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REVIEW

Current and emerging treatment options to prevent renal failure due to autosomal dominant polycystic kidney disease

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ABSTRACT

Introduction: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common inherited cause of end-stage kidney disease (ESKD) in adults. The aim of this narrative review is to analyze current and emerging treatment options to delay ESKD due to ADPKD. Emerging treatments were defined as those that were in clinical trial (according to ClinicalTrial.gov database to July 2020) or in development.

Areas covered: The epidemiology and economic burden of ADPKD; molecular pathogenesis of ESKD; current (first-line; tolvaptan in groups with high-risk for progression to ESKD), emerging treatments under investigation [re-purposed small molecule drugs (SMDs): lixivaptan, venglustat, bardoxolone, tesevatinib, metformin; public health interventions: prescribed fluid intake, vitamin B3, ketone diet] and those in development (RGLS4326, VX-809, MR-L2, 2-doexyglucose).

Expert opinion: Over the next decade, the number of proven treatments will expand, providing opportunities to individualize therapy based on personal preferences and disease ontology; Major barriers to future research include the absence of disease-specific biomarkers, national disease-specific registries. In parallel, there is also a need for need for earlier pre-symptomatic diagnosis and enhancement of health-care service delivery. Addressing these gaps will enable ESKD to become an ultra-rare complication of ADPKD during the 21st century.

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Autosomal dominant polycystic kidney disease; treatment; kidney failure

1. Introduction

Autosomal Dominant Polycystic Kidney Disease (ADPKD) (OMIM ID173900; ICD-11-GB81) is a common single-gene disorder, and the most frequent inherited cause of chronic kidney disease (**CKD**) in adults leading to end-stage kidney disease (**ESKD**) [1–6] (Table 1). In the 1990s, treatment to delay or prevent ESKD due to ADPKD was ineffective and largely supportive [7]. However, the discovery that arginine vasopressin drives kidney cyst growth over the last two decades [8–10] culminated in the regulatory approval of the first disease-modifying drug (**DMD**), tolvaptan (a vasopressin receptor antagonist, V2RA), to slow the decline in renal function in patients at high-risk for ESKD in 2018. The aim of this narrative review is to analyze current and emerging treatment options to delay ESKD due to ADPKD. Current and emerging treatments were defined as those in clinical trial or in development, according to recent comprehensive narrative reviews on this topic [11–13] and search of a search up until July 2020 of the ClinicalTrial.gov database (search term: 'polycystic kidney') [14] and the internet using the Google search engine for media release statements (using the terms: 'polycystic kidney and new treatment').

2. Epidemiology and economic burden of ADPKD

ADPKD occurs in all regions of the world [15–18] suggesting that it probably arose early in human evolution [19] and/or that the PKD genome is naturally susceptible to mutation [19,20]. The genetic prevalence of ADPKD in the population, as defined by high-confidence pathogenic mutations in *PKD1/PKD2*, was 93 (*PKD1*: 68; *PKD2*: 26) per 100,000 [21]. The latter is higher than pathologic phenotype prevalence in population-based studies (68 per 100,000) [22] probably due to incomplete ascertainment of mild cases [23]. In high-income countries (Gross National Product per capita >$US12,055/year), such as Australia, ADPKD accounts for 1 in every 10 patients in the nephrology clinics and 5–10% of the ESKD population [1,2]. ESKD is the most serious clinical complication of ADPKD causing a significant reduction in life-expectancy, quality of life and psychosocial well-being [2], and develops in mid-life, preceded by progressive symptoms in the second to third decades. The life-time risk for ESKD has wide intra- and inter-familial variability, and a classical study from the 1980s showed that the probability of developing this complication was 52% by 73 years of age [24]. The predictors for ESKD are numerous and include demographic factors (younger age at diagnosis, male gender), clinical factors (family history of ESKD,

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Article highlights

- ADPKD is the most frequent monogenic cause of chronic kidney disease in adults, characterised by the growth and formation of multiple fluid-filled cysts in the kidney. It accounts for ~5–10% of the ESKD population;
- arginine vasopressin is a key driver kidney cyst growth and the first disease-modifying drug (**DMD**), tolvaptan (a vasopressin receptor antagonist, V2RA), to slow the decline in renal function in patients at high-risk for ESKD was approved in 2018;
- Current treatment options to prevent options to prevent ESKD are limited and include dietary sodium restriction, maintenance of normal BMI, blood pressure control, using inhibitors of renin-angiotensin system, and tolvaptan for those at high-risk for progression to ESKD;
- While the efficacy of tolvaptan was proven in two landmark randomised controlled trials (TEMPO 3:4 and REPRISE) but long-term effects on slowing the onset ESKD as well as real-world tolerability (due to aquaresis) are not known
- The efficacy of several promising emerging treatments, including public health interventions (Vitamin B3, Prescribed Water, Ketone Diet) and at least eight small molecule drugs (lixivaptan, tesevatinib, venglustat, bardoxolone, pravastatin, hydralazine, pioglitazone, metformin) are currently in progress
- It is expected that over the next 10 years, the number of proven treatments will expand, providing opportunities to individualise therapy based on personal preferences and disease ontology;
- Major barriers to future research include the absence of disease-specific biomarkers, national disease-specific registries. In parallel, there is also a need for need for earlier pre-symptomatic diagnosis and enhancement of health-care service delivery.

This box summarizes key points contained in the article.

Table 1. Characteristic features of ADPKD.

Parameter	Characteristic Feature	References
Gene mutation	Heterozygous germ-line mutations in one of the causative genes (*PKD1* in 85%; *PKD2* in 15%; and <1% in five others such as *GANAB/DNABJ11)* in 90% of patients and ~10% no mutation is detected due to mutations in deep intronic regions, copy number variations and/or unknown genes.	[3–5,28]
Inheritance Pattern	Autosomal dominant but 10% family history may be negative due to *de novo* mutation, mosaicism or non-biological parentage.	[3–5,28]
Renal Phenotype	Almost (close to 100%) full penetrance of the phenotype (adult-onset of multiple kidney cysts) with variable expressivity in kidney cyst number and cyst growth rate (range from <1.5% to >6%/year) and increased life-time risk for end-stage kidney disease.	[6,49]
Systemic Phenotype	Variable development of systemic complications, most commonly hypertension, extra-renal cysts (liver, pancreas, arachnoid), intracranial aneurysm/dissection (cerebral, aorta) and connective tissue defects (hernias, diverticular disease).	[66]

hypertension, a history of cyst-related complications) and disease-markers (rapid rate of renal function decline, baseline kidney size, albuminuria, *PKD1* mutation) [25].

The prevalence of ESKD due to ADPKD is accurately documented in high-income countries in ESKD Dialysis/Transplant Registries. In Australia (population of 25 million people) ~2000 patients receive dialysis or have a kidney transplant due to ADPKD [26]. A 50 year longitudinal follow-up of the Australia and New Zealand Dialysis Registry [26] showed that the: (i) incidence and median age of onset of ESKD has stabilized over the last two decades; and (ii) the 5-year survival rate of patients on dialysis (censored for transplantation and adjusted for age) was ~80%. In contrast, the epidemiology of pre-ESKD ADPKD is not precise due to variations in the time to diagnosis by renal ultrasound leading to incomplete ascertainment [2,21]. This leads to delayed diagnosis, and the HALT Progression of PKD (HALT-PKD) study showed that the average age at diagnosis was 35 years old [27]. Ideally, pre-symptomatic diagnosis could be achieved by genetic testing but not widely performed, in part, due to cost of sequencing the PKD1 gene and lack of government re-imbursement [28]. Therefore blood pressure measurement of asymptomatic at-risk young adults or children has been recommended as a simple method to identify affected patients and introduce interventions earlier [29–31]. In Australia, based on the assumption that the incidence of mutations in PKD genes in general population is ~1:1000 [29], we hypothesize that total number of ADPKD patients in Australia could range between ~10,000 to 25,000 with ~3,000 at risk of ESKD (Figure 1) [32].

ESKD is the highest contributor to the economic cost of ADPKD. An Italian healthcare analysis showed patients with CKD had ten times lower costs compared to those receiving dialysis (Euro 4,287 per year in ADPKD-non-dialyzed patients vs. Euro 45,393 per year) [33]. In Australia with an estimated prevalence of two thousand patients with ESKD due to ADPKD patients the total costs were estimated to be ~1 million dollars per year, based only on the annual cost of dialysis of up to $A79,072 per patient [26,34].

3. Pathogenesis of ADPKD

3.1. Genetics

ADPKD is due to heterozygous germ-line mutations in either *PKD1* (85% of cases; 46 exons in length on chromosome 16p13.3), *PKD2* (15% of cases; 15 exons in length on chromosome 4q21) or rarely other genes in <0.1% of cases (*GANAB* [35], DNAJB11 [36]). In ~10% of patients, no mutation is detected (NMD), possibly due to other genetic mechanisms (mosaicism, bi-allelic transmission of *PKD1* or copy number variations) or else mutations in genes not yet linked to ADPKD [37]. The mutations are typically private with no greater than 2% of families sharing sequence similarities [38]. Cohort studies show that groups with mutations in *PKD1* have an earlier onset of ESKD (50–55 *vs*. 75–80 years old) and twice the number of renal cysts [38,39] than those with mutations in *PKD2*. Similarly, groups with *PKD1*-protein-truncating mutations have more severe renal disease than non-truncating mutations, whereas those with mutations in *PKD2* or NMD have the mildest renal disease [38,39]. Despite these data, the prognosis of an individual is difficult to predict as the clinical phenotype has high intra- and inter-familial heterogeneity, possibly due to interactions between non-modifiable factors (both genic and allelic; modifier genes; gender) and modifiable risk factors (dietary and lifestyle factors that modulate epigenetic pathways) [40,41]. Data from murine models

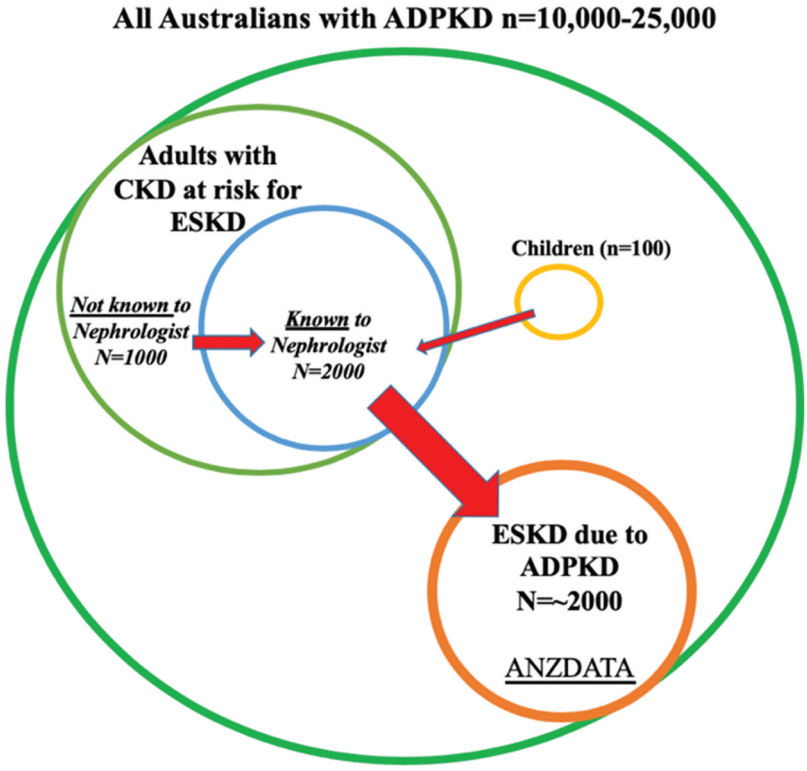

Figure 1. Hypothetical model of the epidemiology of ADPKD in Australia. The size of the total ADPKD population in Australia is unknown (contained within the largest green circle), and we estimate that between ~10,000–25,000 people may have ADPKD based on the genetic prevalence of mutations in PKD genes in the population [21], probability of developing ESKD [22–24] and current 2020 population in Australia of ~25,000,000. Our proposed model hypothesizes that at least half of the ADPKD population will probably have a normal life expectancy with minimal medical complications during life [22–24] but that ~ 3,000 will be at risk of developing ESKD (light green circle), and of those two-thirds (n = 2000) are probably known to a nephrologist, but one-third will be undiagnosed and/or unknown to a nephrologist (n = 1000) (blue circle). The diagnosis of ADPKD in childhood is rare and in Australia estimated to be ~100 children [32] (yellow circle). In 2015 ~ 2000 individuals with ADPKD had end-stage kidney disease and were receiving dialysis or had a kidney transplant and the size of this population is accurately known (orange circle) [26]. Further studies using registry data (such as the ADPedKD) [32] and/or electronic medical records are an opportunity to test this hypothesis in the real-world.

demonstrates that *PKD1* dose is the key rate-limiting determinant of all types of ADPKD and associated with greater severity of the renal phenotype [42].

3.2. Molecular pathogenesis of ADPKD

PKD1 and *PKD2* encode polycystin-1 and polycystin-2 respectively which are members of the transient receptor potential channel protein family [29,43]. Both are membrane proteins and exist as a hetero-oligomeric complex (PKD1:PKD2; 1:3 ratio) on the shaft and basal body of the primary cilia and other subcellular locations (e.g. polycystin-2 is expressed on the endoplasmic reticulum where it acts as a nonselective calcium channel) [44]. The functions of the *PKD1/PKD2* complex are not fully clear but evidence to date shows that it is a homeostatic suppressor of multiple signal transduction pathways (TORC1, c-myc-sirtuin, Wnt, Jak-Stat) in response to ciliary bending with fluid flow during quiescence [45]. Intracellular cyclic adenosine monophosphate (cAMP) and calcium are critical intermediate molecules involved in mediating these signaling pathways [45]. Thus, in ADPKD, the reduction of polycystin-1 below a critical threshold produces an abnormal cell characterized by: (i) increased intracellular cAMP and reduced calcium; (ii) an increased utilization of aerobic glycolysis ('Warburg effect') [46]; and (iii) increased rate in proliferation, loss of differentiation and a more elastic basement membrane [46].

3.3. Mechanisms of focal kidney cyst formation

The dysregulated signal transduction due to polycystin-1 results in the renal phenotype in ADPKD. Interestingly, however, the formation of kidney cysts are focal arising from <5% of the estimated 1 million nephrons per kidney, and develop in haphazard manner, giving the typical multi-cystic and distorted appearance of the end-stage kidney in ADPKD. The focal manner of cyst formation is due to sporadic postnatal reductions in *PKD1* dose in principal cells of the collecting duct, either due to loss of heterozygosity (LOH, 'second hits') [47], stochastic and epigenetic factors and/or mosaicism [43,48]

3.4. Natural history of kidney cyst growth and kidney failure

The initial kidney cysts are microscopic (~200 µm in diameter) and form during early life, grow at a slow exponential rate (<1.5.to >6% per year) [49] and first become detectable by kidney ultrasound two to four decades later when they are ~1 cm and can be detected by renal ultrasound. By middle

adulthood, the cyst burden may increase the total kidney weight by more than five times of normal (1 kg *vs*. 0.2 kg) [50], causing chronic pain, hypertension and renal impairment [29,43]. The growth of kidney cysts is mediated by chloride-driven fluid secretion (*via* cystic fibrosis transmembrane regulator chloride channel, CFTR) and proliferation (*via* multiple signal transduction pathways including TORC1), and a multitude of other mechanisms in parrallel (renal inflammation/fibrosis, angiogenesis/microvascular ischemia, oxidative stress) contribute to the loss of functioning nephrons [40].

3.5. Vasopressin is a key regulator of postnatal renal cyst growth

Arginine vasopressin (AVP) has a well-established as the key extracellular growth factor for kidney cysts in ADPKD. In normal physiology, AVP is released from posterior pituitary in response to serum hyperosmolality, and binds to V_2 receptors on the basolateral membrane of collecting duct principal cells, causing the apical insertion of aquaporin-2 channels and the reabsorption of water from the lumen [51]. In ADPKD, AVP increases intracellular cAMP (by 147%) which mediates CFTR-mediated trans-epithelial fluid secretion (~6-fold) and the proliferation of cyst-forming renal epithelial, [9,52]. *In vivo* the absence of AVP completely abrogated renal cyst formation in rats [53], and V2RAs attenuated renal cyst growth in multiple genetic orthologs of PKD [8,53–56].

4. Medical management of ESKD due to ADPKD

4.1. Overview

ADPKD is a chronic disease and treatment can be challenging and complex due to several factors [57,58]: (i) the phenotypic heterogeneity creates uncertainties in predicting life-time outcomes and the decision to use DMDs; (ii) the long latent period of having few clinical symptoms which leads to young adults ignoring their disease; (iii) the risk for systemic complications and the need for specific counseling (in particular intracranial aneurysms); (iv) under-appreciation by healthcare workers of psychosocial impacts (such as anticipation of end-stage kidney disease, guilt and fear, particularly in light of perceived lack of treatment options; pain); and (v) finally, being a genetic disease, the clinical care involves not only the patient but also their immediate family.

The main principles and goals of medical management, based on clinical practice guidelines position statements [57–62], are summarized in Table 2, and include: (i) the prediction of renal prognosis using either/or: a) simple readily accessible clinical tools, such as age of onset of ESKD in 1st degree family members [4]; rate of decline in renal function using historical and prospective eGFR measurements [61]; renal length on ultrasound [63]; b) other clinical measurements that may not be readily available, such as total kidney volume measurement by MRI [64] and Mayo Imaging Classification [49] and Predicting Renal Outcomes in ADPKD (PROPKD) Risk Prediction Score (which, in part, requires the results of *PKD* DNA sequencing) [65]; (ii) the preservation of quality of life and restoration of normal health-span by reducing the life-time risk of ESKD and cardiovascular disease; and; (iii) the detection and appropriate management of extrarenal disease manifestations [66].

The specific strategies to prevent ESKD may be grouped as either primordial, primary, secondary or tertiary (Table 3). These can be further sub-divided into treatments that are current, emerging (presently in development in clinical trials) and future (those that might be developed in the future) (Table 3) [67].

5. Current treatment options to prevent ESKD

5.1. First-line treatments to prevent ESKD

5.1.1. Diet

Dietary care is the foundation of current treatment, and detailed narrative reviews and clinical practice guidelines are reviewed elsewhere [68,69]. In brief, patients with ADPKD should minimize the dietary intake of salt, as additional observational data suggests that this is likely to reduce renal cyst growth and cardiovascular disease complications [70]. In the HALT-PKD trial, for every 18mEq increase in the mean urinary sodium excretion there was a 0.43%/year rise in ht-TKV (in patients with eGFR>60 ml/min/1.73 m^2) and faster decline in eGFR (−0.09 ml/min/1.73 m^2) in patients with advanced disease (an eGFR between 25–60 ml/min/1.73 m^2) [71]. In addition, a small randomized controlled trial (n = 34) of 2 weeks duration in patients with eGFR>60 ml/min, a ~ 30% reduction in sodium intake with a ~ 40% increase in fluid intake caused a small reduction in serum copeptin (~1 pmol/L) (a surrogate marker of AVP) [72].

In contrast, the restriction of dietary protein intake does not benefit disease outcomes and should be avoided [73]. With regard to caffeine intake, previous studies in animal models and clinical studies have shown the potential harmful effects of caffeine but recent data does not supported this findings [68,69,74–77]. Therefore, caffeine is not contraindicated in ADPKD, but patients may avoid excessive intake. The role of fluid intake and ketone diets are not known and will be discussed in the 'emerging treatment' section.

5.1.2. Bodyweight

A post-hoc analysis of the HALT study showed that being overweight and obese was independently associated with 2–3 fold increased risk of rapid kidney cyst growth (TKV≥7% per year) and greater eGFR decline [70].

5.1.3. Management of blood pressure

The KDIGO Controversy Conference on ADPKD suggested a target BP of ≤130/80 mm Hg in patients with macroalbuminuria (≥25 mg/mmol in males and ≥35 mg/mmol in females) or ≤140/90 mm Hg if no macroalbuminuria [59]. The findings of the subsequent HALT-PKD clinical trial refined this recommendation and found that a target BP of 95/60 to 110/75 mm Hg (vs. 120/70 to 130/80) was associated with a small (1.1%/year) but significant reduction in TKV in young ADPKD patients (15–49 yrs old with preserved renal function) over 8 years (147). Unfortunately, the lower BP target was associated with a 16% increase in dizziness and light-headedness,

Table 2. Seven key elements of medical management in ADPKD.

		Reference
1	**Provision of comprehensive and multi-disciplinary care involving relevant specialists** (primary care provider, nephrologist, geneticist, genetic counselor, hepatologist, neurologist, neurosurgeon)	[57]
2	**Assessment of high-risk for development of ESKD using factors**: a. History (family history of ESKD <58 years old; history of hypertension or urological event <35 years old) b. Renal Function: Stage 2–3 CKD with declining estimated glomerular filtration rate (eGFR) (i) > 5 ml/min/1.73 m^2 or (ii) >2.5 ml/min1.73 m^2 per year over 5 years c. Imaging data (i) Renal length > 16.5 centrimetres or (ii) Height-corrected total kidney volume (Ht-TKV) > 650 millilitres/meter (iii) Mayo Subclass IC to IE d. Genetic testing results: Truncating mutation in *PKD1* (if known)	[4, 61, 63–65, 65, 65]
3.	**Reduce kidney cyst growth and prevent eGFR decline and hypertension** a. Review life-style factors (i) Smoking cessation (ii) Diet: Salt restriction (80–100 mmol/d) and moderate protein intake (iii) Maintain BMI<25 kg/m^2 b. Maintain BP<130/80 mm Hg with Renin Angiotensin System Blocker c. Maintain total cholesterol <4.0 mmol with diet± drug d. If diabetic, maintain glycosylated hemoglobin < 53 mmol/mol or 7.0% e. Avoid nephrotoxic drugs	[57–62]
4	**Evaluate for other renal complications** a. Plan for end-stage kidney if eGFR<30 ml/min b. Assessment of chronic kidney pain c. Evaluation of acute kidney pain (cyst infection, cyst hemorrhage, nephrolithiasis, urinary tract infection)	[57–62]
5	**Evaluate for eligibility and risk-benefit for treatment with disease modifying treatment** (currently tolvaptan)	[61]
6	**Evaluate for extra-renal complications** (cardiovascular disease, intracranial aneurysm)	[66]
7	**Consider referral to a clinical trial**	

Table 3. Current, emerging and possible future treatment strategies to prevent ESKD due to ADPKD.

Prevention Category	Definition in ADPKD	Current Treatments	Under Investigation (Emerging Treatments)	Possible Future Treatments
Primordial	*Elimination of mutation in genes that cause ADPKD*	PGD but long-term risks unknown	PGD with known long-term risk	Advanced and well established PGD
Primary	*Reduce risk of ESKD in patients with a mutation in PKD by reducing the formation and growth renal cyst growth*	Standard Care: Blood pressure lowering; Dietary modification; Lifestyle interventions.	Early Diagnosis Standard care ± validated public health interventions (vitamin B3, prescribed water intake, ketone diet)	Diagnosis at birth; Established Prediction tools; Established treatment pathways
Secondary	*Reduce the progression of CKD in patients with ADPKD by decreasing the rate of renal cyst growth, fibrosis and inflammation*	DMD (Tolvaptan)	DMDs (Lixivaptan, Venglustat, Bardoxolone, Pravastatin, Tesevatinib, Metformin)	Highly effective treatments targeting specific pathways that are safe, tolerable with few side-effects
Tertiary	*Prevent death due to kidney failure*	Dialysis (Peritoneal Dialysis and Hemodialysis) and Transplantation	New technologies in dialysis; Engineered organ replacement in development	New technologies in dialysis; Engineered organ replacement established

Abbreviations: PGD, pre-implantation genetic diagnosis; DMD, disease-modifying drug

and thus the KHA-CARI ADPKD Clinical Practice Guidelines agreed with KDIGO guidelines, and suggested that a lower target blood pressure could be considered in selected patients [78,79].

Inhibitors of renin angiotensin system (RAS), namely angiotensin converting enzyme inhibitors or angiotensin II receptor blockers are preferred first-line agents for blood pressure reduction [78]. There is limited evidence to guide second-line anti-hypertensive choice but the step-wise use of a cardio-selective beta blocker; dihydropyridine calcium channel blocker and/or or a diuretic, is suggested [79]. In addition, it has been shown that nitric oxide (NO) bioavailability is impaired in ADPKD and together with oxidative stress mediates endothelial dysfunction [80–84]. Thus, future clinical trials may investigate NO releasing 3rd generation beta-blockers (such as nebivolol) for evaluation in the ADPKD population [80–84]

5.1.4. Other first-line interventions

All ADPKD patients should avoid their exposure to nephrotoxins (non-steroidal anti-inflammatory drugs, aminoglycosides, radiocontrast] or procedures that increase the risk of acute kidney injury as experimental data shows that it increase risk of renal cyst growth [85]. A single randomized controlled trial in young patients (8–22 years) showed that pravastatin mildly attenuated TKV over 3 years (21% vs. 30% from baseline,

P = 0.02), independent of serum cholesterol [86] but this finding was not confirmed in a post-hoc analysis of the HALT trial [87]. At present, lipid lowering drugs are not recommended specifically for reducing renal cyst growth and further clinical trial data is required.

5.1.5. Effectiveness of first-line treatments

The long-term effectiveness of the combined effects of first-line treatments has not been formally investigated. However, in patients with a low to moderate risk of renal disease progression (which may be up to 50–75% of the total ADPKD population) the application of first-line interventions may potentially curtail the life-time development of ESKD and cardiovascular morbidity, if commenced during the first few decades of life [88].

5.2. Disease-modifying drugs (DMDs) for patients at high-risk for ESKD

DMDs are designed to alter the specific pathobiology of ADPKD. Due to the high frequency of adverse events and uncertainty of efficacy, current DMDs are restricted to clinical trials or in patients at high-risk for ESKD (possibly ~25% of patients) who exhibit features of rapid progression (e.g. 'rapid progressor' or other prognostic factors) despite receiving maximal first-line management. To date, three classes of small molecule drugs (SMD) have been re-purposed for evaluation as DMDs for ADPKD (V2RAs, somatostatin analogs and TORC1 inhibitors), but only V2RAs have achieved regulatory approval for use in ADPKD.

5.2.1. Vasopressin type 2 receptor antagonists (Tolvaptan)

5.2.1.1. Efficacy of tolvaptan in ADPKD. Tolvaptan is an orally active V2RA that has regulatory approval in several countries for selected patients with ADPKD. Two large multicentre RCTs (1–3 years in duration) demonstrated that chronic treatment with tolvaptan for up to 3 years reduced decline in eGFR (by ~1 ml/min/1.73 m^2) and attenuated the increase in ht-TKV [89,90] (see Table 4). Tolvaptan reduced the urine osmolality to less than 300 mosmol/L (a biomarker of V2 suppression) [91] but interestingly, the effect on attenuating the increase in TKV was not sustained after 1 year of treatment [92]. A post-hoc analysis of the TEMPO 3:4 trial showed that tolvaptan was also associated with reduction in kidney pain events (10.1% vs 16.8% in placebo; P <0.001), largely due to a decrease in acute episodes of urinary tract infection, kidney stone and hematuria [93].

5.2.1.2. Adverse effects of tolvaptan. Due to off-target suppression of water reabsorption in the distal nephron, the universal adverse effect of tolvaptan is aquaresis resulting in massive polyuria, pollakiuria, nocturia, thirst and polydipsia. In ADPKD clinical studies, the split-dose twice daily dosing of tolvaptan (90/30 mg) in patients with CKD Stage 1 or 2, caused a mean total daily volume of 7 liters (or a 4 liter increase above baseline urine output), and in Stage 4 patients, this was lower at 5 liters per day (or a 2 liter increase above baseline urine output). The aquaresis requires chronic adaptation in fluid intake behavior to avoid dehydration and may be tolerated in the long-term by up to 60–75% of motivated patients (e.g, those enrolled in clinicals) [94,95]. In addition, in the TEMPO 3:4 trial, 4.9% of ADPKD patients treated with tolvaptan developed clinically important idiosyncratic hepatic toxicity (ALT levels> 3 times the upper limit of normal) compared to 1.2% in the placebo [89]. All episodes were reversible (up to 4 months later) with interruption or drug withdrawal; unlikely to result in chronic hepatocellular injury; and occurred during the first 3 to 18 months of treatment [89,96]. A post-hoc analysis of the TEMPO and REPRISE trials showed that there was a small increased risk for liver function test abnormalities when statins are concurrently prescribed with tolvaptan [97].

5.2.1.3. Uncertainties regarding the efficacy of tolvaptan in ADPKD. Several publications have raised questions regarding the effectiveness of tolvaptan in ADPKD [98]: (i) first, one question raised is that the improvement in eGFR in the tolvaptan group in REPRISE was apparent only after drug

Table 4. Summary of the two key landmark tolvaptan randomized controlled trials in ADPKD [89,90].

Study Acronym	Study Parameters	Details	References
TEMPO 3:4	Study Population	18–50 yrs old, TKV>750 ml, eGFR>60 ml/min/1.73 m^2	[89]
	Sample Size	N = 1445	
	Study Design	3 yr, Phase 3, double-blind, placebo-controlled randomized (2:1) multi-center trial	
	Primary Endpoint	TKV: Increase 2.8%/yr in the tolvaptan group vs. 5.5%/year in the placebo	
	Secondary Endpoints	Slower decline in kidney function (reciprocal of the serum creatinine −2.61 mg/ml/yr *vs.* −3.81 mg/ml/yr; P <0.001); lower rates of worsening kidney function (2 *vs.* 5 events per 100 person-yr, P <0.001) & kidney pain (5 *vs.* 7 events/100 person-yrs follow-up P = 0.007)	
	Adverse Events	Tolvaptan associated with aquaresis, hepatic injury and higher discontinuation rate (23%, *vs.* 14% in the placebo group).	
REPRISE	Study Population	18–55 yrs old (eGFR 25–65 ml/min/1.73 m^2) and 56–65 (eGFR 25–44 ml/min/1.73 m2); and ability to tolerate tolvaptan after an 8-week pre-randomization period	[90]
	Sample Size	N = 1370	
	Study Design	1 yr, Phase 3, double-blind, randomized placebo-controlled (1:1), multi-center trial	
	Primary Endpoint	Change from baseline to 1 yr eGFR: −2.34 1.73 ml/min/m^2 in the tolvaptan *vs.* −3.61 ml/min/1.73 m^2 in placebo, equal to difference of 1.27 ml/min1.73 m^2 P <0.001)	
	Secondary Endpoints	Sub-groups: benefit highest in Stage 3A CKD (eGFR difference 2.34 ml/min1.73 m^2) vs. Stage 3B/4 (2.34 ml/min1.73 m^2), Caucasian and age<55 years old	
	Adverse Events	Overall >80% of participants experienced; 10% unable to tolerate aquaretic side effects during run-in; hepatic Injury (5.6% in tolvaptan group *vs.* 1.2% in the placebo group); drug discontinuation (9.5% vs 2.2%)	

discontinuation, raising the possibility that hemodynamic and other cofounding factors may partly explain this result [99]; (ii) second, the magnitude of the effect size on renal function (a difference of ~1 ml/min/1.73 m^2) was smaller than traditional reno-protective therapies, such as angiotensin converting enzyme inhibitors (e.g. in the REIN study ramipril reduced the annual rate of decline in GFR by ~4 ml/min) [100]; (iii) third, the reduction in TKV occurs within weeks of administration but not sustained beyond 12 months [92]; (iv) fourth, the long-term benefits of tolvaptan on the hard end-point of preventing ESKD is unknown and the data is limited to uncontrolled historical cohort analysis [101] or *in silico* modeling studies [99,102]; and (v) fifth, sub-groups (non-Caucasians, age> 55 years) may have less or no benefit in reducing renal function decline [90]. In addition, other mechanistic questions remain: (i) preclinical studies in *pck* rats suggest that both increased water intake and V2RAs could have similar efficacy on reducing the kidney enlargement by ~30% [54,103] but this has not been addressed in clinical trials; (ii) *in vitro* studies support a direct role for inhibition of AVP on renal cyst growth, but it is not known if human renal cysts express V_2 receptors on their basolateral membrane, as hypothesized in clinical trials. Thus, further post-marketing cohort studies are needed to improve understanding of tolvaptan in ADPKD.

5.2.1.4. Indications for tolvaptan use in ADPKD. Due to the adverse effects and uncertainties in the evidence, in most countries the prescribing of tolvaptan in ADPKD is restricted to those at high-risk of developing ESKD. In Australia, patient eligibility for tolvaptan is based, in part, on the ERA-EDTA Guidelines [61], and requires three criteria to be met: (i) age≥18 years of age; (ii) CKD stage 2–3 (eGFR 30–89 ml/min/1.73 m^2) and (iii) evidence of rapid decline, defined as either an eGFR decline of ≥5 ml/min/1.73 m^2 in one year or ≥2.5 ml/min/1.73 m^2 per year over a period of 5 years. Nephrologists are required to obtain informed consent regarding efficacy and adverse effects, and, the Australian Therapeutic Goods Administration mandated that liver function tests should be checked monthly for the first 1.5 years of treatment and then every 3-months thereafter, for the detection of idiosyncratic hepatic toxicity.

5.2.2. Somatostatin analogs

Although somatostatin analogs (octreotide, lanreotide, pasireotide) reduced renal cyst growth in animal models [104,105], current evidence does not support their use to delay ESKD due to ADPKD. The ALADIN study (a RCT of 75 patients) showed that octreotide transiently reduced the increase in TKV at 1 year but this benefit was maintained after 3 years [104,105]. Moreover, the DIPAK-1 study (191), which compared monthly lanreotide (120 mg; n = 153) with standard care over 2.5 years, showed that there was no change in the decline in eGFR (−3.56 vs. −3.46 ml/min/1.73 m^2 per year), though the rate of increase in TKV was reduced slightly (4.2% vs. 5.6%) (192) [104,105]. These data together with the high rate of gastrointestinal side-effects and the monthly intramuscular route of injections (requiring 18 G needles) does not support use of somatostatin analog monotherapy in ADPKD. Interestingly, in a genetic mouse model of ADPKD, the combination of somatastatin analog with a V2RA was synergistic in reducing cystic disease progression [106] and this hypothesis is currently being evaluated in a small quadruple-blind single-arm crossover design clinical trial (n = 20) in humans (NCT03541447) [107].

5.2.3. TORC1 and src inhibitors

Based on current evidence, TORC1 and Src inhibitors are not recommended for the prevention of ESKD. In the case of TORC1 inhibitors (everolimus, sirolimus), preclinical studies in animal models conclusively demonstrated potent suppression of proliferation of cystic epithelial cells and reduction of renal cyst growth [108]. However, subsequent human clinical trials were associated with minimal efficacy [109] due to a number of factors: (i) patient drop-outs from adverse events (mouth ulcers); (ii) insufficient drug delivered to target tissue [110]; and (iii) trial design, as the intervention was initiated when kidneys had reached their near-maximal volume [111] when efficacy is reduced [108]. Moreover, an additional trial testing the efficacy of sirolimus in ADPKD patients with CKD stage 3B-4 was terminated prematurely due to multiple safety events [112] Nevertheless, as TORC signaling has a critical role in mediating kidney cyst growth, perhaps innovative approaches to dosing (such as pulsed dose of 3 mg sirolimus per week in the Vienna RAP study; NCT020550279 2014–19) [113] and/or drug delivery might allow TORC1 inhibitors to be re-considered in the future [114,115]. Bosutinib is an oral dual Src/Bcr-Abl tyrosine kinase inhibitor used to treat Philadelphia chromosome-positive chronic myeloid leukemia patients, and reduced renal cyst growth in preclinical models [116]. However, in a single phase 2 RCT (n = 172) of ADPKD patients, 68% of patients did not complete the study due to high rate of drug-related adverse effects (primarily diarrhea) [116].

6. Emerging treatment options for the prevention of ESKD due to ADPKD

6.1. Public health interventions in the ADPKD population

6.1.1. Niacinamide

High-dose niacinamide (vitamin B3) (30 mg/kg/day) reduces renal cyst growth in preclinical models of ADPKD by suppressing the sirtuin family of signaling proteins [12]. Two single center clinical trials (n = 10, NCT02140814; n = 36, NCT02558595) [117,118] evaluating the safety and tolerability of niacinamide, have been completed and final results are awaited [12].

6.1.2. Water intake

It has been hypothesized that maintaining a water intake of greater than three liters per day may reduce the progression of renal cyst growth in ADPKD by suppressing AVP release [119], and this is supported by preclinical data [120]. However, the volume of water required to suppress AVP is dependent on amount of dietary solute intake and should be personalized [119]. Although this intervention is low-cost and simple, there is no high-level evidence to support this as

a recommendation for clinical practice [69]. To date, short-term studies (<2 months in duration) demonstrate that vasopressin activation could be reduced at consumption volumes that are tolerable to patients [69,72,121]. However, the long-term efficacy (on renal function decline and renal cyst growth), safety and feasibility of this approach are not known. The only available long-term data in humans is a small non-randomized observational cohort study (n = 33) which showed that the progression of TKV or decline in eGFR in patients who drank 2.5–3.0 L per day was not different to those who consumed lower amounts over 1 year period [122]. This study was non-randomized and of insufficient duration and power [69]. Currently, two clinical trials are currently in progress to evaluate the long-term efficacy and safety of increased fluid intake in PKD [123,124] (Table 5).

6.1.3. Ketone diet, intermittent fasting and/or ketone supplementation

There is significant interest in ketone diet and ketogenesis in ADPKD. The ketone diet [low carbohydrate (5%) and high fat (70%) content] utilizes ketone bodies from the metabolic breakdown of fat to generate energy [125]. Alternatively, ketosis can be induced by intermittent fasting or administration of exogenous ketones [125]. This diet has been popular due to its ability to accelerate weight loss and treatment for epilepsies and neurological disorders [126]. Recent preclinical studies have found that renal cyst formation is largely glucose-dependent [127]. Acute fasting in rat, mouse, and feline models of PKD reduced cyst volume, while oral administration of the ketone β-hydroxybutyrate (BHB) in rats strongly inhibited PKD progression [127]. Time-restricted feeding, without caloric reduction, strongly inhibited TORC1 signaling, proliferation, and fibrosis in kidneys in a PKD rat model [127]. These results confirmed that cystic cells in PKD are metabolically inflexible (Warburg Effect), which could be exploited by dietary interventions or supplementation with BHB [128]. Moreover, a short-term study has concluded that in humans, intermittent-fasting interventions improves insulin resistance, hypertension, and inflammation (but only in the context of restricted feeding) [129]. On the other hand, ketogenic diets increase the risk of nephrolithiasis [130] and are heavily restrictive and difficult to follow for extended periods [131]. Thus, the long-term safety, efficacy and feasibility of a ketone diet and intermittent fasting needs careful evaluation in clinical trials in ADPKD. In this regard, the study protocol of an Italian RCT to assess the effect of a ketogenic diet (modified Atkins diet vs. normo-caloric diet) (n = 90) on the progression of ADPKD was published in early 2020 [132] and others are expected.

Table 5. Long-term clinical trials on water intake in ADPKD.

	PREVENT-ADPKD STUDY	ROGOSIN STUDY	References
Trial Registration	ACTRN12614001216606	NCT03102632	[123,124]
Nature	Multi-center (13 sites)	Single center	
Rationale	Chronic Feasibility, Efficacy, Safety (Chronic)	Chronic Feasibility, Efficacy, Safety	
Funding	NHMRC Danone Nutricia The University of Sydney, PKD Australia Westmead Hospital	The Rogosin Institute	
Sponsor	Westmead Hospital	The Rogosin Institute	
Sample size	N = 180	N = 32	
ADPKD Population	18–67 years old eGFR≥30 ml/min/1.73 m^2	18–65 years old eGFR>40 ml/min/1.73 m^2 Urine osmolality>400 mOsm/L	
Exclusion	Mayo Subclass IA	Tolvaptan	
Allocation	Randomized	Sequential, single arm	
Control Arm	Ad libitum water intake	Usual water intake for 1st 6 months	
Treatment Arm	Prescribed water intake (Personalized to achieve target urine osmolality < 270 mOsm/L) + Dietary intervention to reduce solute intake)	High water intake for next 12 months	
Start Date	December 2015	June 2017	
Finish Date	May 2021	December 2021	
Follow-up period	36 months	18 months	
Primary Outcome	Change in Ht-TKV	Change in TKV	

Abbreviations: NHMRC, National Health and Medical Research Council of Australia; PKD, Polycystic kidney disease, Ht-TKV, height-adjusted total kidney volume

6.2. Small molecule drugs (SMD) re-purposed for ADPKD

At least eight SMDs (lixivaptan, tesevatinib, venglustat, bardoxolone, pravastatin, hydralazine, pioglitazone, metformin) are currently under evaluation in clinical trials [133] (Table 6). Lixivaptan is an orally active and selective V2 receptor antagonist that has pharmacological effects identical to tolvaptan but predicted to have a lower risk for hepatotoxicity [134]. Preclinical studies in the *pck* rat demonstrate that lixivaptan reduces renal cyst growth [135] and a 1-year double-blind randomized clinical trial to evaluate safety and efficacy in human ADPKD is anticipated to start in April 2021 and finish in 2024 (NCT04064346) [136]. (or KD019) is an orally active novel kinase inhibitor that suppresses multiple signal pathways regulating mitosis (tyrosine kinase, EGFR) and angiogenesis (VEGF-2) and under investigation for the treatment of cancer [137]. Preclinical studies in the *pck* rat and *bpk* mice support the efficacy of tesevatinib in PKD [138], and presently in Phase 2 randomized controlled clinical trial (50 mg vs. placebo n = 80) with Ht-TKV as the primary endpoint with the final data expected in 2022 (NCT03203642) [139].

Tesevatinib (or KD019) is an orally active novel kinase inhibitor that suppresses multiple signal pathways regulating mitosis (tyrosine kinase, EGFR) and angiogenesis (VEGF-2) and under investigation for the treatment of cancer [137]. Preclinical studies in the *pck* rat and *bpk* mice support the efficacy of tesevatinib in PKD [138], and presently in Phase 2 randomized controlled clinical trial (50 mg vs. placebo n = 80) with Ht-TKV as the primary endpoint with the final data expected in 2022 (NCT03203642) [139].

Tesevatinib (or KD019) is an orally active novel kinase inhibitor that suppresses multiple signal pathways regulating

Table 6. Small molecule drugs in clinical trials in ADPKD.

Study ID	SMD	MOA	Re-purposed	Phase	n	Years	Sponsor	Reference
NCT04064346	Lixivaptan	V2 receptor antagonist	Yes	3	Planned (n = 1200)	Planned (2021–24)	Palladio Bio	[136]
NCT03541447	Tolvaptan with octreotide	V2 receptor antagonist and somatostatin analog	Yes	2	N = 20	2018–2020	Mario Negri Institute for Pharmacological Research, Italy	[107]
NCT03203642	Tesevatinib	Multi-Kinase Inhibitor	Yes	2	N = 80	2017–2022	Kadmon Corporation	[139,142]
NCT03523728 (STAGED-PKD)	Venglustat	Glucosylceramide synthase inhibitor	Yes	2/3	N = 640	2018–23	Sanofi-Genzyme	[142]
NCT03918447 (FALCON)	Bardoxolone	Nrf2 activator	Yes	3	N = 300	2019–23	Reata Pharmaceuticals	[147]
NCT03273413	Pravastatin	HMG CoA Inhibitor	Yes	4	N = 200	2017–21	University of Colorado, Denver, USA	[148]
NCT04284657 (ADPKD-SAT)	Pravastatin and Sodium Citrate	HMG CoA Inhibitor and oral alkali	Yes	2	N = 30	2019–20	University of Southern California, USA	[149]
NCT03423810	Hydralazine	DNA methyltransferase inhibitor	Yes	1	N = 14	2018-Jan 2020 (Results pending)	University of Kansas Medical Center	[152]
NCT02697617	Pioglitazone	PPAR-γ agonist	Yes	2	N = 18	2016–2020	Indiana University	[154]

Abbreviations: PPAR-γ, peroxisome proliferator-activated receptor-gamma; HMG CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase

mitosis (tyrosine kinase, EGFR) and angiogenesis (VEGF-2) and under investigation for the treatment of cancer [137]. Preclinical studies in the *pck* rat and *bpk* mice support the efficacy of tesevatinib in PKD [138], and presently in Phase 2 randomized controlled clinical trial (50 mg vs. placebo n = 80) with Ht-TKV as the primary endpoint with the final data expected in 2022 (NCT03203642) [139].

Tesevatinib (or KD019) is an orally active novel kinase inhibitor that suppresses multiple signal pathways regulating mitosis (tyrosine kinase, EGFR) and angiogenesis (VEGF-2) and under investigation for the treatment of cancer [137]. Preclinical studies in the PCK rat and *bpk* mice support the efficacy of tesevatinib in PKD [138], and presently in phase 2 randomized controlled clinical trial (50 mg vs. placebo n = 80) with Ht-TKV as the primary endpoint with the final data expected in 2022 (NCT03203642) [139].

Glycosphingolipids (GSLs) are structural components of cell membranes that regulate Akt-TORC1 signaling and accumulate in experimental models of PKD [140]. Pharmacological inhibition reduces cystogenesis in *jck, pcy* and *Pkd1*-null mice [141]. Currently venglustat, an orally active glucosylceramide synthase inhibitor which has been re-purposed from trials in Fabry and Gaucher Disease, is in Phase 2/3 clinic trials in human ADPKD with final data expected in late 2023 (NCT03523728; STAGED-PKD Study) [142].

Bardoxolone is a potent antioxidant activator of the Nrf2 pathway (and suppresses NF-κB) which was initially evaluated in Stage 4 CKD due to diabetic nephropathy but a 1.8-fold increase in cardiovascular events (due to heart failure possibly due to suppression of endothelin signaling) led to early termination [143,144]. However, the sponsor subsequently hypothesized that it may be beneficial in preserving eGFR in patients with rare inherited kidney diseases (Alport Syndrome and ADPKD) who do not have preexisting significant cardiovascular disease [145]. Thus, clinical trials examining this hypothesis are concurrently in progress in both Alport Syndrome (NCT03019185; the CARDINAL Study) [146], and ADPKD (NCT03918447, the FALCON study) [147] and the safety of bardoxolone (especially on cardiovascular events and effects of increasing eGFR, such as increased albuminuria) will be carefully assessed [145].

Several other SMDs (pravastatin, hydralazine, pioglitazone, metformin) used widely in clinical practice for managing common condition have also been repurposed for evaluation in clinical trials in ADPKD. For example, preclinical studies demonstrate that statins reduce G-protein mediated cell proliferation and renal cyst growth in animal models, and feasibility studies support this hypothesis [86]. Consequently, a 2-year randomized controlled trial (n = 200) comparing pravastatin (40 mg/day) to placebo is in progress and will report on the efficacy on change in TKV (NCT03273413) [148]. A smaller open-label study (n = 30) of pravastatin (40 mg/day) with or without sodium citrate is also in progress and will be completed in December 2020 (NCT04284657) [149]. Hydralazine is a well-known anti-hypertensive agent that has DNA demethylating properties which may be relevant in the pathogenesis of ADPKD [48,150,151]. Thus, a single-arm open label pilot study (n = 14) will assess the dose-response relationship between hydralazine (5 to 50 mg bd) and DNA methyltransferase in PKD patients to determine if urinary polycystin-1 levels will be altered after 6 weeks of treatment (NCT03423810) [152]. Pioglitazone is an oral thiazolidinedione antidiabetic agent used for adjunctive treatment to type 2 diabetes, and is a potent agonist of peroxisome proliferator activated receptor gamma (PPARγ) [11,13]. Preclinical studies demonstrated that thiazolidinediones attenuate renal cyst growth in several rat models of PKD (PCK, Wpk and Han:Sprd rat) though not in iKspCre-*Pkd1*^{del} mice [153]. Currently, a Phase-2 double-blind cross-over safety trial (n = 18) using is in progress with pioglitazone in ADPKD adults and will be competed in late 2020 (NCT02697617) [154]. Metformin is a well-known anti-diabetic biguanide derivative [155], and

Table 7. Clinical trials of metformin in ADPKD.

Study ID	Phase	n	Design	Centers	Expected Completion	References
NCT02656017 (TAME)	2	97	RCT: Metformin (1 g/d) vs. Placebo) 18–60 yrs old; Primary Outcome: Safety and Tolerability	University of Maryland, Baltimore, USA Tufts Medical Center, Boston, USA	Dec 2020	[159]
NCT02903511	2	50	RCT: Metformin (1 g/d) vs. Placebo) 30–60 yrs old; eGFR 50–80 ml/min/ 1.73 m^2; Primary Outcome: Safety and Tolerability	University of Colorado, Denver, USA	Oct 2020	[160]
NCT03764605 (METROPOLIS)	3a	150	RCT: Metformin (1 g/d) vs. Tolvaptan (up to 90/30 mg/d): 18–50 yrs old, PKD1 truncating mutation, eGFR≥45 ml/min/ 1.73 m^2; Primary outcome: change in eGFR over 25 months	Azienda Ospedaliero-Universitaria Consorziale Policlinico (AOUC), Bari, Italy	Planned (2018–2022)	[161]
AKTN 16.01 (IMPEDE-PKD)	3a	1164	RCT: Metformin (1 g) vs. standard of care in adults with CKD Stages 2–3a and rapidly progressing ADPKD; Primary outcome: Change in eFDR at 104 weeks; Commencing early 2021	Royal Brisbane Hospital, University of Queensland, Australasian Kidney Trials Network and multipe centers in Australia, Europe, USA and Asia	Planned (2021–25)	[162]

hypothesized to be candidate for the treatment of ADPKD as it suppresses cystic fibrosis transmembrane and TORC1 signaling [156]. There are some inconsistencies in the preclinical data and clinical trial data is needed to evaluate the hypothesis [157,158]. Presently two safety and tolerability clinical trials are in progress [159,160] and another two trials are expected to commence recruiting in 2021 [161,162], including a large multi-center international RCT (IMPEDE-PKD) (see Table 7 for details).

6.3. Strategies to reduce tolvaptan-induced aquaresis

Reducing the dietary intake of solutes may be a partial determinant of 24-hour urine volume with tolvaptan but this intervention requires repeated educational counseling to implement [163,164]. Two studies are currently evaluating the role of reducing dietary sodium and intake tolvaptan-induced aquaresis. The *Wishing to Decrease Aquaresis in ADPKD Patients Treated with a V2Ra* trial is a n = 12 cross-over study of 8 weeks will examine the effect of regulating dietary salt and protein on aquaresis; NCT043102319) [165]. The other is the *Dietary Intervention in ADPKD on Tolvaptan* trial which is a n = 15 single-arm study of 3 month duration (NCT03858439) [166]. Observational data also indicates that the combined administration of hydrochlorothiazide may also reduce the severity of tolvaptan-induced aquaresis [167]. On the other hand, data from the PCK rat suggests that the addition of hydrochlorothiazide might also offset the effectiveness of tolvaptan on slowing renal cyst growth [168], and therefore prospective study in humans is required to evaluate this question.

6.4. Other therapies in development (Other SMDs, stem cell-based therapies, 2-deoxyg-glucose)

RGLS4326 (Regulus Therapeutics) is a first-in-class short oligonucleotide that suppresses miR-17 (and de-represses *Pkd1*/*Pkd2*), localizes preferentially to the kidney and collecting duct-derived cells in preclinical studies [169], and currently under review for evaluation in human ADPKD. Lumacaftor (VX-809, Vertex Pharmaceuticals) is augments CFTR and in preclinical studies reduced cyst growth probably through a novel mechanism of action of reducing renal cyst fluid secretion [170]. MR-L2 (Mironid Ltd, UK) is allosteric activator of phosphodiesterase-4 family that lowers intracellular cAMP levels, and reduces cyst growth *in vitro* [171]. The efficacy of cell-based therapies, such as autologous mesenchymal stromal cells (MSCs) and other genetic approaches remain unclear. A single-arm phase 1 1 year trial in human ADPKD in 6 ADPKD patients [172] revealed no safety issues but an experimental data from PCK rats suggest that a single dose of MSCs was insufficient to alter the chronic and life-long process of cystogenesis [173]. Lastly, a 3-month phase 1 trial involving 18 ADPKD using 2-deoxy-glucose, based on the principal that cystic-lining epithelial cells are predominantly reliant on aerobic glycolysis (Warburg Effect) is in development [11].

6.5. Preimplantation genetic diagnosis (PGD) and *In vitro* fertilization (IVF)

PGD has been increasingly considered and utilized as an approach to prevent genetic transmission in families with a generational history of severe kidney disease [174]. In a survey of 96 UK patients with ADPKD, the majority (>95%) were concerned about the risk of genetic transmission and most (>80%) were interested in PGD [175]. In China, 40% of ADPKD patients (18–45 years old; n = 260 total) did not intend to have a family due to fear of genetic transmission but ~80% wished to consider PGD [176]. However, there are several questions in the use of PGD in ADPKD: (i) the pyschological acceptance by patients and availability/affordibility of centers with expertise in PGD may be variable [176]; (ii) the ethical dilemma of the use of PGD in families predicted to have benign clinical outcomes in ADPKD requires broader discussion [177]; and. (iii) finally, the long-term outcomes of PGD in ADPKD are unknown

but will be informed by an ongoing multi-center ESPERANCE observational cohort study in China (NCT02948179) [176].

7. concluding

This review, outlining the current and emerging treatments for the prevention of ESKD due to ADPKD, has revealed that an era of immense translational discovery is unfolding. While current treatments are imperfect, in our opinion, the simple approaches, such as early diagnosis together with effective implementation of proven first-line treatments and validated interventions with few side-effects (primary prevention), will probably be sufficient to curtail life-time risk of ESKD in individuals with favorable prognostic features that are identified during the pre-symptomatic stage. In contrast, more complex interventions involving DMDs and other specific approaches likely to be required for those with markers of rapid disease progression. Together these strategies will allow ESKD due to ADPKD to become an ultra-rare complication during the 21st Century.

8. Expert opinion on treatment options for the prevention of ESKD due to ADPKD

8.1. Expansion of treatment options and refinement of V2RAs in ADPKD clinical care

V2RAs have generated renewed interest in ADPKD, leading to an abundance of new interventions being evaluated in clinical trials, as discussed earlier. Thus, over the next decade, the number of proven treatments will expand, providing opportunities to individualize therapy based on personal preferences and disease ontology. Moreover, over the next 5 years, ongoing post-market cohort studies such as the German ADPKD Tolvaptan Treatment Registry (2015–27, NCT02497521); the Canadian Medical Assessment of JINARC Outcomes Registry (C-MAJOR study, 2016–22, NCT02925221) [178,179] will allow the long-term uncertainties of V2Ras in ADPKD to be addressed. In addition, studies in sub-groups, such as pediatric ADPKD patients [180] and in Korea (the ESSENTIAL trial, NCT03949894) [181], will provide much needed data.

8.2. Major barriers in clinical translational research in ADPKD can be addressed

The development of tolvaptan required nearly two decades of research effort with considerable resource investment but it is anticipated future therapeutic advances will be accomplished in a more efficient manner. One of the main challenges, of course, is that ADPKD is a chronic life-long disease with 'deferred consequences' [182] with a long asymptomatic phase [183–185]. The latter situation means that that success and adherence to treatment will be influenced by the degree of change in behavior required to implement the treatment. Moreover, Smith and Sautenet have also emphasized the tremendous research waste associated with non-standardized clinical trial designs [186,187]. In this regard, to conduct an objective analysis of the research that has been undertaken in ADPKD, we performed a preliminary analysis of the characteristics of clinical trials conducted in PKD over the last 20 years. Two surprising observations are important to mention: (i) the final results were reported in only ~20% of studies (Figure 2); (ii) the global inequity of clinical trials in PKD is shown in Figure 3, with the majority of PKD trials performed over the last 20 years have been undertaken in North America and Europe.

There are several solutions for accelerating research outcomes and address the challenges mentioned in the above paragraph: (i) the core unmet need is an urgent need to develop short-term disease-specific biomarkers trial outcomes and other computational models that accurately predict long-term outcome of ESKD [12,186]; (ii) a second but equally important unmet need are ADPKD Registries (such as that developed by U.S. PKD Foundation, NCT04039061 which will enroll 3000 patients over 10 years) [188] to enable accurate tracking of disease outcomes as new treatments are introduced, reveal unmet disease-specific needs and more efficient recruitment to clinical trials; (iii) the selection of re-purposed drugs for clinical trials must be based on compelling preclinical and pilot data (as it was for V2RAs) together with better understanding of long-term tolerability; (iv) new trials should increase efficiency through innovative design (such as prognostic enrichment, cross-over, adaptive, platform, pragmatic, N-of-1) together with consideration of convenience to

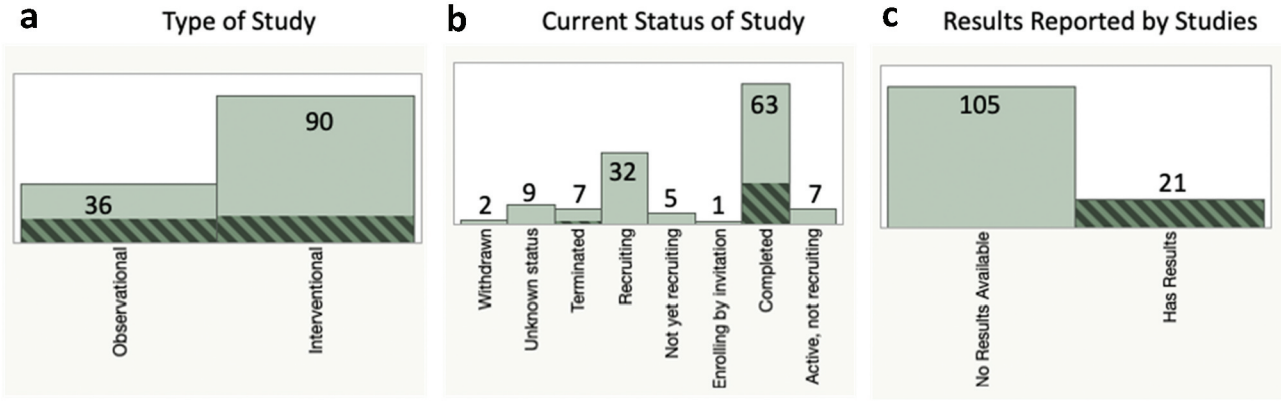

Figure 2. Characteristics of clinical trials performed in ADPKD in the clinicaltrials.gov database [14] between 2000 to 2020. A total of 126 clinical trials in ADPKD were recorded during this period involving 53,942 patients. The majority of studies were interventional (n = 90) (Panel A) and had been completed (n = 63) (Panel B) but only 21 studies had results reported (Panel C). The hatched areas indicate the studies which have results reported. The data was accessed from ClinicalTrials.gov website in September 2019 and analyzed using Excel and JMP Statistical Software (version 14.0).

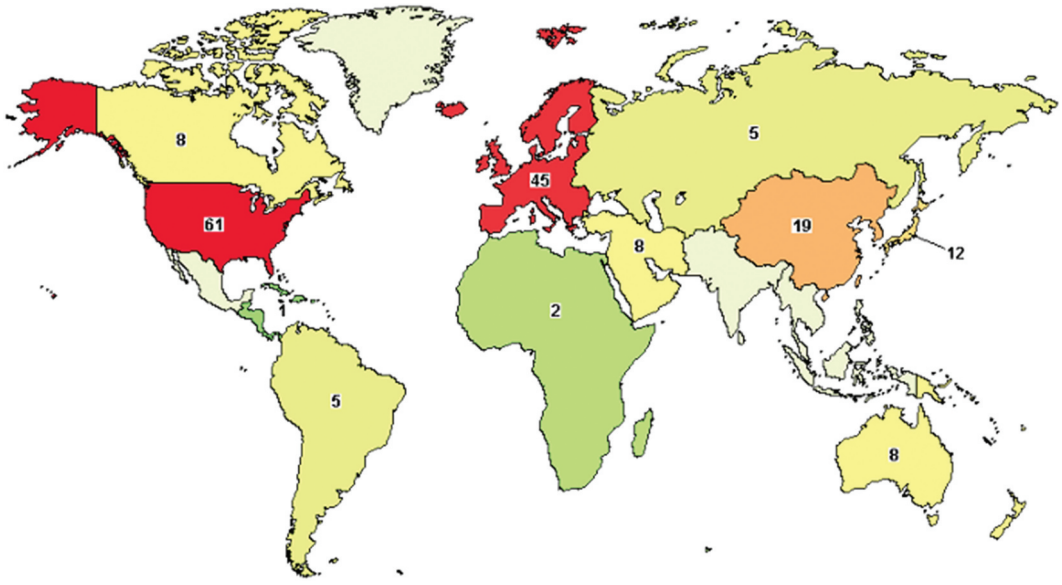

Figure 3. Global distribution of clinical trials performed in ADPKD in the ClinicalTrials.gov database [14] (2000–2020). A total of 126 clinical trials were recorded during this period involving 53,942 patients, and the majority were conducted in the North America (n = 69) and Europe (n = 45) Data was accessed and figure created using tools from ClinicalTrials.gov website [14] in September 2019.

participants (e.g. using remote and virtual monitoring of endpoints, simplification of outcome measures) [189]; (v) government funding to support interventions without commercial value (e.g. vitamin B3, fluid intake, re-purposed drugs); (vi) perhaps in the long-term re-configuration of roles played by industry and government in drug development for rare inherited diseases is needed, as suggested by Chandra [190]; and finally, (vii) given that treatment responses to DMDs vary across populations [89], the establishment of global research networks, such as the RAPID-ADPKD consortium in the Asia-Pacific, are needed to address this problem [191].

8.3. Need for earlier pre-symptomatic diagnosis and enhanced health-service delivery

Finally, while the current treatments to prevent ESKD due to ADPKD are not ideal, better outcomes could also be also achieved by implementing two high-value strategies: (i) enhancement of the delivery of medical care [192]; and (ii) earlier diagnosis and follow-up (e.g. reducing the average age of diagnosis from 35 years old [30]). In this regard, policy initiatives, such as the ADPKD Road Map by PKD International, and government-ADPKD community partnerships will ensure that these strategies remain at the forefront [193].

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