Mechanisms and management of hypertension in autosomal dominant polycystic kidney disease

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited kidney disease, characterized by progressive cyst growth and renal enlargement, resulting in renal failure. Hypertension is common and occurs early, prior to loss of kidney function. Whether hypertension in ADPKD is a primary vasculopathy secondary to mutations in the polycystin genes or secondary to activation of the renin–angiotensin–aldosterone system by cyst expansion and intrarenal ischemia is unclear. Dysregulation of the primary cilium causing endothelial and vascular smooth muscle cell dysfunction is a component of ADPKD. In this article, we review the epidemiology, pathophysiology and clinical characteristics of hypertension in ADPKD and give specific recommendations for its treatment.

Keywords: autosomal dominant polycystic kidney disease, endothelial dysfunction, hypertension, renin–angiotensin–aldosterone system, treatment

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary systemic disorder, occurring in 1:400 to 1:1000 individuals [1]. Renal manifestations relate to gradual cystic expansion and enlarged kidneys leading to hypertension, pain, urinary tract infections, gross hematuria and nephrolithiasis. Progressive renal insufficiency is common, but occurs late, often leading to end-stage renal disease (ESRD) in the fifth or sixth decade of life.

Mutations in two genes, the PKD1 gene (85% of cases) located on chromosome 16p13.3 and the PKD2 gene (15% of cases) located on chromosome 4q21, have been identified to cause ADPKD [2]. PKD1 and PKD2 mutations encode the membrane-associated proteins polycystin-1 (PC1) and polycystin-2 (PC2), respectively. Both PC1 and PC2 are localized on the primary cilia, which are critical extracellular organelles found on the surface of almost all cells including renal epithelial cells and endothelia cells. PC1 is a large integral membrane protein that has the structure of a receptor or adhesion molecule and regulates intracellular cyclic Adenosyine Monophosphate (cAMP) levels. PC2 is a nonselective cation channel, TRPP6 channel, belonging to the family of transient receptor potential (TRPP), with high permeability to calcium (Ca^{2+}). PC2 interacts with and may be regulated by PC1, and also plays a role in the regulation of intracellular calcium (iCa^{2+}) homeostasis by increasing calcium release from the endoplasmic reticulum [3–6].

Epidemiology and clinical characteristics of hypertension in ADPKD

Hypertension is the initial presentation for many ADPKD patients (30%) and is usually diagnosed 15 years earlier than in those with essential hypertension. Hypertension is common and of early onset at ∼30 years of age. Sixty percent of patients are diagnosed before any substantial decline in renal function and 20% develop hypertension by the age of 20.

Based on a 22-year follow-up study in Canada performed in the 1980s, antihypertensive therapy was initiated earlier in PKD1 than PKD2 patients (median 46 versus 51 years) [7], but the age of initiation of therapy is probably lower now. Hypertension in an affected parent has been associated with an increased frequency and earlier age at onset of hypertension in ADPKD offspring [8]. In addition, men are more often hypertensive than women and have higher blood pressure (BP) levels. Hypertension is common in children and also in young adults with ADPKD, occurring in 20, 35 and 49%, respectively [1, 9, 10], and is often the main clinical finding in these young individuals. Many children present with abnormal circadian BP levels [8, 10]. Importantly, an observational study of 312 children with PKD reported that high BP associates with faster renal cyst growth. PKD children with high BP have faster renal growth than those with lower BP [11]. This suggests that hypertension is a risk factor for cyst growth in PKD, independent from kidney function [12, 13].
Specific characteristics of the circadian variation of BP in ADPKD have been identified using 24-h ambulatory blood pressure monitoring (ABPM). A study of 36 young (age 21–31) ADPKD patients, with normal renal function and office BP of <140/90, revealed that 6 of 36 (16.7%) patients were hypertensive based on ABPM readings, indicating masked hypertension. The amplitude of nocturnal dipping is lower [14], and nondipping, defined as >10% drop in systolic BP during the night compared with daytime, is more common in PKD [44% of both prehypertensive and hypertensive patients with ADPKD and chronic kidney disease (CKD) stages II and III] [15]. This constitutes a significant risk factor for end-organ damage and cardiovascular events.

Positive correlations between average 24-h systolic blood pressure (SBP) and left ventricular mass index (LVMI) in both normotensive and hypertensive ADPKD patients have been shown [16]. Moreover, biventricular diastolic dysfunction is present in both hypertensive and normotensive patients with ADPKD and preserved renal function [17]. Cardiac studies in ADPKD adults have reported left ventricular hypertrophy (LVH) in 48% of cases, based on echocardiographic assessment [18]. Increased LVMI has been documented in both pediatric and adult ADPKD patients [19, 20]. A more recent evaluation of LVH by magnetic resonance imaging (MRI) in the large HALT-PKD trial [patients with CKD-I and -II, of whom 59% were on blockers of the renin–angiotensin–aldosterone system (RAAS)], showed a much lower prevalence of LVH (3.9 and 0.93% by using non-indexed LVM and LVMI, respectively) [21]. It is not clear why such a difference in LVH exists in these two patient populations, but recent data from a large UK general practice network showing decreased mortality rates from 1991 to 2008 associated with better control of BP and increased use of RAAS inhibitors suggest possible explanations to the observed differences in HALT-PKD trials [22].

Evidence for renoprotective role of RAAS inhibitors in ADPKD is accumulating. In the Modification of Diet in Renal Disease (MDRD) trial, the use of enalapril or amlodipine was associated with a differential decline in glomerular filtration rate (GFR) in ADPKD patients (3.4 versus 5.8 mL/min/year) [23]. Retrospective data from the Danish cohort of ADPKD patients shows a later onset (4.3 years) of ESRD in patients treated with blockers of the RAAS [24].

**PATHOPHYSIOLOGY OF HYPERTENSION IN ADPKD**

The mechanisms responsible for the development of elevated BP in ADPKD, particularly in the early stages of disease, remain incompletely elucidated. There are two major theories that could explain the pathogenesis of hypertension in ADPKD. There is evidence for inherent cardiovascular dysfunction related to abnormal ciliary and vascular function, leading to hypertension. Alternatively, there is much evidence that the cystic kidney leads to intrarenal ischemia and activation of the RAAS and elevated BP (Figure 1) [25]. Finally, activation of the sympathetic nervous system (SNS) has been reported in a number of studies [26, 27].

**Cystic growth, intrarenal ischemia and the activation of the RAAS**

In the 1980s, evidence for activation of the RAAS preceded its link to total kidney volume (TKV) and cyst growth, where pathologic data from autopsy and renal surgical specimens showed juxtaglomerular apparatus to be markedly hyperplastic and mislocated. These renin-containing cells were found with increased abundance and in islands of scarred renal tissue [28]. The presence of renin in cystic fluid confirmed the *in situ* production of the hormone by cyst-lining epithelial cells [29]. Other components of the RAAS, namely angiotensinogen, angiotensin-converting enzyme (ACE), angiotensin II Type 1 receptor and angiotensin I and II (Ang I and II), have all been found in ADPKD renal tissue. Importantly, cyst-derived cells in culture continue to express all components of the RAAS, and ACE-independent production of Ang-II by chymase-like activity has been shown in ADPKD [30].

Clinical studies were less consistent regarding increased activation of the circulatory RAAS in ADPKD patients. In one study, Plasma Renin Activity (PRA) was found to be significantly higher in hypertensive ADPKD patients in the supine and upright position and after single-dose captopril administration compared with matched patients with essential hypertension [31]. Interestingly, the PRAs were comparable between normotensive ADPKD and normal subjects. However, in another double-blind, placebo-controlled study, the effect of a high versus low salt diet was compared between hypertensive ADPKD patients and essential hypertensive patients where no difference in PRA or aldosterone levels were found on either salt diets or after ACE inhibition [32].

More recent observations from the Consortium for Radiologic Imaging Studies in Polycystic Kidney Disease (CRISP) cohort showing that the reduction in renal artery blood flow precedes a decline in GFR and inversely correlates with kidney volume strongly suggest a causal relationship between intrarenal ischemia secondary to cyst expansion and development of hypertension [33, 34] (Figure 1).

**Systemic cardiovascular dysfunction related to ciliopathy: importance of endothelial dysfunction**

Evidence for endothelial dysfunction has been reported in both animal models and human studies of PKD. In rodent models, both PKD1 and PKD2 are expressed in endothelial and vascular smooth muscle cells of all major vessels. Impaired endothelial-dependent relaxation has been demonstrated from cells of aortas from pkd1 knockout mice due to a defect in nitric oxide (NO) release from the endothelium correlating with a decrease in Ca2+-dependent endothelial NO synthesis activity [35].

Interactions between PC1 and 2 have been demonstrated in vascular smooth muscle cells in the sarcoplasmic membrane suggesting a central role in regulating intracellular Ca2+ levels [36]. In pkd2+/− mice, vascular smooth muscle cells show altered intracellular Ca2+ homeostasis with reduced total intracellular and sarcoplasmic reticulum Ca2+ levels [5]. PC2, which is normally conserved in drosophila, when reduced or altered its link to total kidney volume (TKV) and cyst growth, where pathologic data from autopsy and renal surgical specimens showed juxtaglomerular apparatus to be markedly hyperplastic and mislocated. These renin-containing cells were found with increased abundance and in islands of scarred renal tissue [28]. The presence of renin in cystic fluid confirmed the *in situ* production of the hormone by cyst-lining epithelial cells [29]. Other components of the RAAS, namely angiotensinogen, angiotensin-converting enzyme (ACE), angiotensin II Type 1 receptor and angiotensin I and II (Ang I and II), have all been found in ADPKD renal tissue. Importantly, cyst-derived cells in culture continue to express all components of the RAAS, and ACE-independent production of Ang-II by chymase-like activity has been shown in ADPKD [30].

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**Pathophysiology of hypertension**

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contractility [37]. Importantly, other studies have demonstrated that stretch-activated channels that respond to significant changes in vascular tone are regulated by PC1–PC2 complexes in vascular smooth muscle cells [38]. PC1 and PC2 co-localize to the cilia of mouse and human vascular endothelial cells [39]. Normal PC1 and PC2 function are required for endothelial cilia to sense fluid shear stress through a complex biochemical cascade involving calcium, calmodulin, Akt/Protein kinase B (Akt/PKB) and protein kinase C [39–41]. Fluid shear stress on normal endothelial cells over hours results in PC1 undergoing proteolytic cleavage. Abnormal ciliary PC2 function leads to compromised fluid sensing as well, which impairs synthesis of NO, a mediator for other downstream signaling pathways involved in vascular smooth muscle relaxation. In response to fluid shear stress, mouse Pkd2−/− endothelial cells lose the ability to generate NO. Therefore, it appears that PC1 and PC2 may have a specific shear-sensing role in endothelial cilia.

In human studies, plasma concentrations of NO were found to be reduced in PKD patients compared with healthy controls. [42]. Furthermore, levels of asymmetric dimethylarginine (an inhibitor of NO synthase) were significantly increased in patients with early PKD compared with healthy age-matched individuals [43]. Endothelium-dependent relaxation is also impaired, and endothelial NO synthase activity is decreased in patients with PKD [44, 45]. The imbalance in endothelium-derived vasoactive mediators such as NO might therefore be an important factor in the pathogenesis of hypertension in ADPKD [46, 47]. It is been speculated that endothelial dysfunction may be primary in the vascular ADPKD phenotype, which includes hypertension but also intracranial aneurysms, atherosclerosis, dissection, edema, hemorrhage and vascular ectasia [25].

**The sympathetic nervous system**

The activation of efferent sympathetic nerves has been implicated in the generation of different forms of hypertension. The renal afferent sensory nerves respond to mechanoreceptors (stimulated by changes in renal blood flow or intrarenal pressure) and chemoreceptors (stimulated by ischemic metabolites or uremic toxins). Theoretically, the chronic intrarenal ischemia and capsular stretch caused by cyst growth activate the renal SNS, contributing to hypertension. Whether this activation is a cause, a consequence, or a parallel phenomenon of the activation of the RAAS is not clear. Hypertensive ADPKD patients with normal renal function have demonstrated significantly higher levels of adrenaline and noradrenaline, and the latter levels correlated closely with BP [26]. Hypertensive PKD patients with normal renal function had increased muscle sympathetic nervous activity (MSNA) compared with normal controls. Additionally, ADPKD patients with renal insufficiency have higher MSNA compared with ADPKD patients with preserved renal function. In this study, MSNA was found to correlate closely with mean arterial pressure [27].

**TREATMENT OF HYPERTENSION IN ADPKD**

Hypertension is the most treatable associated feature of ADPKD, and the medical community has been increasingly proactive in enhancing patient and physician awareness about the importance of BP control. A recent comprehensive review

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**FIGURE 1**: Mechanisms responsible for development of hypertension in ADPKD. PC1: Polycystin 1; PC2: Polycystin 2; eNOS: Endothelial nitric oxide synthases; SNS: Sympathetic nervous system; NO: Nitric Oxide; ACE: Angiotensin converting enzyme; ACE-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin II receptor blocker.
of the electronic patient records of 1877 adults with ADPKD from the UK General Practice Database between 1991 and 2008 showed a significant increase (32–62%) in the use of antihypertensive therapy in patients with ADPKD, which paralleled an increased use of the inhibitors of the RAAS (from 7 to 46%). The management of hypertension resulted in a drop in average BP from 142/85 mmHg in 1991 to 133/80 in 2008 [22].

Given the risk that hypertension confers for progression to renal failure in ADPKD and that cardiovascular causes are still the most common cause of death in this disorder, these are remarkable accomplishments.

**Diet and lifestyle modification**

As in the general hypertensive population, diet and lifestyle changes should be the first-line treatments for hypertension in ADPKD patients. Dietary salt restriction (2000 mg/day, even though difficult to achieve), limitation of caffeine intake, smoking cessation and regular exercise should be offered to all ADPKD patients. Salt restriction may be of particular importance, since a positive correlation between urinary sodium excretion (a surrogate marker of sodium intake) and total kidney volume [but not the decline in estimated glomerular filtration rate (eGFR)] was shown in 205 participants in the CRISP cohort. The discrepancy between the effect on cyst growth and kidney function may be due to the lag time between structural and functional changes in ADPKD and may become apparent with a longer follow-up [48]. In the absence of an adequate response to these lifestyle modifications, pharmacotherapy should be started.

The role of increased water intake (and the optimal amount) remains unclear in ADPKD. The hypothetical benefits of high water intake to delay cyst growth by suppressing antidiuretic hormone (ADH) and cAMP pathway have been suggested by animal models and small size human studies [49, 50]. These data suggest that an increase in fluid intake to 3 L/day suppresses urine osmolality and partially suppresses serum ADH levels. A higher water intake may provide more complete suppression of ADH and cAMP. Awaiting the results of a larger clinical trial from Japan, we recommend a liberal fluid intake of above 3 L/day. The serum sodium should be closely monitored if eGFR is <30 mL/min/1.73 m², or in those at risk for hyponatraemia (such as patients on a thiazide diuretic). Patients who have an estimated GFR <15 mL/min/1.73 m² should not exceed 3 L/day.

**Inhibitors of the renin–angiotensin–aldosterone system**

ACE inhibitors. The recommended use of ACE-I in ADPKD as a first-line antihypertensive therapy is based on the understanding of the pathophysiology of hypertension in this disease and also on limited evidence from clinical trials. A prospective randomized clinical trial comparing the use of a calcium-channel blocker (amlodipine) versus an ACE-I (enalapril) in 24 hypertensive ADPKD patients with creatinine clearances >50 mL/min/1.73 m² showed a similar degree of BP control and progression of kidney disease at 5 years of follow-up on both agents. However, enalapril, but not amlodipine, had a consistent antiproteinuric effect [23]. A larger meta-analysis of eight clinical trials by Jafar et al. [51] identified 142 ADPKD patients with detectable proteinuria (mean value of 920 mg/day) and showed a slower rate of progression of kidney disease in patients on ACE-Is versus those without ACE-Is over a mean follow-up period of 2.3 years. Urinary protein excretion significantly decreased in the ACE inhibitor group versus the control group (−0.33 versus +0.19 g/day) with a nonsignificant trend toward reduced progression of renal dysfunction (29 versus 41%; P = 0.17). The study was confounded by including patients with >1 g/day of proteinuria which is atypical in ADPKD and may indicate the presence of another renal disorder.

A retrospective analysis of a longitudinal cohort of ADPKD patients comparing the renal outcomes of 33 patients (14 patients on a diuretic and 19 patients on an ACE inhibitor) showed a similar BP control over a mean follow-up period of 5.2 years. However, the annual decline in creatinine clearance was significantly greater in the diuretic group (5.3 versus 2.7 mL/min/1.73 m²). Additionally, urinary protein excretion was significantly increased in the diuretic, but not in the ACE-inhibitor, group [52].

Given that the hypertension in ADPKD is due to bilateral intrarenal ischemia, particular attention should be paid to the risk of acute renal failure after initiation of ACE-I. A reversible rise in serum creatinine of <90 µmol/L (or 1.02 mg/dL) may occur in about 3% of patients [53, 54]. This complication is primarily seen in patients with underlying renal insufficiency, massive cystic disease, concomitant diuretic use or acute cyst hemorrhage. Finally, it should be noted that enalapril did not show any significant effect on the rate of kidney disease progression in 61 normotensive ADPKD patients who were enrolled in a placebo-controlled, randomized clinical trial over a 3-year follow-up period [55]. Whether normotensive ADPKD patients should be on any antihypertensive therapy is not clear at this time.

**Angiotensin receptor blockers and direct renin inhibitors.** Based on the pathophysiology of the RAAS in ADPKD, it is possible that use of angiotensin receptor blockers (ARBs) is as effective as ACE-Is in treating hypertension and preventing progression to renal failure. However, there are limited, randomized clinical trials or evidence on the use of ARBs in ADPKD. To date, there is only one randomized trial comparing the effect of candesartan versus amlodipine in 49 hypertensive ADPKD patients [56]. The study showed an equal effectiveness on BP control in both groups with a lower decline in creatinine clearance on candesartan compared with amlodipine, at a mean follow-up of 36 months (−5 versus −21 mL/min/3 years). Importantly, there are no data on the use of direct renin inhibitors in ADPKD population.

**Treatment of hypertension in ADPKD with combined ACE-I and ARB.** The rationale behind the dual blockade of the RAAS is founded on several observations: renal chymase, which locally activates angiotensin II through non-ACE pathways, is elevated in ADPKD kidneys [30]. Systemic angiotensin II levels do not suppress with chronic ACE-I therapy in ADPKD, suggesting that non-ACE-I dependent activation of the RAAS exists in ADPKD. Systemic and renal hemodynamic responses to exogenous angiotensin I and II persist in the
presence of ACE-I monotherapy in ADPKD [57, 58]. Additionally, although ARB therapy prevents the action of angiotensin II in systemic and renal circulations by binding to the angiotensin II Type 1 receptor, angiotensin II levels increase with chronic ARB therapy and exogenous angiotensin II responses are also not totally suppressed [57, 58]. As ANG II levels and action are important in regulating BP and renal plasma flow and in promoting cyst growth in ADPKD, combination therapy with ACE-I and ARB to maximally block ANG II production and action seems logical.

It is based on this rationale that the HALT-PKD trials were designed to evaluate the role of dual inhibition of the RAAS on renal outcomes in ADPKD. Two National Institutes of Health-funded placebo-controlled, randomized clinical trials assess the efficacy of a combination of lisinopril + telmisartan versus lisinopril + placebo to slow the progression of kidney disease in 1044 hypertensive patients with ADPKD. Study A follows a 2 × 2 factorial design; randomizing patients with eGFR >60 mL/min/1.73 m² and age between 18 and 50 to either ‘standard BP goal’ (average BP, 120–130/70/80 mmHg) or ‘low BP goal’ (average BP <110/75), with a novel primary end point of change in total kidney volume measured by MRI. In Study B, patients with eGFR between 25 and 59 mL/min/1.73 m² and age 18–64 are all treated to a similar BP goal of 120–130/70–80 mmHg. The follow-up for both studies is 6–9 years. Decisions for dose titration and addition of new agents are based on home BP monitoring. Awaiting the results of HALT-PKD trials (expected in November 2014), we cannot make any specific recommendations on the dual blockade of the RAAS in ADPKD [59].

**β-Blockers**

β-Blockers are effective antihypertensive agents in ADPKD and have mild RAAS-inhibitory properties. A randomized controlled trial of 46 ADPKD patients investigated the efficacy of β-blocker therapy for the management of hypertension by randomizing 23 patients to metoprolol versus ramipril and showed a similar decreases in mean arterial BP of 6–8 mmHg. After 3 years, no difference in GFR, LVMI or urinary albumin excretion was observed between the two groups [60]. Another study of 28 hypertensive ADPKD patients randomized to atenolol or enalapril showed that patients randomized to atenolol needed additional agents more often than patients on enalapril. However, the study did not show any difference between the two interventions on the rate of decline of kidney function or microalbuminuria [55].

**Calcium-Channel blockers**

As mentioned earlier, amlodipine (a dihydropyridine calcium-channel blocker) has been shown to be as effective as enalapril in controlling BP in ADPKD patients. However, another retrospective study comparing a group of 31 ADPKD patients either on a calcium channel blocker (CCB) or on a blocker of the RAAS (ACE-I or ARB) showed a significant reduction in eGFR with the use of CCBs. The authors concluded that the use of CCBs should be avoided as a first-line treatment in ADPKD unless treatment of resistant hypertension is needed [61]. The use of the target organ benefits of amlodipine may also differ from ACE-I, where improvement of LVH and reduction in urinary protein excretion are not as apparent. Therefore, this class of agent is an effective line of antihypertensive therapy but should be used after other blockers of the RAAS have been implemented.

**Diuretic**

Antihypertensive therapy in ADPKD is controversial given that diuretics activate the RAAS and current recommendations are to use them judiciously in addition to ACE inhibitors. There are no data on specific diuretic classes or agents used in human studies of ADPKD. A retrospective study of 33 hypertensive PKD patients [52] showed a greater decline in renal function in those receiving any diuretic therapy in isolation versus those receiving any ACE inhibitor therapy (74–46 versus 83–71 mL/min), despite similar BP control. The amount of urinary protein excretion was increased in the patients treated with diuretics, which was not present in the ACE inhibitor group. The use of diuretics as a first-line therapy also required additional antihypertensive agents in 64% of the patients compared with 21% in the ACE inhibitor group. Another study of 75 ADPKD patients added Spirinolactone, HCTZ or amiloride after initiation of ACE-Is to achieve target BP control and did not report on any differential effect of these individual agents [62].

The preliminary data on the beneficial role of amiloride on reduction of cyst growth in MDCK cysts have not been replicated in human studies.

It is important to note that currently, there is no disease-specific BP target for hypertensive ADPKD patients. A subset analysis of the MDRD study, which included 200 ADPKD participants, was performed by Klahr et al. [63]. The MDRD study included two studies (Study A and Study B) with respective eligibility criteria for GFRs of 25–55 and 13–24 mL/min/1.73 m², where patients were randomized to a standard (MAP ≤113 mmHg if age >60 and MAP ≤107 mmHg if age ≤60) versus low (MAP ≤92 mmHg if age ≤60, and MAP ≤88 mmHg if age >60) BP target and also a low versus standard protein and phosphorus diet. There was no difference in the rate of decline of GFR based on the randomized BP target in Study A. However, in Study B, a somewhat faster rate of decline was noticed in the low MAP group. The study was limited by not including patients with conserved renal function and a short follow-up duration (2.2 years).

In another prospective randomized trial, 75 patients with ADPKD, hypertension and LVH, were randomly assigned to rigorous (<120/80 mmHg) or standard BP control (135–140/85–90 mmHg) using either amlodipine or enalapril [62]. If needed, hydrochlorothiazide, clonidine, spironolactone or a combination of agents was used as additional lines of treatment. Throughout the 7 years of study, substantial BP separation was obtained, with mean BP of 90 and 101 mmHg for the rigorous and standard BP control groups, respectively. There were no differences in renal function at the end of 7 years of therapy, but LVMI decreased to a significantly greater degree in the rigorous BP control group (161–104 g/m² or 35.4%) versus the standard BP control group (156–123 g/m² or 21.2%), especially with enalapril than with amlodipine. This study
suggests that rigorous BP control may be beneficial in ADPKD patients with LVH.

The question of the optimal BP goal for ADPKD patients with conserved renal function (CKD I and II) is currently under investigation in HALT-PKD trials where patients have been randomized to two BP targets (120–130/70–80 versus 95–110/60–70 mmHg) [59]. Final results are expected in November 2014.

**Special cases of pregnancy, lactation and children with ADPKD**

All ADPKD females of child-bearing age should be educated about the chances of transmitting the disease to their offspring and also about the teratogenicity and maternal and fetal harms associated with the use of antihypertensive agents (particularly inhibitors of the RAAS) at the time of initiation of therapy. These risks include oligohydramnios, skull hypoplasia, cardiovascular congenital defects, anuria, real failure and death for the fetus and maternal acute kidney injury particularly during the late stages of pregnancy. Therefore, ACE-Is and ARBs should be avoided in pregnant women (category C during first trimester and category D during the second and third trimesters) [64]. If possible, family planning should be started after stopping the blockers of the RAAS and introducing antihypertensive agents with the best pregnancy safety profiles (Aldomet or Labetalol). In case of intrauterine exposure to ACE-I, every effort should be made to stop ACE-Is and ARBs as soon as a pregnancy is confirmed. Neonates with intrauterine exposure to ACE-I and ARBs should be carefully monitored for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of BP and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function (Food and Drug Administration insert pack for Lisinopril) [64].

Lactation and breastfeeding also constitute a contraindication to the use of ACE-Is since those agents may be excreted in the maternal milk. Because no human information is available on the use of ARBS during breastfeeding, an alternate drug may be preferred, especially while nursing a newborn or preterm infant.

There is no specific data on the pediatric use of ACE-I or ARBs in ADPKD. The US Food and Drug Administration has approved several ACE-Is and ARBs for treatment of hypertension and multiple observational and randomized clinical trials have concluded on the safety and efficacy of these agents in children older than 6 years of age [65]. As an example, lisinopril and losartan can be used at respective doses of 0.15 and 0.7 mg/kg of body weight in children older than 6 years of age [66]. Therefore, we recommend the use of ACE-Is or ARBs in children older than 6 years of age. The data for children younger than 6 years of age are scattered. A recently published report from the California poison control system on 296 patients exposed to Lisinopril in a 13-year-long study, showed a low rate of true hypotensive episodes (2.7%) with an estimated minimal dose of 3.9 mg/kg of body weight being necessary to cause hypotension [67].

**REFERENCES**


**CONFLICT OF INTEREST STATEMENT**

Dr. Chapman is a consultant to Otsuka on Tolvaptan, and also a consultant to Pfizer and Sanofi.

**SUMMARY**

Hypertension is extremely common, a significant cardiovascular risk factor and a risk factor for progression to renal failure in ADPKD. It is a treatable complication in PKD and may be due to a primary vasculopathy in this condition. Defects in primary cilia causing endothelial dysfunction and the activation of the RAAS are central pathophysiologic explanation for development of hypertension in ADPKD.

Treatment of hypertension effectively reduces cardiovascular mortality and may also slow down the progression of kidney disease. After implementing diet and lifestyle modification strategies and in the absence of contraindications, an ACE inhibitor should be the initial antihypertensive agent in this population. Careful monitoring of renal function and serum potassium levels is indicated after institution of an ACE inhibitor. An ARB could be considered in case of intolerance to ACE inhibitors. The use of ACE-I or ARBs is also indicated in normotensive ADPKD patients with increased LVMI or albuminuria or in those with masked hypertension.

β-Blockers are also effective in reducing BP in ADPKD patients. Their use may be particularly useful in hypertensive ADPKD patients with significant elevations in serum creatinine concentrations, concomitant cardiac disease and intolerance to both ACE inhibitors and ARBs. β-Blockers may be a better choice than calcium-channel blockers since they have mild RAAS-inhibitory properties. Calcium-channel blockers should be added for control of hypertension after using ACE-I, ARBs and β-blockers. Diuretics should only be considered in conjunction with inhibitors of the RAAS and under careful monitoring of serum creatinine, particularly in patients with advanced renal insufficiency where the risk of acute deterioration of kidney function on the combination therapy with a diuretic is higher.

Based on currently available evidence, we recommend a BP goal of <130/80 mmHg for hypertensive ADPKD patients with or without LVH. The results of ongoing randomized clinical trials such as HALT-PKD trials (ending in 2014) will establish whether a more aggressive BP target is beneficial in this population.

**REFERENCES**


**CONFLICT OF INTEREST STATEMENT**

Dr. Chapman is a consultant to Otsuka on Tolvaptan, and also a consultant to Pfizer and Sanofi.

**REFERENCES**


Late referral of patients with chronic kidney disease (CKD) and unforeseeable deterioration of residual renal function in known CKD patients remain a major problem leading to the need of unplanned start on chronic dialysis without a mature access for dialysis. In most centres worldwide, these patients are started on haemodialysis (HD) using a temporary tunnelled central venous catheter (CVC) for access. However, during the last decade, increasing clinical experience with unplanned start on peritoneal dialysis (PD) right after PD catheter implantation has been published. Key studies are reviewed in the present paper, and the results seem to indicate that compared with patients starting PD in a planned setting with peritoneal resting

Can peritoneal dialysis be applied for unplanned initiation of chronic dialysis?

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**ABSTRACT**

Late referral of patients with chronic kidney disease (CKD) and unforeseeable deterioration of residual renal function in known CKD patients remain a major problem leading to the need of unplanned start on chronic dialysis without a mature access for dialysis. In most centres worldwide, these patients are started