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Management of autosomal-dominant polycystic kidney disease—state-of-the-art

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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) [4]. 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,

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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 (*DNAJB11*, *GANAB*) play a minor role taking into account the low frequency in ADPKD patients [10]. Importantly, truncating *PKD1* mutations leads—on 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 tolvaptan having been approved for the treatment of ADPKD patients in Europe, Canada, Japan and recently in the USA [15]. Here, based on these new advances, we are summarizing the current state-of-the art in managing ADPKD with a focus on measures alleviating estimated glomerular filtration rate (eGFR) loss.

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—as 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 m^2; 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

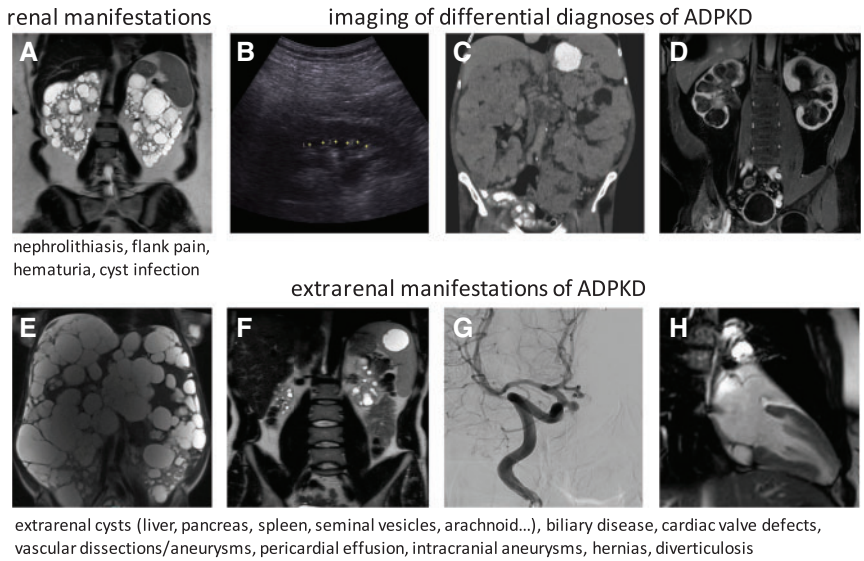

FIGURE 1: Renal and extrarenal manifestations in ADPKD. The clinical diagnosis of ADPKD is primarily based upon imaging of the kidneys showing bilateral kidney enlargement with cysts dispersed throughout the entire parenchyma (**A**). Importantly, this phenotype has to be distinguished from other polycystic diseases such as nephronophthisis (**B**), tumor syndromes accompanied by kidney cysts (Birt-Hogg-Dubé syndrome syndrome in **C**, image modified from Bartram *et al.* [16]) and hydronephrosis due to postrenal obstruction (**D**). Furthermore, typical renal symptoms (listed below the images) and typical extrarenal manifestations (listed below the images) help in making the diagnosis. Example images from ADPKD patients: polycystic liver disease (**E**), splenic cyst (**F**), ICAs (**G**) and cardiac phenotypes including coronary dissections (**H**: left ventricular aneurysm due to left anterior descending artery obstruction by dissection in 30-year-old female patient). Images kindly provided by Thorsten Persigehl, Department of Radiology, University of Cologne.

Table 1. Supportive measures in ADPKD

Supportive measures in ADPKD	Degree of evidence
Blood pressure control	RCT in ADPKD patients [14]
Limiting NaCl intake to <5–7 g/day	Association of salt intake with disease progression in a *post hoc* analysis of an RCT (ADPKD patients) [27]
Sufficient fluid intake (>3 L/day)	Preclinical data, pathophysiological considerations (vasopressin/ADH suppression) [23–25, 60]
Avoid estrogen intake (which stimulates liver growth)	Preclinical data, small non-randomized clinical trial in ADPKD patients [7, 61–63]
Healthy diet (e.g. Mediterranean diet)	RCT in patients with increased cardiovascular risk, no specific data for ADPKD patients [28, 34]
Quit smoking	Large epidemiological studies in the (general and CKD population) [45, 47]
Increase physical activity	Large epidemiological studies and several RCTs (general and CKD population) [54, 57, 64]
Maintain a normal body weight	Association of overweight with disease progression in a *post hoc* analysis of an RCT (ADPKD patients) [35]

compared dual with single RAS-blockade in late ADPKD (age <65 years, eGFR 20–60 mL/min/1.73 m^2; 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 ∼3.1 L 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 m^2) [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 in low-fat dairy products and low in fat combined with higher fibre and higher protein content—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 m^2 and TKV > 1000 mL	Data published; TKV growth significantly slower in everolimus group[a]; 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[a] 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[a] 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[a] 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 m^2 or Age 56–65 years and eGFR 25–44 mL/min/1.73 m^2; No TKV criterion	Data published; significant benefit regarding eGFR loss[a] (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 m^2; No TKV criterion	Data published; significant benefit regarding eTKV increase at 1 year[a], trend at 3 years[a]; 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 m^2; No TKV criterion	Completed; unpublished primary outcome TKV change after 1 year and GFR decline after 3 years[a]
	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 m^2; No TKV criterion	Completed; unpublished; data presented at ERA-EDTA 2018: no benefit regarding eGFR loss[a], 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 m^2; 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 m^2; TKV ≥750 mL	Data published; significantly slower TKV growth[a]; 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 m^2 TKV ≥900 mL	Recruiting; primary outcome TKV increase[a]
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 m^2; Mayo classes 1C–E	Recruitment not started yet; primary outcome TKV increase[a] and eGFR loss[a]

(continued)

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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	Age 25–60 years and eGFR ≥60 mL/min/1.73 m^2; TKV >500 ml	Recruiting; primary outcome TKV increase[a]
	Cadnapaphornchai *et al.* [112], 110 paediatric patients, 36 months; double-blind placebo-controlled RCT; pravastatin	Age 8–22 years; No TKV or GFR criterion	Data published; significantly slower TKV growth[a]; no benefit regarding UAE[a] and LVMI[a] (composite endpoint)
Metformin	NCT02656017 (TAME) 96 patients, 24 months; double-blind placebo-controlled RCT	Age 18–60 years; No TKV or GFR criterion	Recruiting; primary outcome: tolerability/safety eGFR and TKV change among secondary endpoints
	NCT02903511 50 patients, 12 months; double-blind placebo-controlled RCT	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 Wong *et al.* [23], ACTRN12614001216606 180 patients, 36 months, open-label RCT; prescribed water consumption	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 Schrier *et al.* [14], 558 patients, 60–96 months, double-blind placebo-controlled RCT; low versus standard blood pressure target	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 Torres *et al.* [18], 486 patients, 60–96 months, double-blind placebo-controlled RCT; dual versus single RAS-blockade	Age 18–64 years and Hypertensive and eGFR 25–60 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	NCT03493802 27 patients, 18 months, prospective case–control study	Age 18–40 years and eGFR >60 mL/min/1.73 m^2 And Mayo Class 1B–D	Recruiting; TKV and GFR change among primary outcome measures[a]
	NCT02558595 (NIAC-PKD2); 36 patients, 12 months, double-blind placebo-controlled RCT	Age 18–60 years and eGFR >50 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	NCT03342742 40 patients, 12 months, open-label RCT; daily caloric restriction versus intermittent fasting	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.

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

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 recommended 30 min of moderate physical activity on 5 days a week for CKD patients. However, future trials in ADPKD patients on the outcome of increased 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 could show 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 PCK 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 PCK *Avp* (+/+) 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 m^2) [15].

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 hyperbilirubinaemia)—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 [90]. 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 m^2 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 m^2, 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 liver function tests screening strategy employed, which is also used in the clinical setting. An ongoing post-authorization safety study with a global target of 3000 patients will provide additional data on safety in the real-world setting (NCT02964273). Taken together, close to 2000 ADPKD patients have been treated in the setting of randomized controlled trials (RCTs) by now, confirming both the safety and efficacy of this approach. As a consequence, tolvaptan was also approved by the Food and Drug Administration for ADPKD in April 2018. Additionally, a currently enrolling trial is examining tolvaptan in children and adolescents with ADPKD (NCT02964273).

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 [[14, 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 often 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. diarrhoea, 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 WGIKD 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,

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 m^2 in 1 year[a] • Decrease in eGFR of ≥2.5mL/min/1.73 m^2/ year for >5 years[b]
TKV: Mayo classification	• Mayo classification: model based on one-time htTKV, sex and eGFR predicting future eGFR loss (AUC last eGFR ≤45 versus predicted 0.945)[c] • Classes 1C–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 m^2 (men/women)
PROPKD score	• Incorporates genetics, early onset of urological 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)].
[a]Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int Suppl* 2013; 3: 1–150. Doi: https://doi.org/10.1038/kisup.2012.73.
[b]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).
[c]Irazabal MV *et al. J Am Soc Nephrol* 2015; 26: 160–72. Doi: 10.1681/ASN.2013101138.
[d]Ref. [11]; Cornec-Le Gall E *et al. NDT*. 2017; 33: 645–652.

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 patients with severe polycystic liver involvement due to their effects on hepatic growth [101, 106–108]. Currently, another phase 2 trial in the USA is examining pasireotide for this indication and will hopefully add more evidence to this use of somatostatin analogues (NCT01670110).

Repurposing drugs in ADPKD

A very attractive strategy that may lead to rapid translation into clinical use is the use of drugs with long-term clinical experience for other indications and a good safety profile that are repurposed for ADPKD [109]. Here statins are a prominent example. Lovastatin treatment has shown a benefit to preserve kidney function and prevent cyst growth in the Han:SPRD rat model [110, 111]. This effect was confirmed in a paediatric double-blind randomized phase 3 trial examining pravastatin versus placebo in 110 children [112]. However, a recent *post hoc* analysis of the HALT-PKD trials regarding the impact of statin use did not show any beneficial effect [113]. Thus, the results of a currently enrolling phase 4 study in adult patients with early ADPKD will help clarify the role of statins in ADPKD (NCT03273413). Waiting for the results of this trial, there is no general recommendation to use statins in ADPKD beyond their indication in the general population at the moment and no specific low density lipoprotein targets for this group of patients have been defined.

Both the cystic fibrosis transmembrane conductance regulator and the mTOR pathway are central to cyst formation in 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

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 nephronophthisis [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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