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In-depth Review

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Hypertension in autosomal-dominant polycystic kidney disease (ADPKD)

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Abstract
Cardiovascular (CV) complications are the major cause of death in autosomal-dominant polycystic kidney disease (ADPKD) patients. Hypertension is common in these patients even before the onset of renal insufficiency. Blood pressure (BP) elevation is a key factor in patient outcome, mainly owing to the high prevalence of target organ damage together with a poor renal prognosis when BP is increased. Many factors have been implicated in the pathogenesis of hypertension, including the renin–angiotensin–aldosterone system (RAAS) stimulation. Polycystin deficiency may also contribute to hypertension because of its potential role in regulating the vascular tone. Early diagnosis and treatment of hypertension improve the CV and renal complications of this population. Ambulatory BP monitoring is recommended for prompt diagnosis of hypertension. CV risk assessment is mandatory. Even though a nonpharmacological approach should not be neglected, RAAS inhibitors are the cornerstone of hypertension treatment. Calcium channel blockers (CCBs) should be avoided unless resistant hypertension is present. The BP should be <140/90 mmHg in all ADPKD patients and a more intensive control (<135/85 mmHg) should be pursued as soon as microalbuminuria or left ventricle hypertrophy is present.

Keywords: ambulatory blood pressure monitoring; blood pressure profile; cardiovascular risk; polycystic kidney disease; renal size

Introduction

Autosomal-dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder, affecting one in 400–1000 live births. It accounts for ∼5–7% of cases of end-stage renal disease (ESRD) requiring renal replacement therapy in Europe and the USA [1]. It is characterized by the development of renal cysts. Although there is considerable phenotypic variability, in general during the first three decades only a few renal cysts are clinically detectable, while by the fifth decade many renal cysts can be found [2]. Progressive cyst expansion leads to massive enlargement and distortion of the kidney's architecture and, ultimately, to ESRD in most patients [3].

ADPKD is genetically heterogeneous with two genes causing the disease, *PKD1* and *PKD2* [4]. *PKD1* accounts for 85% of cases in clinically identified populations and *PKD2* accounts for the remaining 15% [5]. *PKD1* causes more severe disease, with a mean age at the onset of ESRD of 53 years, compared with 69 years in cases due to *PKD2* [6]. Studies in animal models have shown that ADPKD shows abnormal primary cilia function. The primary cilium is a microtubule-based antenna-like structure rooted in the mother centriole (the basal body) that projects from the surface of virtually all cells in the mammalian body. This cilium is a sensory organelle that receives mechanical and chemical signals from other cells and the environment, and transmits these signals to the nucleus to elicit a cellular response. Polycystins are the ADPKD proteins; they form a complex that localizes to primary cilia and may act as a mechanosensor essential for maintaining the differentiated state of epithelia lining tubules in the kidney and other tissues [7]. Therefore, ADPKD is a systemic disease, with cyst development also in the liver, pancreas, spleen, seminal vesicles, ovary and arachnoid. Vasculature is also affected, and intra- and extracranial aneurysms are more common in ADPKD patients than in the general population. Cardiac and valvular disorders have also been described [8]. These cardiovascular (CV) disorders contribute to the high CV morbidity and mortality affecting ADPKD patients. In addition, hypertension is a common symptom of ADPKD that occurs in nearly 60% of patients before deterioration of renal function [9]. Hypertension is associated with rapid progression to ESRD and is also a major CV risk factor [10]. The present article reviews the main characteristics of hypertension in ADPKD patients, including pathophysiological factors and treatment strategies.

Arterial hypertension

Arterial hypertension is highly prevalent in ADPKD patients compared with patients with other types of renal disease. Nearly 60% of ADPKD patients have hypertension before any decrease in the glomerular filtration rate [9]. Hypertension occurs earlier and more frequently in *PKD1* than in *PKD2* and in those ADPKD patients whose affected or unaffected parents also have hypertension [11]. ADPKD children also have a high prevalence of hypertension [12] and data from large registries show that ADPKD children show 4–6 mmHg higher blood pressure than their age- and sex-matched controls and more frequently a non-dipper profile in the ambulatory blood pressure (BP) monitoring [13] Indeed, this prevalence may be even higher if ambulatory BP monitoring is used to make the diagnosis, owing to the high proportion of masked hypertension in this population [14]. BP monitoring helps us to make an early diagnosis of hypertension and to identify non-dipping circadian BP rhythm (<10% decline in nocturnal systolic or diastolic BP), which is common (∼45%) in ADPKD patients [15]. The CV risk associated with hypertension has two components, the BP elevation and the BP circadian rhythm alteration. Many studies have demonstrated that blunted nocturnal dip is associated with high CV risk and that reversal of the non-dipping status improves the CV prognosis [16, 17]. In addition, ambulatory BP monitoring has been demonstrated to improve the diagnosis of hypertension, avoiding the under- and overestimation associated with BP control at the office [18]. Nowadays, clinical guidelines on hypertension worldwide recommend the use of ambulatory BP monitoring to diagnose and follow up hypertensive patients [19].

Hypertensive ADPKD patients also have a greater incidence of target organ damage compared with other age-matched hypertensive patients. Nearly 50% of hypertensive ADPKD patients exhibit left ventricular hypertrophy on echocardiography [20]. Early diastolic dysfunction, including biventricular diastolic dysfunction, and impaired coronary flow velocity reserve have also been demonstrated [21]. These cardiac alterations have been associated with hemodynamic factors including systolic BP and lower nocturnal fall in BP rhythm [22]. However, normotensive ADPKD patients also exhibit ventricular hypertrophy (23%), which has not been associated with blunted nocturnal fall in BP [23]. It appears that further factors may be involved in left ventricular hypertrophy in these patients. Recently, the HALT PKD study has shown a lower incidence of left ventricular hypertrophy using cardiac magnetic resonance [24].This low prevalence has been attributed to the high use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).

Urinary albumin excretion rate and glomerular filtration rate are reliable markers for hypertension-related renal damage. Moreover, albuminuria has a prognostic CV value [25, 26]. In ADPKD patients, a higher albuminuria level is associated with increased mean BP and more severe renal cystic involvement [27]. Glomerular filtration, however, appears to be stable in ADPKD for a long period, despite progression of renal structural abnormalities due to compensatory hyperfiltration [28]. Therefore, unlike in other nephropathies, the glomerular filtration rate is not a reliable marker of disease severity. Recently, the total renal volume has been proposed as a marker for disease severity and progression [29–31]. Indeed, the renal volume can stratify ADPKD patients into high and low risks for disease progression, the poorest prognosis existing among those with the greatest renal volume [32].

ADPKD patients present early pathology in the arterial system. Young normotensive ADPKD patients have an impaired endothelium-dependent relaxation in small resistance vessels and an amplification of the pulse wave that may contribute to a higher left ventricular afterload [33]. At this early stage, radial or aortic pulse wave velocities are within the normal range. In hypertensive ADPKD patients, however, there is an increase in intima-media thickness of the carotid arteries as well as a greater prevalence of fibromatous areas in the carotid wall [34]. Later in the course of the disease, when renal insufficiency appears, there are important alterations in the large arteries.

There are other important clinical data related to hypertension in this population. First of all, there is an association between hypertension and the increase in kidney volume compared with normotensive ADPKD patients [12, 35]. The exact mechanism of this association is not completely clear although stimulation of the RAAS could play an important role (see 'Pathogenesis of hypertension'). Second, there is an association between hypertension and the decrease in kidney function. Many studies have shown that hypertension is an independent prognostic factor for progression to ESRD [10]. Typically, ADPKD kidney histology from patients with ESRD presents significant BP damage manifested by sclerosis of renal arterioles and global glomerulosclerosis, a marker of renal ischaemia [36].

Taken together, these data show significant target organ damage in both normotensive and hypertensive ADPKD patients which may explain in part the high CV morbidity and mortality in these patients. A reduction in CV mortality has been demonstrated, however, in the past decade. This reduction has been attributed to early diagnosis and treatment of ADPKD complications, especially hypertension [37]. In this regard, early BP treatment has decreased the prevalence of left ventricular hypertrophy in ADPKD patients [24].

Therefore, CV risk assessment should be applied to ADPKD patients. This includes measurement of target organ damage (Table 1), evaluation of classic CV risk factors apart from hypertension (smoking habits, body weight, lipid variables, etc.), and diagnostic studies of diabetes and other CV clinical conditions (cerebrovascular disease, heart disease, peripheral artery disease, etc.)

Table 1. Subclinical organ damage[a]

(i)	Electrocardiographic LVH (Sokolow–Lyon >38 mm; Cornell >2440 mm × ms) or echocardiographic LVH (LVMI M > 125 g/m^2, F > 110 g/m^2)
(ii)	Carotid intima-medial thickening >0.9 mm or plaque
(iii)	Carotid-femoral pulse wave velocity >12 m/s
(iv)	Ankle/brachial BP index <0.9
(v)	Slight increase in plasma creatinine: M: 115–133 mmol/L (1.3–1.5 mg/dL); F: 107–124 mmol/L (1.2–1.4 mg/dL)
(vi)	Low eGFR[b] (<60 mL/min/1.73 m^2) or creatinine clearance[c] (<60 mL/min)
(vii)	Albuminuria 30–300 mg/24 h or albumin–creatinine ratio: ≥22 (M) or ≥31 (F) mg/g creatinine

[a]M, males; F, females; BP, blood pressure; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index with a wall thickness/radius of ≥0.42.
[b]Cockroft–Gault formula.
[c]MDRD formula.

[25]. In patients with important CV risk factors, like ADPKD, early interventions should be implemented to improve their risk profile. The main features of ADPKD hypertension are summarized in Table 2.

Pathogenesis of hypertension

Activation of the RAAS seems to have a major role in the pathogenesis of hypertension in ADPKD patients. Plasma renin activity and plasma aldosterone concentration are increased in ADPKD patients compared with essential hypertensive patients matched for age, sex, kidney function, sodium intake and degree of hypertension [38]. Along with this systemic stimulation of the RAAS, local stimulation has also been demonstrated. ADPKD kidneys show hyperplasia of the juxtaglomerular apparatus [39]. In addition, radiolabelling of renin and messenger RNA for renin has been detected in the cyst wall epithelium together with high renin activity in the cyst fluid [40]. It has been postulated that renal cysts enlarge and compress the renal vasculature, favouring intrarenal ischaemia and stimulation of the RAAS. Angiotensin II has an important haemodynamic effect, but it is known that it may act as a growth factor enhancing renal cyst growth and contributing to this vicious circle. These data suggest that inhibition of the RAAS may be important in controlling the BP level, reducing the rate of cyst growth and renal enlargement, and finally slowing down the progression to ESRD.

Other pathogenic factors might also be involved in hypertension. Intrarenal ischaemia/hypoxia is a potent stimulator of erythropoietin concentration, which is increased in patients with ADPKD [41]. Intrarenal ischaemia also affects renal tubular sodium handling and increases the activity of the sympathetic nervous system, which is known to be overstimulated in ADPKD patients prior to any decrease in the glomerular filtration rate [42, 43]. Concentration ability is altered in hypertensive ADPKD patients, possibly owing to increased circulating vasopressin levels. This vasopressin elevation may also contribute to the development of hypertension [44].

Vasoconstrictor factors appear to be increased in ADPKD patients. Endothelin 1 is expressed in the kidney cyst epithelium, in the cyst fluid, and also in plasma at a higher concentration compared with normotensive and hypertensive patients. On the other hand, endothelial nitric oxide synthase activity is diminished, facilitating the impaired endothelium-dependent relaxation observed in ADPKD patients. Therefore, these patients appear to have an imbalance between vasoconstrictor and vasodilatation factors that may contribute to hypertension [8]. Renal tissue nitric oxide synthase activity is also reduced, which may activate local oxidative stress pathways contributing to the renal damage [45].

Recently, it has been demonstrated that decreased polycystin 1 or 2 expression in the cilia of endothelial cells and in vascular smooth muscle cells is associated with abnormal vascular structure and function. Polycystin 1 and 2 function is required for endothelial cilia to sense fluid shear stress through a complex biochemical cascade involving many factors, including nitric oxide. Indeed, Pkd1/Pkd2 deficiency reduces nitric oxide levels and alters the endothelial response to shear stress [13]. Polycystin deficiency interferes with the vascular tone and may explain why hypertension is a primary feature in ADPKD patients. This is a new pathogenic factor that needs further investigation. Apart from the prevalence of hypertension, it is not known whether the CV profile is different between *PKD1* and *PKD2* patients. The main pathogenic factors of ADPKD hypertension and CV risk are summarized in Table 3.

Treatment of hypertension

Early and effective treatment of hypertension is very important in ADPKD in order to slow down the progression to ESRD and prevent CV complications. Even though many questions remain unanswered, there are certain points in its treatment that should be taken into account.

Lifestyle changes

Lifestyle changes should not be forgotten in these hypertensive patients. Maintenance of ideal body weight, regular aerobic exercise and a diet limited to a maximum intake of 6 g of salt daily are suitable recommendations, even though they have not been explicitly studied in patients with ADPKD [2].

Vasopressin is a potent activator of renal cyclic adenosine monophosphate (cAMP), which increases the proliferation of epithelial cells in cyst walls and the rate of fluid secretion into cysts and thus leads to kidney enlargement, which has been shown to be the better predictor of kidney disease progression in ADPKD [29]. The usefulness of vasopressin inhibitors in slowing down the progression of renal enlargement and deterioration of estimated glomerular filtration rate (eGFR) in patients with ADPKD has been demonstrated in a placebo-controlled trial (TEMPO study) [46]. It has also been suggested that a high fluid intake would behave similarly to V2 receptor blocking [47, 48]. Based on the TEMPO trial results and, especially, on the outcome of the control group, which was advised to drink a lot of fluids, it seems reasonable to recommend a water intake of ~3000 mL

Table 2. Main features of hypertension in ADPKD[a]

(i)	Associated with activation of the RAAS
(ii)	Imbalance between vasoconstriction and vasodilatation factors
(iii)	Appears early in the course of the disease, before a decrease in renal function
(iv)	High prevalence of non-dipping circadian rhythm
(v)	High prevalence of target organ damage (ventricular hypertrophy, increased carotid intima-media thickness, etc.)
(vi)	Closely related to the kidney volume
(vii)	Important prognostic factor for progression to ESRD

[a]RAAS, renin–angiotensin–aldosterone system; ESRD, end-stage renal disease.

Table 3. Potential pathophysiological mechanisms of hypertension and cardiovascular risk in early ADPKD

(i)	Cyst growth and renal enlargement
(ii)	Renal ischaemia/hypoxia
(iii)	Increased in erythropoietin
(iv)	Activation RAAS
(v)	Increased in vasopressin and cAMP
(vi)	Vascular dysfunction
(vii)	Decreased nitric oxide production
(viii)	Cardiac and valvular disorders

per day to reduce AVP levels. This recommendation should be given with caution because it can lead to hyponatraemia [2, 49].

Pharmacological treatment

The role of the different antihypertensive drugs in relation to renal and CV outcomes will be analysed in this section.

RAAS inhibitors. Activation of the RAAS seems to be the cornerstone of the pathophysiology of hypertension in ADPKD; therefore, most studies have investigated the renoprotective and CV effects of RAAS inhibitors compared with other antihypertensive treatments. In this regard, ACE inhibitors, e.g. enalapril and ramipril, and ARBs, e.g. candesartan, have shown, compared with dihydropyridine calcium channel blockers (CCBs), better antialbuminuric effect and lower reduction in creatinine clearance independent of BP levels [50, 51] and also greater reduction of left ventricular hypertrophy [52]. Compared with RAAS inhibitors, however, beta-blockers (atenolol and metoprolol) have not shown worse results in terms of eGFR, urinary albumin excretion or left ventricular hypertrophy (even though the inhibition of the RAAS caused by beta-blockers might have obscured the potential beneficial effects of ACE inhibitors) [53, 54]. On the other hand, compared with ACE inhibitors, diuretic treatment has shown a significantly greater decline in renal function despite similar BP control, suggesting a role of the RAAS independent of BP levels in the progression of chronic kidney disease in ADPKD patients [55]. It must be noted, however, that diuretics cause activation of the RAAS, which may have interfered with these results. In addition, diuretics may cause a certain volume depletion which can also induce vasopressin release and an increase in cAMP. It is known that ACE inhibitors and ARBs alone fail to completely suppress the RAAS; the usefulness of the combination of these two classes of the drug will be checked in the HALT trial, where ADPKD patients in different stages of chronic kidney disease have been randomized to receive ACE inhibitors plus angiotensin receptor blocking agents or ACE inhibitors versus ARB alone [56] The role of the direct renin inhibitor aliskiren in ADPKD patients is not yet known; however, it could be relevant given that this is the only RAAS inhibitor which also suppresses plasma renin activity [57, 58].

To our knowledge, no study has yet compared the renal or cardiovascular outcomes between ADPKD patients treated with ACE inhibitors and those treated with ARBs alone. Nor is there any evidence available on potential beneficial effects of adding spironolactone to ACE inhibitors or to ARBs.

Calcium channel blockers. cAMP accelerates the proliferation of cyst-derived cells in ADPKD, but does not activate proliferation of normal renal cells. This phenotypic difference in the proliferative response to cAMP appears to be secondary to differences in basal intracellular calcium levels, which have been shown to be reduced in epithelial cells isolated from human ADPKD cysts compared with normal renal cells [59]. The CCB verapamil had no effect on kidney morphology in wild-type rats while ADPKD rats showed greater kidney weight and cyst index and increased cell proliferation and apoptosis, with consequent exacerbation of renal cystic disease [60]. In humans, dihydropyridine CCBs have been compared with RAAS inhibitors (ACE inhibitors and ARBs), and patients receiving CCB treatment appeared to have a poorer renal function outcome [61]. Because of these findings, both dihydropyridine and non-dihydropyridine CCBs should probably be avoided as first- and probably second-line treatment in patients with ADPKD. However, considering that ADPKD patients often show resistant hypertension and CCBs are good antihypertensive drugs, they should certainly be third-line treatment.

Diuretics. Because aldosterone levels are greater in hypertensive ADPKD patients than in essential hypertensives, and higher aldosterone levels may lead to sodium retention, diuretics should be considered as second-line treatment in hypertensive ADPKD. It must be noted, however, that diuretic treatment may lead to an extra activation of the RAAS owing to volume depletion. In hypertensive ADPKD patients with normal renal function, thiazide diuretics are the first choice. In those with impaired renal function and glomerular filtration rate <30 mL/min/1.73 m^2, long-acting loop diuretics must be the first choice.

To our knowledge, other drug treatments (e.g. alpha-blockers, direct vasodilators) have not been compared with RAAS inhibitors and may play a secondary role in hypertension treatment in this population.

Blood pressure goal

Another important point to be considered is the BP goal. The Modified Diet in Renal Disease study, which included 200 participants with ADPKD, compared two levels of BP control in patients with a glomerular filtration rate between 13 and 55 mL/min/1.73 m^2. No benefits were found in the lower BP control (mean BP <92 versus <107 mmHg) group in terms of renal function decline, although the fact that patients already had substantial renal impairment may have masked the results [62]. However, it has been demonstrated that intensive BP control (BP 120–125/80 mmHg) results in a reduction in urinary albumin excretion and left ventricular hypertrophy (both indirect markers of cardiovascular and renal prognosis), suggesting that this intensive BP target might offer major benefits [54]. Again, the results of the HALT trial, expected by 2013, may give an answer on the real beneficial effects of intensive (BP <95–110/60–75 mmHg) versus standard (BP <120–130/70–80 mmHg) BP control in early stages of ADPKD (eGFR >60 mL/min/1.73 m^2).

In summary, until more evidence is available, hypertensive ADPKD patients should have a BP of <140/90 mmHg. Even though, as stated in the *'Reappraisal of guidelines on hypertension management'* of the European Society of Hypertension in relation to essential hypertension and knowing that ADPKD patients show greater target organ damage than their essential hypertensive controls, it might be recommended to try to reach BP levels closer to 130–135/80–85 mmHg in those with target organ damage already present [63]; this is a

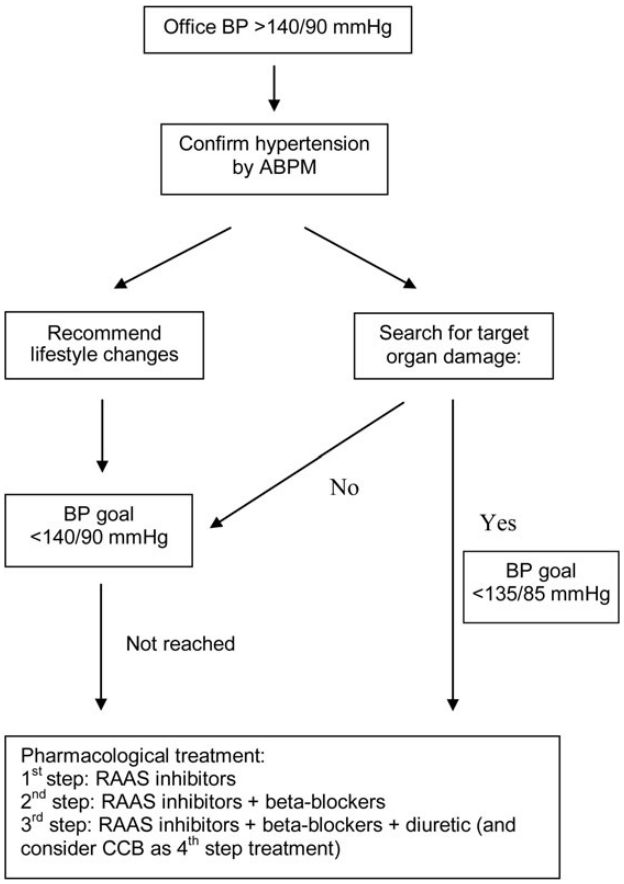

Fig. 1. Hypertension treatment in ADPKD patients. BP, blood pressure; ABPM, ambulatory BP monitoring; RAAS, renin–angiotensin–aldosterone system; CCBs, calcium channel blockers.

recommendation not based on evidence, as to date there have been no studies giving a clear answer to this.

Summary

CV complications are the major cause of death in ADPKD patients. Hypertension is common in these patients even before the onset of renal insufficiency. BP elevation is a key factor in patient outcome, mainly owing to the high prevalence of target organ damage together with a poor renal prognosis when BP is increased. Many factors have been implicated in the pathogenesis of hypertension, including RAAS stimulation. Polycystin deficiency may also contribute to hypertension because of its potential role in regulating the vascular tone. Early diagnosis and treatment of hypertension improve the CV and renal complications of this population. Ambulatory BP monitoring is recommended for prompt diagnosis of hypertension. CV risk assessment is mandatory. Even though a nonpharmacological approach should not be neglected, RAAS inhibitors are the cornerstone of hypertension treatment. CCBs should be avoided unless resistant hypertension is present. The BP should be <140/90 mmHg in all ADPKD patients and a more intensive control (<135/85 mmHg) should be pursued as soon as microalbuminuria or left ventricle hypertrophy is present [64]. Pharmacological regimens must include an RAAS inhibitor as first option and probably a beta-blocker as a second option, leaving CCBs for those with resistant hypertension and diuretics for those with impaired renal function and water overload. Other modifiable CV risk factors must be promptly treated; statins should be started if LDL cholesterol levels are >130 mg/dL (3.37 mmol/L) and smoking cessation must be encouraged (Figure 1).

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