Chapter 5

Blood Pressure Control for Polycystic Kidney Disease

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Abstract

Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent genetic kidney disease and affects 6 to 12 million patients worldwide. The disease is characterized by the progressive development of innumerable renal cysts that gradually replace normal kidney tissue, leading ultimately to the loss of renal function starting from the 5th decade of life. Most patients with ADPKD develop arterial hypertension. High blood pressure

develops early in the course of the disease and is caused by the activation of the renin-angiotensin-aldosterone system (RAAS) and other significant pathogenic mechanisms. Hypertension is a major contributing factor for the increased cardiovascular morbidity and mortality in patients with ADPKD. Optimal treatment of hypertension is essential to improve the prognosis of the cystic disease and the associated cardiovascular diseases. Target blood pressures and choice of antihypertensive drugs for patients with ADPKD have not been firmly defined in guidelines, but the recently published results from the HALT-PKD studies suggest that a blood pressure goal of <130/80 mm Hg should be targeted, preferably with inhibitors of the RAAS.

Key Words: Hypertension; Polycystic kidney disease; Renin-angiotensin-aldosterone-system

Introduction

The autosomal dominant form of polycystic kidney disease (ADPKD) is the most common monogenic kidney disease in humans and is the cause of end-stage kidney disease (ESKD) in 7-10% of dialysis patients (1). Mutations in the PKD1 gene (85% of cases; clinically severe form) and PKD2 (15% of cases; clinically more slowly progressive form) are primarily responsible for the disease (2). ADPKD is usually manifested between 25 and 45 years of age. The most common primary manifestations include 1) arterial hypertension at early age; 2) abdominal or flank pain, often in the context of cyst hemorrhage or cyst infection; 3) hematuria, mostly microscopic but sometimes macroscopic as a manifestation of cyst bleeding; and 4) moderate polyuria, manifesting as nocturia. The progression of ADPKD is characterized by a large inter-individual variability. Patients with PKD1 mutation reach ESKD in their mid-fifties, and those with PKD2 mutations in their mid-seventies (3).

The disease is characterized by increasing formation and expansion of fluid-filled cysts in the parenchyma of both kidneys. During the course of the disease, there is progressive enlargement of the cysts which is due to aberrant proliferation of the cyst epithelial cells and the secretion of cyst fluid. Thereby, the surrounding kidney tissue is compressed and injured, leading ultimately to a reduction of the glomerular filtration rate (GFR). At the start of dialysis, the kidneys are massively enlarged due to the growth of the cysts, and the normal renal parenchyma has been replaced by atrophic tubules and fibrotic areas.

In addition to the above mentioned renal characteristics, patients with ADPKD develop several well characterized extrarenal manifestations which include the formation of cysts in the liver and pancreas, colonic diverticula, abdominal hernias, mitral valve prolapse (rarely mitral insufficiency), aortic valve anomalies and the dreaded intracranial aneurysms. The

latter may lead to rupture and potentially fatal subarachnoid hemorrhage. Fortunately this complication is rare, however aneurysms occur more frequently in certain families (4).

Arterial hypertension in ADPKD

General aspects

Arterial hypertension occurs in patients with ADPKD relatively early in the disease course, usually much earlier than in the general population (5, 6). The median age at diagnosis of hypertension is 32 years for men and 34 years for women (7). In case of a PKD1 mutation, treatment for hypertension is required about 5 years earlier than in case of a PKD2 mutation, and 50-70% of patients will develop hypertension before renal function is limited (8). The extent of hypertension correlates with the volume and the growth rate of the renal cysts (9). The development of left ventricular hypertrophy (LVH) is tightly linked to arterial hypertension and is associated with an increased cardiovascular risk in these patients. Thus, hypertension is a modifiable risk factor for cardiovascular diseases in ADPKD patients and should be treated in order to reduce the burden of cardiovascular complications. In addition, there is more and more evidence that hypertension contributes to disease progression in ADPKD. Early diagnosis and optimal treatment are therefore of great importance, first of all to prevent cardiovascular complications in these patients, and then also to retard cyst growth (10, 11).

Pathophysiology of hypertension in ADPKD

Hypertension occurs in patients with ADPKD when the excretory renal function is still normal and thus cannot exclusively be explained by altered salt excretion or other non-specific mechanisms of renal hypertension. Rather, a number of specific mechanisms seem to be responsible for the development of hypertension in ADPKD (Figure 1) (12, 13). The RAAS plays a predominant role, since cyst formation leads to compression of vessels and creates local ischemia which leads to the activation of the intrarenal RAAS. This has been demonstrated in numerous experimental and clinical studies (12). In addition, the sympathetic nervous system is activated in ADPKD and contributes to the pathogenesis of hypertension (14). Furthermore, due to the renal concentrating defect and the consecutive tendency to polyuria, a latent stimulation of vascular vasopressin V1 receptors occurs, leading to vasoconstriction and a consecutive increase in blood pressure. Finally, polycystin 1 and 2 are expressed by endothelial cells and vascular smooth muscle cells where they contribute to the regulation of the vascular tone through endothelin, nitric oxide (NO) and the homeostasis of intracellular calcium (8, 12).
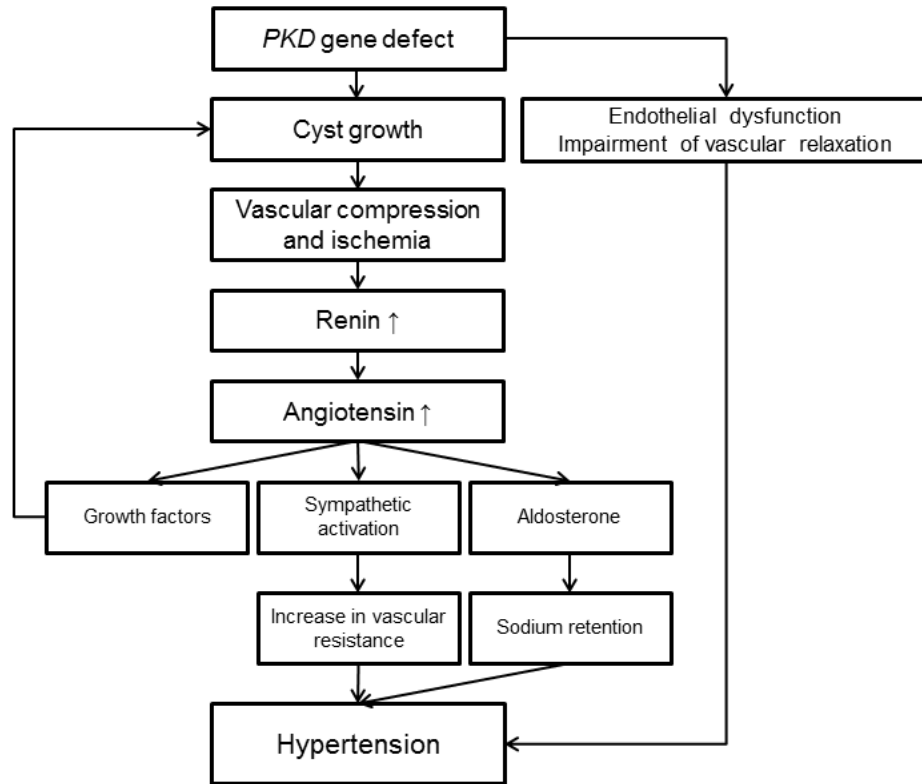
Figure 1. Pathogenesis of hypertension in autosomal dominant polycystic kidney disease (ADPKD). The major pathogenic mechanisms for hypertension are depicted, highlighting the important role of the RAAS.

Treatment of hypertension in ADPKD

General aspects

Early and timely initiation of effective and long-term treatment is essential in the management of hypertension in patients with ADPKD (15). The development of hypertension can in general be equated with a progression of cyst growth. It has been recommended that blood pressure target values with drug treatment should aim to values of <130/80 mm Hg in adults, and below the 75th percentile in children (16). As in other patients with hypertension, the goals of antihypertensive therapy consist in the reduction of

extrarenal complications (LVH, arteriosclerosis) and hypertensive renal damage (nephroangiosclerosis, glomerulosclerosis). In addition there is evidence that intrarenal RAAS activation and hypertension may favor cyst growth. Thus, animal studies have shown that Angiotensin Converting Enzyme Inhibitors (ACEI) could arrest the cyst growth by antagonizing the mitogenic effect of the RAAS (17, 18). When treating hypertension in ADPKD the following three questions need to be addressed: (1) which drug classes (or non-drug therapies) are preferable; (2) what is the optimal blood pressure target and at which blood pressure values should drug therapy be initiated; (3) do ACEI or Angiotensin Receptor Blockers (ARB) have protective effects which are independent of blood pressure control?

Therapeutic options for the treatment of hypertension in ADPKD

In patients with ADPKD the general principles of non-drug treatment of hypertension apply, including, limiting the intake of salt and caffeine, regular exercise and smoking cessation. In general, high blood pressure in patients with ADPKD is relatively easy to treat, because drug resistance is quite rare. Often, a single medication is sufficient to control hypertension, particularly when combined with a thiazide diuretic. Due to pathophysiological considerations, RAAS inhibitors (ACEI and ARB) appear to be well suited as first choice therapy, particularly in light of the recently published results of the large HALT-PKD studies (see below). There is no study with a sufficiently large patient number that has demonstrated the superiority of RAAS inhibitors against other blood pressure regimens, but there are many small studies which provide indirect evidence that ACEI/ARB are the preferred classes of antihypertensive compounds. The following small-scale studies are noteworthy:

- In a non-randomized study in hypertensive ADPKD patients (n=33), GFR declined faster with a diuretic than with an ACEI. The annual decrease in creatinine clearance was 5.3 ml/min/1.73 m^2 in the diuretic group and 2.7 ml/min/1.73 m^2 in the ACEI group (P<0.05) (19).

- In a prospective randomized study of 24 patients, the effects of the calcium channel blocker amlodipine and the ACEI enalapril on blood pressure, proteinuria and GFR over 5 years was examined. At comparable blood pressure control only enalapril reduced the proteinuria, but both drugs showed a similar decline in GFR (20).

- In another small prospective study, 49 patients were randomized and treated with amlodipine or the ACEI candesartan for 3 years. At comparable blood pressure control, it was observed that, with amlodipine, 24% of the patients showed a doubling of serum creatinine compared to only 4.2% with candesartan (21).

- A small and non-conclusive 2-year study in 26 patients comparing the effect of calcium channel blockers with ACEI and found no difference in blood pressure control or serum creatinine (22).

- A retrospective study of 32 patients also documented a greater loss of GFR with calcium channel blockers than with RAAS inhibition of ACEI or ARB (23).

- A study in 61 normotensive and 28 hypertensive ADPKD patients compared the ACEI enalapril with the beta-blocker atenolol or placebo and found no difference in GFR loss (24).

- A study of 85 children with ADPKD showed that enalapril could stabilize renal function and left ventricular mass index but that the kidney volume continued to increase (25).

- Finally, a meta-analysis of 11 randomized clinical trials was performed which studied 1860 patients with non-diabetic nephropathies, including 142 patients with ADPKD. Compared with other blood pressure medications, ACEI were more effective in reducing proteinuria, particularly in patients with advanced ADPKD, and especially in patients with larger proteinuria. However, the influence of ACEI on the progression towards renal failure was not conclusive. Of note, the ADPKD study population seemed to be unusual, since a significantly higher proteinuria was found in these patients at baseline (26).

In summary, up to the year 2014 there was no clear evidence for superior efficacy and safety of RAAS blockers over other antihypertensive drugs, particularly with respect to clinically relevant endpoints such as GFR decline and total kidney volume (TKV) growth. The above mentioned studies were too small and of too short duration to provide conclusive results. Nevertheless, these smaller studies have provided good evidence that inhibition of the RAAS with ACEI or ARB allows effective and safe treatment of hypertension in ADPKD and that they should be preferred over calcium channel blockers or diuretics alone.

Blood pressure targets in ADPKD

Disease-specific blood pressure targets have not yet been conclusively defined for ADPKD. A subgroup analysis of the Modification of Diet in Renal Disease (MDRD) study was performed in 200 patients with ADPKD with a GFR of 25 to 55 ml/min/1.73 m², showing no difference between normal (mean arterial pressure [MAP] target ≤113 mm Hg over 60

years and ≤107 below 60 years) and strict (MAP target ≤92 mm Hg over 60 years and ≤88 below 60 years) blood pressure control. However, in patients with a GFR of 13 to 24 ml/min/1.73 m² there was a slightly more rapid GFR decline in the group with strict blood pressure control (27). Another randomized controlled trial with 75 ADPKD patients found no difference in renal function with a strict (<120/80 mm Hg) compared to a normal (135-140/85-90 mm Hg) blood pressure regimen using enalapril or amlodipine over 7 years. However, a significant positive effect was found on LVH (28).

HALT-PKD results

The question of blood pressure target values and whether the progression of renal disease (cyst growth and GFR loss) can be inhibited by a dual RAAS blockade were the focus of the HALT-PKD study program. It has been so far the largest and methodologically well-conducted study on the treatment of hypertension in ADPKD (29, 30).

The HALT-PKD study program was carried out from 2006 to 2014. It examined the effect of RAAS blockade and strict control of blood pressure on the progression of renal disease in adults with ADPKD (Figure 2). This study examined the effect of RAAS blockade with the ACEI lisinopril alone or in combination with the ARB telmisartan on the progression of the disease in patients with preserved GFR (Study A; GFR >60 ml/min/1.73 m²; n = 558) and in patients with advanced renal disease (Study B; GFR 25-60 ml/min/1.73 m²; n = 486). Study A had a 2x2 factorial design: patients were randomly assigned to one of two blood pressure goals [standard BP (120/70 to 130/80 mm Hg) versus low BP (95/60 to 110/75 mm Hg)] and to either monotherapy with an ACEI or dual RAS blockade [(lisinopril + placebo) versus (lisinopril + telmisartan)]. In Study B, [lisinopril + placebo] versus [lisinopril + telmisartan] were compared at the same target blood pressure goal (110-130/70-80 mm Hg). In Study A, the primary endpoint was defined as the TKV, while in study B, the combined primary end point evaluated the improvement of the GFR decline, occurrence of end-stage kidney failure and death.

In study A, patients with the lower BP target had a significant reduction of the kidney volume growth (5.6 vs 6.6%, P = 0.006), thus meeting the primary endpoint of the study, although the effect was small (Figure 3). However, there was no difference in the level of renal function (GFR annual loss -2.9 vs -3.0 ml/min/1.73 m²) (Table 1). A significant reduction of left ventricular mass index (LVMI) and albuminuria was observed in the treatment group with the lower BP goal, but it resulted in frequent orthostatic complaints such as dizziness. When [lisinopril + placebo] was compared with [lisinopril + telmisartan], there was no difference in the growth of kidney volume (Figure 3), GFR loss, albuminuria and LVMI.
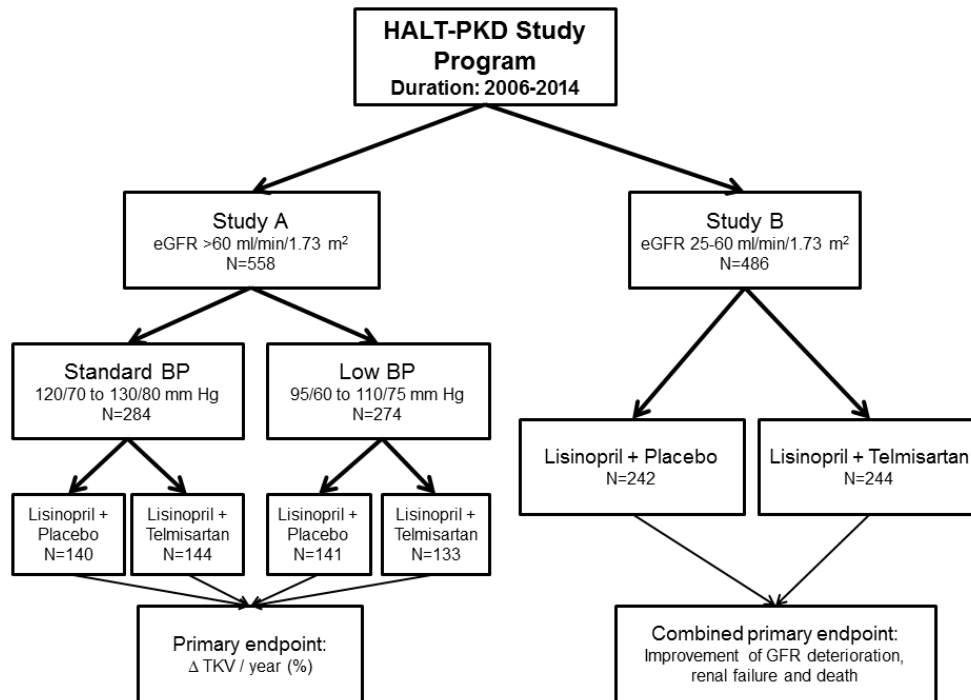
Figure 2. Schematic representation of the HALT-PKD study program and the eGFR criteria for inclusion in study A (preserved GFR) and B (reduced GFR). Study A has a 2x2 factorial design (standard vs. lower BP, and comparing lisinopril/placebo vs. lisinopril/telmisartan).

In Study B, patients in both treatment groups [lisinopril + placebo] versus [lisinopril + telmisartan] had more advanced cystic disease than in study A (i.e. older age, lower GFR). There was no difference in the combined primary endpoint (improvement of GFR decline, reaching ESKD or death), and no difference in GFR loss and albuminuria between the treatment groups. Under dual therapy with lisinopril and telmisartan, the risk of hyperkalemia and acute renal failure was not increased.

In summary, the HALT-PKD study results suggest that lowering BP more intensely in earlier stages of ADPKD has a favorable effect on the course of the disease, but at the cost of increased hypotensive side effects. Dual RAAS blockade was comparable to monotherapy with an ACEI, even in patients with advanced disease. Of note, the complication rate was not increased with dual therapy, unlike other studies with diabetic patients where a higher risk of hyperkalemia and acute renal failure has been noticed (31).
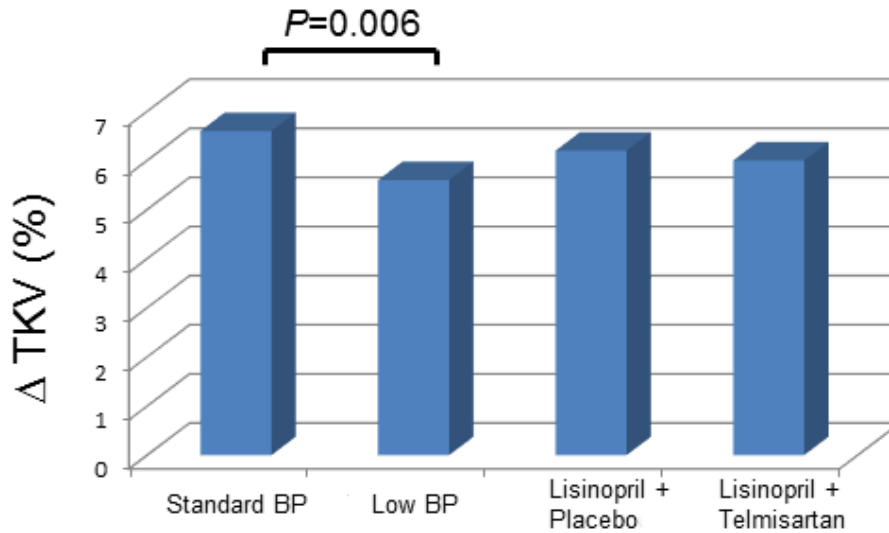
Figure 3. Annual change in total kidney volume (ΔTKV) in percent in the HALT-PKD Study A. The lower BP was associated with decreased growth (5.6 vs 6.6%, relative difference 14.2%, P = 0.006), whereas the addition of telmisartan to lisinopril did not change TKV growth (6.0 vs 6.2%, P = 0.52).

Finally, it must be noted that in both studies (A and B) the dose of the ACEI in the dual RAAS blockade group was lower than in the ACEI monotherapy group. Furthermore, the blood pressure was similar in both treatment groups and there was no difference in the suppression of urine aldosterone. Hence, it can be concluded that the suppression of the RAAS in both treatment groups was comparable and the combination of ACEI and ARB was not more effective than monotherapy with an ACEI at a higher dose. Unfortunately, there was no control arm without inhibitors of the RAAS in the HALT-PKD studies, so ultimately it is still unclear whether the inhibition of the RAAS to control blood pressure is superior to other drug regimens (beta-blockers and/or diuretics). Nevertheless, a lower BP appears to significantly inhibit renal cyst growth, but it remains to be seen whether this strategy can delay the occurrence of ESKD.

Table 1. Study results of the HALT-PKD studies (from Schrier (29) and Torres (30))

	Study A	Study B
Number of participants	558	486
Age category	15-49 years	18-64 years
GFR	>60 ml/min/1.73 m²	25-60 ml/min/1.73 m²
Study arms	Standard (120-130/70-80 mm Hg) vs. low (95-110/60-75 mm Hg) blood pressure Lisinopril + Placebo (L/P) vs. Lisinopril + Telmisartan (L/T)	Lisinopril + Placebo vs. Lisinopril + Telmisartan
Primary Endpoint	Change in cyst growth in low blood pressure group: Δ TKV 5.6% vs. 6.6% Similar cyst growth in L/P and L/T: Δ TKV 6.2% vs. 6.0%	50% reduction of eGFR, ESKD or death: HR 1.08, CI 0.82 – 1.42
Secondary Endpoint	Significant reduction of LVMI and albuminuria at a low BP, no difference in eGFR loss No differences between L/P and L/T with respect to LVMI, albuminuria and eGFR loss	No difference in eGFR and albuminuria loss
Side Effects	Dizziness and light-headedness more common in low BP group No differences between L/P and L/T	No difference in hyperkalemia and acute renal failure

eGFR, estimated Glomerular Filtration Rate; ESKD, End-Stage Kidney Disease; L/P, Lisinopril + Placebo treatment arm; L/T, Lisinopril + Telmisartan treatment arm. Δ TKV, yearly change in Total Kidney Volume.

Conclusions for clinical practice

Patients with ADPKD develop hypertension early in the disease process. Hypertension contributes to disease progression and increased cardiovascular risk. Generally, hypertension is easy to treat and resistant forms are very rare. Because there is marked intrarenal activation of the RAAS, treatment with ACEI or ARB, optionally in combination with a thiazide diuretic, is recommended as the preferred drug regimen. The target blood pressure should be below 130/80 mm Hg. Based on new data from the HALT-PKD studies, a greater blood pressure reduction can be recommended, provided that patients tolerate it and do not develop hypotensive side effects.

Conflict of interest

The authors declare that they have no conflicts of interest with respect to research, authorship and/or publication of this book chapter.

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