breakthrough in our understanding of the molecular pathogenesis and the management of ADPKD. Several large clinical trials resulted in new insight into specific management of blood pressure, body weight and eating behaviour as well as the identification of new disease-modifying drugs. Besides the development of entirely novel agents, repurposing of drugs as described above and potential combination therapies [125, 126] hold the promise to improve the benefit of pharmacological treatment in ADPKD whilst limiting side effects to a tolerable level. Future clinical trials will certainly further promote our understanding of the management of this important disease.

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CONFLICT OF INTEREST STATEMENT

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