Supportive Evidence Document:
BLOOD PRESSURE MONITORING AND TARGETS IN ADPKD

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Introduction

Hypertension is a common complication of ADPKD, and it precedes the onset of renal decline in 50%-75% of cases (1). It is estimated to occur in 30% of children with ADPKD, and the median age at diagnosis of hypertension is within the third decade of life (32 years in males, 34 years in females) (2).

Hypertension increases the rate of renal decline (3). In ADPKD patients, it is implicated in the development of left ventricular hypertrophy (1), and it may also contribute to cerebral hemorrhage, aneurysmal subarachnoid hemorrhage, and cardiovascular death (3). In one 5-year study of patients aged 4 to 21 years that compared hypertensive and normotensive children/young adults, it was found that hypertensive individuals demonstrated a greater but not statistically significant increase in renal volume over time, as well as higher left ventricular mass index (LVMI) throughout the study (4).

It is therefore important to detect hypertension as early as possible and to treat to appropriate blood pressure (BP) targets using non-pharmacological measures +/- antihypertensives.

Summary of the Evidence

Blood Pressure Monitoring

Office BP monitoring:

The utility of office BP measurements is limited in patients with white coat hypertension or masked hypertension. In essential hypertensives, both home BP monitoring and ambulatory blood pressure monitoring (ABPM) have been shown to be more accurate than office BP monitoring (5).

Home BP monitoring:

Home BP monitoring is useful for diagnosing sustained hypertension (5). In patients with essential hypertension, there is evidence suggesting that it is more accurate in predicting cardiovascular risk than office BP monitoring (5). However, it cannot be used to detect nocturnal hypertension or to determine whether patients have normal “dipping” of BP overnight.

24-hour ambulatory BP monitoring (ABPM):

There is increasing evidence that 24-hour ABPM is a useful tool in the ADPKD population, and it is endorsed in several ADPKD expert reviews and guidelines (Table 1). A summary of the evidence for 24-hour ABPM in ADPKD is presented in Table 2.

Three studies demonstrated that 24-hour ABPM was useful in detecting hypertension that would otherwise have been missed through office BP or home BP measurements (6-8).

A number of studies, mostly with very small sample sizes, have found significant associations between 24-hour ABPM and various cardiovascular/renal parameters in adult ADPKD patients, such as left ventricular mass index, presence of intracranial aneurysms, and kidney length (9-12). Furthermore, three small studies done in pediatric ADPKD patients found associations between 24-hour daytime/nighttime APBM measurements and pertinent renal parameters, including renal concentrating capacity, renal volume, renal length, and/or number of renal cysts (8, 12-13). Further studies are needed to confirm these findings.

Particular attention has been drawn to nocturnal dipping, as non-dipping is considered to be a risk factor for cardiovascular complications, such as left ventricular hypertrophy (14, 15). Nocturnal "dipping status" was examined in several studies (8, 12, 16-20). Overall, ADPKD patients were shown to have a higher prevalence of non-dipping and/or lower amplitude of nocturnal dipping, compared to controls. However, 24-hour ABPM was performed only once in the majority of studies, and one study by Rahbari-Oskoui et al. demonstrated that "dipping status" was only modestly reproducible on repeated ABPM measurements (20).

Blood Pressure Targets

BP target statements/recommendations provided in expert reviews and guidelines are presented in Table 3. A summary of the evidence for BP targets is presented in Table 4.

Young patients with preserved renal function:

Currently, the best evidence examining BP targets in ADPKD patients is HALT-PKD Study A (21). In this multicenter, double-blind, randomized controlled trial, 558 ADPKD patients 15-49 years of age with eGFR > 60 mL/min/1.73 m^2 were randomized to a low BP target of 95/60-110/75 mm Hg or a standard BP target of 120/70-130/80 mm Hg, with the use of home BP measures (21). All patients were also randomized to either lisinopril or lisinopril/telmisartan as first-line therapy, and additional open-label medications were added as needed to reach the target BP (21). After a follow-up time of 5-8 years, a 14.2% slower annual increase in total kidney volume was observed in the low BP group, and this was statistically significant (21). The low BP target was associated with additional favorable outcomes compared to the standard BP group, including a reduction in urinary albumin excretion (vs. an increase in the standard BP group) and a greater reduction in LVMI (21). However, the annual change in eGFR was similar between the two groups (21). The patients in the low BP group were prescribed a median of 2.0 open-label antihypertensives, compared to 1.0 in the standard BP group (21). More patients experienced dizziness/lightheadedness in the low BP group (21). No significant differences were found in the frequencies of death, serious cardiovascular or renal events, hyperkalemia, acute kidney injury, or cancer (21).

Patients who are older and/or have reduced renal function:

Evidence for BP targets in ADPKD patients that are older and/or have reduced renal function is limited to small studies that had less stringent age and renal function criteria than HALT-PKD Study A.

A 7-year prospective study of 79 ADPKD patients compared rigorous BP control (<120/80 mmHg) to standard BP control (135-140/85 mm Hg) (22). Each BP measurement was recorded as a mean of 3 sitting measurements performed at the research center by a trained professional and/or at home by the patient (22). A significant reduction in LVMI was seen in both groups, but a significantly higher proportion of patients in the rigorous BP control group achieved LVMI in the normal range (22). The mean number of antihypertensives required was 2.7 in the rigorous BP control group, vs.

0.8 in the standard BP control group (22).

A post-hoc analysis of a 3-year, double-blind randomized controlled trial of 46 ADPKD patients also found a lower mean LVMI in patients who had achieved mean arterial pressure (MAP) ≤ 97 mm Hg (mean 24h ambulatory BP achieved was 125/78 mm Hg), compared to those who had MAP ≥ 97 mm Hg (mean 24h ambulatory BP achieved was 136/86 mm Hg) (23). The number of antihypertensives used in each group was not reported. Due to the analysis being post-hoc, this result was hypothesis-generating only.

Of note, safety data were not reported in either of the two studies discussed above, and many of the included patients would have qualified for HALT-PKD Study A, as the mean age was 40-41 years and the mean eGFR/CrCl was ~88 mL/min in both studies (22, 23). Adverse effects of antihypertensives are of particular concern in patients who are older and/or have reduced renal function. The SPRINT trial, which excluded polycystic kidney disease patients, examined BP targets in patients 50 years of age or older with cardiovascular risk factors, and 28% had chronic kidney disease (24). The lower BP target was associated with a higher risk of several adverse events, including hypotension, syncope, electrolyte abnormalities, and acute kidney injury or acute renal failure (24). These risks are likely to be similar in the older subset of ADPKD patients, and they need to be considered when making individualized decisions about BP targets.

Statements/Recommendations

Blood Pressure Monitoring

- We suggest that, whenever possible, ADPKD patients should be taught to self-monitor BP.
- 24-hour ambulatory BP monitoring is a useful tool to diagnose hypertension early, to identify masked hypertension, and to detect any diminution of the normal fall in overnight BP.

Blood Pressure Targets

- Patients with ADPKD who are younger than 50 years with eGFR > 60 mL/min/1.73 m^2 and without significant cardiovascular morbidities should have a target BP ≤ 110/75 mm Hg (as measured by home BP monitoring), recognizing that in some patients, an individual target may be needed.
  - In HALT-PKD Study A, most patients required at least 3 antihypertensive agents to reach this target BP.
- For older patients or patients with more advanced CKD, limited data is available. Although evidence suggests that achieving BP values < 130/80 mm Hg (as measured using various methods in studies) is associated with lower left ventricular mass indices compared to higher BP values, further studies are needed to establish BP targets in these populations.
- In all cases, BP targets should be individualized. Considerations when making decisions about BP targets should include patient-specific risks of adverse events and pill burden.

References

1. Krishnappa V, Vinod P, Deverakonda D, Raina R. Autosomal dominant polycystic kidney disease and the heart and brain. *Cleve Clin J Med.* 2017 Jun 1;84(6):471–81.

2. Helal I, Al-Rowaie F, Abderrahim E, Kheder A. Update on the pathogenesis, management, and treatment of hypertension in autosomal dominant polycystic kidney disease. *Saudi J Kidney Dis Transpl.* 2017 Mar-Apr;28(2):253-260.

3. Wa T, Macnicol A, Watson M. Ambulatory blood pressure in hypertensive patients with autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant.* 1997 Oct 1;12(10):2075–80.

4. Cadnapaphornchai MA, McFann K, Strain JD, Masoumi A, Schrier RW. Prospective Change in Renal Volume and Function in Children with ADPKD. *Clin J Am Soc Nephrol.* 2009;4(4):820–9.

5. Lamb SA, Nerenberg K, Zarnke KB, Leung AA, Dasgupta K, Butalia S, et al. Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children. *Can J of Cardiol.* 2018:doi: 10.1016/j.cjca.2018.02.022.

6. Seeman T, Dusek J, Vondrichová H, Kyncl M, John U, Misselwitz J, et al. Ambulatory blood pressure correlates with renal volume and number of renal cysts in children with autosomal dominant polycystic kidney disease. *Blood Press Monit.* 2003;8(3):107-10.

7. Sans Atxer L, Roca-Cusachs A, Torra R, Calero F, Arias P, Ballarin J, et al. Relationship between renal size and blood pressure profile in patients with autosomal dominant polycystic kidney disease without renal failure. *Nefrologia.* 2010;30(5):567-72.

8. Seeman T, Sikut M, Konrad M, Vondrichová H, Janda J, Schärer K. Blood pressure and renal function in autosomal dominant polycystic kidney disease. *Pediatr Nephrol.* 1997;11(5):592-6.

9. Valero FA, Martinez-Vea A, Bardaji A, Gutierrez C, Garcia C, Richart C, et al. Ambulatory blood pressure and left ventricular mass in normotensive patients with autosomal dominant polycystic kidney disease. *J Am Soc Nephrol.* 1999;10(5):1020-6.

10. Martinez-Vea A, Valero FA, Bardaji A, Gutierrez C, Broch M, Garcia C, et al. Left ventricular hypertrophy in hypertensive patients with autosomal dominant polycystic kidney disease: influence of blood pressure and humoral and neurohormonal factors. *Am J Nephrol.* 2000;20(3):193-200.

11. Niemczyk M, Pilecki T, Gradzik M, Bujko M, Niemczyk S, Pączek L. Blood pressure and intracranial aneurysms in autosomal dominant polycystic kidney disease. *Kidney Blood Press Res.* 2014;39(6):630-5.

12. Massella L, Mekahli D, Paripović D, Prikhodina L, Godefroid N, Niemirska A, et al. Prevalence of Hypertension in Children with Early-Stage ADPKD. *Clin J Am Soc Nephrol.* 2018;13(6):874-883.

13. Seeman T, Dusek J, Vondrák K, Bláhová K, Simková E, Kreisinger J, et al. Renal concentrating capacity is linked to blood pressure in children with autosomal dominant polycystic kidney disease. *Physiol Res*. 2004;53(6):629-34

14. Yano Y, Kario K. Nocturnal blood pressure and cardiovascular disease: a review of recent advances. *Hypertens Res*. 2012;35(7):695-701.

15. Rodrigues JCL, Amadu AM, Ghosh Dastidar A,

Harries I, Burchell AE, Raticliffe LEK, et al. Noctural dipping status and left ventricular hypertrophy: A cardiac magnetic resonance imaging study. *J Clin Hypertens (Greenwich)*. 2018;20(4):784-793.

16. Li Kam Wa TC, Macnicol AM, Watson ML. Ambulatory blood pressure in hypertensive patients with autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant.* 1997; 12(10): 2075-80.

17. Cerasola G, Vecchi M, Mulè G, Cottone S, Mangano MT, Andronico G, et al. Sympathetic activity and blood pressure pattern in autosomal dominant polycystic kidney disease hypertensives. *Am J Nephrol*. 1998;18(5):391-8.

18. de Almeida EA, de Oliveira EI, Lopes JA, Almeida AG, Lopes MG, Prata MM. Ambulatory blood pressure measurement in young normotensive patients with autosomal dominant polycystic kidney disease. *Rev Port Cardiol*. 2007;26(3):235-43.

19. Turgut F, Oflaz H, Namli S, Alisir S, Tufan F, Temiz S, et al. Ambulatory blood pressure and endothelial dysfunction in patients with autosomal dominant polycystic kidney disease. *Ren Fail.* 2007;29(8):979-84.

20. Rahbari-Oskoui FF, Miskulin DC, Hogan MC, Fielder O, Torres VE, Bost JE, et al. Short-term reproducibility of ambulatory blood pressure monitoring in autosomal dominant polycystic kidney disease. *Blood Press Monit.* 2011;16(2):47-54.

21. Schrier RW, Abebe KZ, Perrone RD, Torres VE, Braun WE, Steinman TI, et al. Blood pressure in early autosomal dominant polycystic kidney disease. *N Engl J Med*. 2014;371(24):2255-66.

22. Schrier R, McFann K, Johnson A, Chapman A, Edelstein C, Brosnahan G, et al. Cardiac and renal effects of standard versus rigorous blood pressure control in autosomal-dominant polycystic kidney disease: results of a seven-year prospective randomized study. *J Am Soc Nephrol*. 2002;13(7):1733-9.

23. Zeltner R, Poliak R, Stiasny B, Schmieder RE, Schulze BD. Renal and cardiac effects of antihypertensive treatment with ramipril vs metoprolol in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant.* 2007;23(2):573–9.

24. SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med.* 2015;373(22):2103-16.

Table 1: Statements/Recommendations Regarding Blood Pressure Monitoring in ADPKD

PUBLICATION TYPE	PUBLICATION	YEAR OF PUBLICATION	STATEMENT/RECOMMENDATION
Guideline	Spanish guidelines for the management of autosomal dominant polycystic kidney disease (1)	2014	• "The use of ambulatory blood pressure monitoring may help to make an early diagnosis of hypertension and to identify patients with masked hypertension, which is highly prevalent among ADPKD patients." • "Ambulatory or home blood pressure monitoring is recommended for early diagnosis of hypertension (D)."
	KHA-CARI guideline recommendations for the diagnosis and management of autosomal dominant polycystic kidney disease (2)	2016	• "We suggest that all patients with ADPKD be taught of self-management skills for blood pressure monitoring (2D)" • "...given that hypertension may promote the growth of unruptured ICAs, patients with ADPKD should have their blood pressure monitored regularly and treated appropriately."
	European ADPKD Forum multidisciplinary position statement on autosomal dominant polycystic kidney disease care (3)	2018	• "In children and adults, 24-h ambulatory blood pressure monitoring can be helpful to detect prehypertension and any diminution of the normal fall in overnight blood pressure."
Review Article	Sans-Axter et al. (4)	2013	• "Ambulatory BP monitoring is recommended for prompt diagnosis of hypertension."
	Krishnappa et al. (5)	2017	• "Ambulatory blood pressure monitoring may play an important role in diagnosing hypertension early in the prehypertensive stage of ADPKD"
	Helal et al. (6)	2017	• "Currently, ambulatory BP monitoring represents the best tool for the diagnosis and follow-up of patients with hypertension according to the new clinical guidelines, and we have to apply this recommendation to our ADPKD patients."
	Chebib et al. (7)	2018	• "Early detection [of hypertension] is essential"
	Torra et al. (8)	2019	• "Early detection of high blood pressure influences disease progression."

References

1. Ars E, Bernis C, Fraga G, Martínez V, Martins J, Ortiz A, et al. Spanish guidelines for the management of autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2014;29 Suppl 4:iv95-105.
2. Rangan CK, Alexander SI, Campbell KL, Dexter MA, Lee VW, Lopez-Vargas P, et al. KHA-CARI guideline recommendations for the diagnosis and management of autosomal dominant polycystic kidney disease. *Nephrology*. 2016;21(8)705-16.
3. Harris T, Sandford R, de Coninck B, Devuyst O, Drenth JPH, Ecder T, et al. European ADPKD Forum multidisciplinary position statement on autosomal dominant polycystic kidney disease. *Npehrol Dial Transplant.* 2018;33(4)563-73.
4. Sans-Axter L, Torra R, Fernández-Llama P. Hypertension in autosomal-dominant polycystic kidney disease (ADPKD). *Clin Kidney J.* 2013; 6(5): 457-463.
5. Krishnappa V, Vinod P, Deverakonda D, Raina R. Autosomal dominant polycystic kidney disease and the heart and brain. *Cleve Clin J Med.* 2017 Jun 1;84(6):471–81.
6. Helal I, Al-Rowaie F, Abderrahim E, Kheder A. Update on the pathogenesis, management, and treatment of hypertension in autosomal dominant polycystic kidney disease. *Saudi J Kidney Dis Transpl.* 2017 Mar-Apr;28(2):253-260.
7. Chebib FT, Torres VE. Recent Advances in the Management of Autosomal Dominant Polycystic Kidney Disease. *Clin J Am Soc Nephrol.* 2018 Nov 7;13(11):1765-76.
8. Torra R. Recent advances in the clinical management of autosomal dominant polycystic kidney disease. F1000Res. 2019;8.

Table 2: Evidence Summary for 24-Hour Ambulatory Blood Pressure Monitoring in ADPKD

STUDY	STUDY DESIGN	ADPKD POPULATION	CONTROL POPULATION	MEASUREMENTS	OUTCOMES	RESULTS (ADPKD VS. CONTROL, UNLESS OTHERWISE SPECIFIED)
Zeier et al. 1993 (1)	Prospective study	• 24 ADPKD patients: 12 children aged < 15 years old, 12 young adults	• 24 non-affected controls matched for age, sex, BSA	• 24h ABPM once • Echocardiographic examination	• Mean MAP (daytime and nighttime) • Echocardiographic findings	• Most blood pressures and LVMIs were within normal range in both groups • Left ventricular systolic function was normal in all patients In children: • No significant differences in daytime MAP or in nighttime MAP • Median VSD, PWD, and LVMI were significantly higher In young adults: • Higher daytime and nighttime MAP • Similar differences in echocardiographic findings as those found in children, and differences were even more pronounced
Seeman et al. 1997 (2)	Prospective study	• 32 children and adolescents with ADPKD • Mean age 12.3 ± 4.7 years (range 3.4-19.4 years)	• Sex-matched controls for BP readings	• Casual BP measurement prior to ABPM • 24h ABPM twice (second was done 5-13 months after the first study in 16 patients)	• 24h ambulatory BP profile • Diagnosis of HTN • Relationship between 24h ambulatory BP profile and renal volume, eGFR,	Data below pertains only to ADPKD patients, unless otherwise specified Casual BP • SBP >95th percentile in 2 patients

STUDY	STUDY DESIGN	ADPKD POPULATION	CONTROL POPULATION	MEASUREMENTS	OUTCOMES	RESULTS (ADPKD VS. CONTROL, UNLESS OTHERWISE SPECIFIED)

		• Mean eGFR 87.0 ± 18.1 mL/min/1.73 m^2 (range 65-153 mL/min/1.73 m^2)		• Abdominal ultrasonography
				• eGFR (estimated from SCr and height)
				• Urine dipstick
				• 24h protein
				• Plasma renin activity
				• Renal concentraing capacity
					proteinuria, plasma renin activity, and renal concentrating capacity	• DBP >95th percentile in 3 patietns
						
						1st 24h ambulatory BP
						
						• ADPKD patients, compared to controls:
						  • Females: Both mean SBP and DBP significantly higher in both daytime and nighttime
						  • Males: Onl mean nighttime SBP and DBP significantly higher in ADPKD patients compared to controls
						  • 61% and 82% of ADPKD patients had mean SBP and/ or DBP above the mean of controls during daytime and nighttime, respectively
						  • Mean nocturnal dip 12±4% (range 3-18%) for SBP and 19±7% (range 1-31%) for DBP, compared to 13±6% and 23±9% in controls, respectively

STUDY	STUDY DESIGN	ADPKD POPULATION	CONTROL POPULATION	MEASUREMENTS	OUTCOMES	RESULTS (ADPKD VS. CONTROL, UNLESS OTHERWISE SPECIFIED)

						• 11 patients in total had mean SBP or DBP > 95th percentile
						  • 4 had HTN exclusively in daytime
						  • 4 had HTN exclusively at nighttime
						  • 3 had HTN in daytime and nighttime
						• Compared to casual BP:
						  • Elevated SBP and/or DBP detected in 4 of 28 patients with normal casual BP
						  • 1 of 4 patients reclassified as normotensive during daytime
						
						2nd 24h ambulatory BP (n=16)
						• Slight but insignificant decrease in mean SBP and DBP compared to first study
						
						Correlations between 24h ambulatory BP profile and other outcomes:
						• No significant correlation between ABPM results and total proteinuria,

STUDY	STUDY DESIGN	ADPKD POPULATION	CONTROL POPULATION	MEASUREMENTS	OUTCOMES	RESULTS (ADPKD VS. CONTROL, UNLESS OTHERWISE SPECIFIED)
						renal concentrating capacity, eGFR, or PRA • Significant correlation between mean daytime/ nighttime systolic and diastolic standard deviation scores and standard deviations scores of renal volume or renal length (r=0.52, p=0.048, and r=0.86, p=0.0003, respectively) • Borderline correlation between daytime DBPT and microalbuminuria (4=0.36, p=0.08)

Wa et al. 1997 (3)	Prospective study	• 25 patients with HTN (SBP > 140 mm Hg and/or DBP > 90 mm Hg on at least 2 occasions)
		• Mean age 39 years
		• Mean SCr 104 ± 21 umol/L
			• 25 non-affected patients with HTN (SBP > 140 mm Hg and/or DBP > 90 mm Hg on at least 2 occasions)
			• Mean age 42 years
			• Mean SCr 92 ± 10 umol/L
				• 24h ABPM once	• 24h ambulatory BP profile	• Day-night differences in BP were significantly lower
						  • Mean nocturnal fall in SBP: 17.2±7.4 mm Hg (11.5±5.1%), vs. 22.9 ± 8.3 mm Hg (15.1±5.4%), p=0.01
						  • Mean nocturnal fall in DBP: 16.3±6.1mm Hg (16.5±6.2%), vs. 20.2±6.4 mm Hg (19.8±6.4%), p=0.03
						• Smaller nocturnal reduction in pulse rate, p=0.03
						• No significant difference in 24h BP variability

STUDY	STUDY DESIGN	ADPKD POPULATION	CONTROL POPULATION	MEASUREMENTS	OUTCOMES	RESULTS (ADPKD VS. CONTROL, UNLESS OTHERWISE SPECIFIED)
Cerasola et al. 1998 (4)	Prospective study	• 30 ADPKD patients with HTN • 17 with no "renal failure" (mean age 42 years, mean CrCl 109 mL/min/m^2) • 13 with "renal failure" (mean age 57 years, mean CrCl 35 mL/min/m^2)	• 50 patients with essential HTN, matched for sex, BMI, known HTN duration, clinic BP • Mean age 45 years • Mean CrCl 114 mL/min/m^2	• 24h ABPM once • Plasma renin activity • Plasma catecholamines	• 24h ambulatory BP profile • Plasma renin activity and catecholamines • Correlation between BP and plasma renin activity/ catecholamines	• Higher nighttime diastolic BP • Lower percentage day-night difference in mean BP • In ADPKD, BP significantly correlated with plasma noradrenaline, independent of renal function • No significant differences between ADPKD with and without "renal failure" with respect to plasma catecholamines, 24h daytime and nighttime ambulatory BP and percentage day-night difference in mean BP
Valero et al. 1999 (5)	Prospective study	• 26 normotensive ADPKD patients with normal renal function • Mean age 27 years	• 26 healthy controls • Mean age 26 years	• 24h ABPM once • 2-dimensional echocardiography	• 24h ambulatory BP profile • LVMI	• Similar average 24h and daytime systolic, diastolic, and mean BP values • Significantly higher nighttime mean and diastolic BP; similar nighttime systolic BP • Significantly lower average and percentage nocturnal decrease of SBP (10.0 mm Hg [-3 to 24] vs. 15.5 mmHg [24 to 31], p= 0.009, and 9.0%

STUDY	STUDY DESIGN	ADPKD POPULATION	CONTROL POPULATION	MEASUREMENTS	OUTCOMES	RESULTS (ADPKD VS. CONTROL, UNLESS OTHERWISE SPECIFIED)
						[22 to 22] versus 14.2% [22 to 25], p=0.016, respectively) • Non-dippers: 54% vs. 31% (p=0.092) • Significantly higher posterior wall thickness, ventricular septal thickness, left ventricular mass, and LVMI • In ADPKD, 24h systolic BP was the only variable linked to LVMI on multiple regression analysis
Martinez-Vea et al. 2000 (6)	Prospective study	• 20 hypertensive ADPKD patients • Mean age 47 years • Mean SCr 112 umol/L • Mean clinic BP 147/98 mm Hg	• 20 essential hypertensive subjects, matched for age and sex • Mean age 46 years • Mean clinic BP 149/100 mm Hg • Mean SCr 78 umol/L	• 24h ABPM once • Echocardiography and Doppler studies • Plasma renin activity, noradrenaline, angiotensin II, aldosterone, atrial natriuretic peptide, insulin-like growth factor I	• Relationship between BP, humoral/ neurohormonal factors, and LVMI in ADPKD patients	• Similar ambulatory BP and LVMI overall • Male ADPKD patients had higher LVMI than their matched controls • LVH in 40% vs. 30% • Significantly higher noradrenaline levels; similar levels of other hormonal factors • ADPKD patients with LVH had similar hormonal parameters, but higher ambulatory BP compared to those without LVH • In ADPKD, no significant association between LVMI and any hormonal factor. 24h diastolic BP

STUDY	STUDY DESIGN	ADPKD POPULATION	CONTROL POPULATION	MEASUREMENTS	OUTCOMES	RESULTS (ADPKD VS. CONTROL, UNLESS OTHERWISE SPECIFIED)
						was the only independent variable linked to LVMI on multiple regression analysis

Seeman et al. 2003 (7)	Prospective study [extension of another study by Seeman et al. (7)]	• 62 children with ADPKD and normal renal function
		• Mean age 12 years
			• N/A	• 24h ABPM once
				• Renal ultrasonography
					• HTN, defined as a mean SBP and/or DBP at daytime and/or night-time ≥95th percentile for normal pediatric population
					• Correlations between SBP/DBP and renal volume, renal length and number of renal cysts
						• HTN diagnosed in 35%
						  • 10 had isolated nighttime HTN
						• Mean nocturnal dip not significantly different from mean values in normal pediatric population
						• Significant correlations between SBP/DBP (both daytime and nighttime) and renal volume, renal length, and number of renal cysts
						  • Exception is NSS correlation between nighttime DBP and renal length
						• Hypertensive patients had significantly greater mean renal volume and mean number of cysts

Seeman et al. 2004 (8)	Prospective study	• 53 ADPKD pediatric patients • Mean age 12 years • None on BP medications	• N/A	• 24h ABPM one day before standardized renal concentrating test	• Presence of HTN (mean SBP and/or DBP ≥95th percentile)	• HTN in 12 patients (23%) • Prevalence of HTN significantly higher in patients with decreased renal concentrating capacity, compared to those with normal renal

STUDY	STUDY DESIGN	ADPKD POPULATION	CONTROL POPULATION	MEASUREMENTS	OUTCOMES	RESULTS (ADPKD VS. CONTROL, UNLESS OTHERWISE SPECIFIED)

		• Normal GFR (mean 114 mL/min/1.73 m^2)		• Standardized renal concentrating capacity test (urine osmolality measurement 4 hours after nasal application desmopressin)
				• Renal ultrasonography
					• Correlation between ambulatory renal concentrating capacity and: ambulatory BP, renal structure, and GFR	concentrating capacity (35% vs. 5%, p<0.05)
						• Significant difference between renal concentrating capacity in patients with HTN compared to children with normal BP (793±150 mOsmol/kg vs. 901±129 mOsmol/kg, p<0.05)
						• Significant negative correlations between renal concentrating capacity and:
						  • Daytime SBP
						  • Daytime DBP
						  • Nighttime SBP
						  • Number of renal cysts
						  • CrCl
						• Correlation with renal concentrating capacity more powerful for SBP than for DBP

de Almeida et al. 2007 (9)	Prospective study	• 36 ADPKD patients <31 years old with no known HTN (BP< 140/90) • Mean age 26 years • Mean baseline BP 91.8 mm Hg	• 24 individuals <31 years old with no known HTN (BP< 140/90), no known disease (renal or other), and not taking any medication • Mean age 25 years • Mean baseline BP 89.1 mm Hg	• 24h ABPM once during which they were told to maintain normal diet and activity • LVMI	• 24 ambulatory BP profile • Dipper status, defined as a variation > 10% between daytime and nighttime BP	• Significantly higher means of SBP, DBP, and 24h BP • Significantly higher means of nighttime SBP, DBP and BP • Higher pulse pressure, but NSS difference • Higher percentage of dippers, but NSS difference (66.6% vs. 58.8%)

STUDY	STUDY DESIGN	ADPKD POPULATION	CONTROL POPULATION	MEASUREMENTS	OUTCOMES	RESULTS (ADPKD VS. CONTROL, UNLESS OTHERWISE SPECIFIED)
						• Significantly higher LVMI (85.3±23.3 vs. 73.7±12.5, p < 0.04)

Turgut et al. 2007 (10)	Prospective study	• 41 ADPKD patients with well-preserved renal function, subsequently divided into dippers (nocturnal fall of ≥10% in SBP) and non-dippers
		• Mean age 38 years
		• Mean GFR ~98 mL/min
			• N/A	• 24h ABPM once during which they were told to maintain normal activity
				• UAE using 24h urine samples
				• Echocardiographic examination
				• Brachial artery measurements to determine endothelium-dependent dilatation
					• Dipper status
					• Comparison between dippers and non-dippers with respect to: 24h ambulatory BP profile, UAE, endothelial-dependent dilatation, LVMI
						• 20 (49%) dippers, 21 (51%) non-dippers
						• Nocturnal fall in SBP: 11.1 ± 1.2% in dippers vs. 0.98 ± 0.9% in non-dippers (p = 0.001)
						• Dippers vs. non-dippers:
						  • Similar mean 24h SBP, 24h DBP, and 24h pulse rate
						  • NSS difference in mean daytime SBP, or in mean daytime or nighttime DBP
						  • Significantly lower mean nighttime SBP
						  • NSS difference in UAE
						  • NSS difference in LVMI
						  • Significantly higher endothelial-dependent dilatation (6.22 ± 4.14% versus 3.57 ± 2.52%, p = 0.025)

STUDY	STUDY DESIGN	ADPKD POPULATION	CONTROL POPULATION	MEASUREMENTS	OUTCOMES	RESULTS (ADPKD VS. CONTROL, UNLESS OTHERWISE SPECIFIED)

Sans-Axter et al. 2010 (11)	Prospective study	• 37 ADPKD patients with eGFR > 60 mL/min/1.73 m^2 and no known HTN (home BP <135/84 mm Hg, but patients not trained in home BP monitoring)
		• Mean age ~38 years
			• N/A	• 24h ABPM once
				• BP measured in clinic
				• Renal echography
					• HTN diagnosis
					  • White coat: Clinic BP ≥ 140/90 mm Hg, 24h ABPM < 130/80 mm Hg
					  • Masked: Clinic BP <140/90 mm Hg, 24h ABPM ≥ 130/80 mm Hg
					  • True HTN: Clinic BP ≥140/90 mm Hg, 24h ABPM ≥ 130/80 mm Hg
					  • True normotensive: Clinic BP <140/90 mm Hg, 24h ABPM ≥ 130/80 mm Hg
					• Relationship between 24h ambulatory BP profile and kidney size in normotensive group
						• HTN:
						  • White coat: 4 (10.8%)
						  • Masked: 11 (29.7%)
						  • True HTN: 9 (24.3%)
						  • True normotensive: 13 (35.1%)
						• Positive correlation found between renal size and DBP variability in normotensive group

STUDY	STUDY DESIGN	ADPKD POPULATION	CONTROL POPULATION	MEASUREMENTS	OUTCOMES	RESULTS (ADPKD VS. CONTROL, UNLESS OTHERWISE SPECIFIED)

Rahbari-Oskoui et al. 2011 (12)	Prospective study	• 25 hypertensive or pre-hypertensive ADPKD patients
		• Mean age 43.1 years
		• Mean eGFR 63 mL/min/1.73 m^2
			• N/A	• 24h ABPM on 2 occasions, 7-15 days apart	• Correlations and concordance coefficients for SBP, DBP and heart rate based on Night:Day and Asleep:Awake ratios	• ABPM measurements of SBP, DBP, MAP, and heart rate were strongly reproducible
						• Dipping status was modestly reproducible
						• Dipper status:
						  • 11 (44%) non-dippers on both days
						  • 6 (24%) dippers on both days
						  • 8 (32%) dippers only on 1 day

Niemczyk et al. 2014 (13)	Prospective study	• 68 pre-dialysis ADPKD patients with no history of subarachnoid hemorrhage
		• Mean age 45 years (range 19-75 years)
		• Mean GFR 68 mL/min
		• 46 (67.6%) diagnosed with HTN and treated with BP medications
			• N/A	• 24h ABPM once
				• MR angiography of the brain to screen for intracranial aneurysm
					• Presence of intracranial aneurysm
					• Comparison of ambulatory BP parameters between patients with and without intracranial aneurysm
						• Intracranial aneurysm in 10 patients (15%)
						• Intracranial aneurysm-positive vs. intracranial aneurysm-negative:
						  • Significantly higher nighttime maximum DBP; maximum nighttime delta of DBP; standard deviation of daytime MAP
						• In patients aged >45 years, intracranial aneurysm-positive vs. intracranial aneurysm-negative:
						  • Significantly higher maximum 24h and daytime SBP; maximum 24h, daytime, and

STUDY	STUDY DESIGN	ADPKD POPULATION	CONTROL POPULATION	MEASUREMENTS	OUTCOMES	RESULTS (ADPKD VS. CONTROL, UNLESS OTHERWISE SPECIFIED)
						nighttime DBP; maximum daytime and nighttime positive delta of DBP

Massella et al. 2018 (14)	Retrospective, multicenter study	• 310 ADPKD patients aged < 18 years
		• Mean age 11.5 years
		• Mean eGFR 120 mL/min/1.73 m^2
		• 80% on no BP medications
			• N/A	• 24h ABPM recordings
				• Kidney ultrasonographic data
					• Prevalence of HTN (mean SBP and/or DBP >95th percentile)
					• 24h ambulatory BP profile
					• Association between BP and categorical "cyst score" (score created for this study)
					• Association between BP and kidney length
						• Prevalence of HTN and/or on BP medication:
						  • Daytime 31%
						  • Nighttime 42%
						  • Entire 24h 35%
						• Isolated nocturnal HTN in 18%
						• No nocturnal dipping in 52%
						• Daytime HTN, nighttime HTN, and 24h HTN all significantly associated with "cyst score"
						• Nighttime HTN significantly associated with kidney length

ABPM = ambulatory blood pressure monitoring; ADPKD = autosomal dominant polycystic kidney disease; BP = blood pressure; DBP = diastolic blood pressure; HTN = hypertension; eGFR = estimated glomerular filtration rate; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; MAP = mean arterial pressure; NSS = non-statistically significant; PWD = posterior wall thickness in diastole; SBP = systolic blood pressure; SCr = serum creatinine; UAE = urinary albumin excretion; VSD = ventricular septal thickness in diastole

References

1. Zeier M, Geberth S, Schmidt, KG, Mandelbaum A, Ritz A. Elevated blood pressure profile and left ventricular mass in children and young adults with autosomal dominant polycystic kidney disease. *J Am Soc Nephrol.* 1993;3(8):1451-7.
2. Seeman T, Sikut M, Konrad M, Vondrichová H, Janda J, Schärer K. Blood pressure and renal function in autosomal dominant polycystic kidney disease. *Pediatr Nephrol.* 1997;11(5):592-6.
3. Li Kam Wa TC, Macnicol AM, Watson ML. Ambulatory blood pressure in hypertensive patients with autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 1997; 12(10): 2075-80.
4. Cerasola G, Vecchi M, Mulè G, Cottone S, Mangano MT, Andronico G, et al. Sympathetic activity and blood pressure pattern in autosomal dominant polycystic kidney disease hypertensives. *Am J Nephrol*. 1998;18(5):391-8.
5. Valero FA, Martinez-Vea A, Bardaji A, Gutierrez C, Garcia C, Richart C, et al. Ambulatory blood pressure and left ventricular mass in normotensive patients with autosomal dominant polycystic kidney disease. *J Am Soc Nephrol.* 1999;10(5):1020-6.
6. Martinez-Vea A, Valero FA, Bardaji A, Gutierrez C, Broch M, Garcia C, et al. Left ventricular hypertrophy in hypertensive patients with autosomal dominant polycystic kidney disease: influence of blood pressure and humoral and neurohormonal factors. *Am J Nephrol.* 2000;20(3):193-200.
7. Seeman T, Dusek J, Vondrichová H, Kyncl M, John U, Misselwitz J, et al. Ambulatory blood pressure correlates with renal volume and number of renal cysts in children with autosomal dominant polycystic kidney disease. *Blood Press Monit.* 2003;8(3):107-10.
8. Seeman T, Dusek J, Vondrák K, Bláhová K, Simková E, Kreisinger J, et al. Renal concentrating capacity is linked to blood pressure in children with autosomal dominant polycystic kidney disease. *Physiol Res.* 2004;53(6):629-34.
9. de Almeida EA, de Oliveira EI, Lopes JA, Almeida AG, Lopes MG, Prata MM. Ambulatory blood pressure measurement in young normotensive patients with autosomal dominant polycystic kidney disease. *Rev Port Cardiol*. 2007;26(3):235-43.
10. Turgut F, Oflaz H, Namli S, Alisir S, Tufan F, Temiz S, et al. Ambulatory blood pressure and endothelial dysfunction in patients with autosomal dominant polycystic kidney disease. *Ren Fail*. 2007;29(8):979-84.
11. Sans Atxer L, Roca-Cusachs A, Torra R, Calero F, Arias P, Ballarin J, et al. Relationship between renal size and blood pressure profile in patients with autosomal dominant polycystic kidney disease without renal failure. *Nefrologia.* 2010;30(5):567-72
12. Rahbari-Oskoui FF, Miskulin DC, Hogan MC, Fielder O, Torres VE, Bost JE, et al. Short-term reproducibility of ambulatory blood pressure monitoring in autosomal dominant polycystic kidney disease. *Blood Press Monit.* 2011;16(2):47-54.
13. Niemczyk M, Pilecki T, Gradzik M, Bujko M, Niemczyk S, Pączek L. Blood pressure and intracranial aneurysms in autosomal dominant polycystic kidney disease. *Kidney Blood Press Res*. 2014;39(6):630-5.
14. Massella L, Mekahli D, Paripović D, Prikhodina L, Godefroid N, Niemirska A, et al. Prevalence of Hypertension in Children with Early-Stage ADPKD. *Clin J Am Soc Nephrol.* 2018;13(6):874-883.

Table 3: Statements/Recommendations Regarding Blood Pressure Targets in ADPKD

PUBLICATION TYPE	PUBLICATION	YEAR OF PUBLICATION	STATEMENT/RECOMMENDATION

Guideline	Spanish guidelines for the management of autosomal dominant polycystic kidney disease (1)	2014	• "The clinic blood pressure target for ADPKD patients should be similar to other CKD patients until results from the HALT trial become available (D)."
			  • "However, there are some discrepancies between guidelines regarding blood pressure targets for individuals with CKD."
			  • "In this regard, until new evidence becomes available, such as might be provided by the HALT clinical trial, there is no firm evidence to recommend specific blood pressure targets for patients with ADPKD."

	Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference (2)	2015	• "Data supporting disease-specific blood-pressure (BP) targets are limited. The general advice of the 2012 KDIGO Clinical Practice Guideline for the Management of BP in chronic kidney disease can therefore be followed, suggesting a BP target ≤140/90 mm Hg. In accordance with this guideline, blood pressure targets should be individualized, taking comorbidities into account."
	KHA-CARI Autosomal Dominant Polycystic Kidney Disease Guideline: Pharmacological Management (3)	2015	• "We recommend the use of antihypertensive therapies to treat hypertension among those with autosomal dominant polycystic kidney disease (1B) with a suggested blood pressure target of less than or equal to 130/80 mm Hg (2B).' • "Targeting a low blood pressure target (95/60 to 110/75 mm Hg) rather than a higher blood pressure target (120/70 to 130/80 mm Hg) may be considered in selected patients with early stage renal disease (estimated glomerular filtration rate [eGFR] > 60 mL/min/1.73 m^2) who are less likely to experience associated side effects or adverse events. This has been associated with the surrogate marker of slowed total kidney volume (TKV) expansion, although not slowing of progression of renal dysfunction. It is also associated with a greater reduction in in left ventricular mass index (LVMI), providing potential cardiovascular benefit."
	KHA-CARI guideline recommendations for the diagnosis and management of autosomal dominant polycystic kidney disease (4)	2016	• Same statements as those listed for "KHA-CARI Autosomal Dominant Polycystic Kidney Disease Guideline: Pharmacological Management" • "Reduction of TKV: targeting a lower blood pressure target in some patients may slow TKV progression."
	Assessing Risk of Disease Progression and Pharmacological Management of Autosomal Dominant Polycystic Kidney Disease: A Canadian Expert Consensus (5)	2017	• "We recommend that patient with ADPKD who are younger than 50 years with eGFR > 60 mL/min/1.73 m^2 and without significant cardiovascular morbidities should have a target blood pressure ≤ 110/75 mm Hg, realizing that in some patients an individual target may be needed."

PUBLICATION TYPE	PUBLICATION	YEAR OF PUBLICATION	STATEMENT/RECOMMENDATION
	Updated Canadian Expert Consensus on Assessing Risk of Disease Progression and Pharmacological Management of Autosomal Dominant Polycystic Kidney Disease (6)	2018	
	European ADPKD Forum multidisciplinary position statement on autosomal dominant polycystic kidney disease care (7)	2018	• "The KDIGO CKD blood pressure target of ≤ 140/90 mmHg is recommended for individualized use, taking comorbidities into account." • "Data from the HALT PKD study suggests that a lower target might benefit young hypertensive ADPKD patients (15-49 years) at CKD Stages 1 or 2 and without diabetes mellitus or significant cardiovascular comorbidities. It this group, a target of 95/60-110/75 was associated with a slower increase in total kidney volume (TKV), though no overall change in the eGFR, together with greater decline in the left ventricular-mass index and a greater reduction in urinary albumin excretion, as compared with a target of 120/70-130/80 mmHg. A cardiology referral is needed if signs or symptoms of cardiac disease are evident."
Review Article	Fall and Prisant (8)	2005	• "Until further randomized, controlled trials are conducted in patients with PCKD, a BP goal of less than 130/80 mm Hg, as recommended by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP (JNC 7), should be the target unless there is evidence of cardiovascular disease"
	Sans-Axter et al. (9)	2013	• "The BP should be <140/90 mm Hg in all ADPKD patients and a more intensive control <<135/85 mm Hg) should be pursued as soon as microalbuminuria or left ventricle hypertrophy is present"
	Rangan et al. (10)	2016	• Maintain BP≤130/80 with ACEI/ARB • "The HALT-PKD trial failed to demonstrate that aggressive blood pressure control slows disease progression in stages 4–5 CKD"
	Krishnappa et al. (11)	2017	• "We recommend a target blood pressure less than 110/75 mm Hg in hypertensive ADPKD patients with preserved renal function who can tolerate this level, and less than 130/80 mm Hg in ADPKD patients with stage 3 chronic kidney disease." • "However, no studies have established the safest lower limit of target blood pressure in ADPKD."

PUBLICATION TYPE	PUBLICATION	YEAR OF PUBLICATION	STATEMENT/RECOMMENDATION
	Helal et al. (12)	2017	• "Until more evidence is available, in patients with ADPKD, we recommend adopting BP target of less than 130/80 mm Hg and should be pursued as soon as microalbuminuria or LVH is present."
	Chebib et al. (13)	2018	• "We recommend a rigorous BP target (≤110/ 75 mm Hg) if tolerated in young hypertensive adults with an eGFR >60 ml/min per 1.73 m^2, particularly those with severe kidney disease (class C–E by the imaging classification) or cardiovascular associations such as intracranial aneurysms or valvular heart disease." • "In other patients with ADPKD, a target ≤130/85 mm Hg is appropriate."
	Torra et al. (14)	2019	• If hypertension: Goal ≤ 110/75 mmHg if 18-50 y.o. and eGFR >60 ml/min; otherwise 130/85

References

1. Ars E, Bernis C, Fraga G, Martínez V, Martins J, Ortiz A, et al. Spanish guidelines for the management of autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant*. 2014;29 Suppl 4:iv95-105.
2. Chapman AB, Devuyst O, Eckardt KU, Gansevoort RT, Harris T, Horie s, ET AL. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 2015;88(1):17-27.
3. Mallett A, Lee V, Mai J, Lopez-Vargas P, Rangan GK. KHA-CARI Autosomal Dominant Polycystic Kidney Disease Guideline: Pharmacological Management. *Semin Nephrol.* 2015; 35(6):582-589.
4. Rangan CK, Alexander SI, Campbell KL, Dexter MA, Lee VW, Lopez-Vargas P, et al. KHA-CARI guideline recommendations for the diagnosis and management of autosomal dominant polycystic kidney disease. *Nephrology.* 2016;21(8)705-16.
5. Soroka S, Alam A, Bevilacqua M, Girard L-P, Komenda P, Loertscher R, et al. Assessing Risk of Disease Progression and Pharmacological Management of Autosomal Dominant Polycystic Kidney Disease: A Canadian Expert Consensus. *Can J Kidney Health Dis.* 2017;4:205435811769578.
6. Soroka S, Alam A, Bevilacqua M, Girard L-P, Komenda P, Loertscher R, et al. Updated Canadian Expert Consensus on Assessing Risk of Disease Progression and Pharmacological Management of Autosomal Dominant Polycystic Kidney Disease. *Can J Kidney Health Dis.* 2018; 5:205435811880158.
7. Harris T, Sandford R, de Coninck B, Devuyst O, Drenth JPH, Ecder T, et al. European ADPKD Forum multidisciplinary position statement on autosomal dominant polycystic kidney disease. *Npehrol Dial Transplant*. 2018;33(4)563-73.
8. Fall PJ, Prisant M. Polycystic Kidney Disease. *J Clin Hypertens (Greenwich).* 2005;7(10):617-9, 625.
9. Sans-Axter L, Torra R, Fernández-Llama P. Hypertension in autosomal-dominant polycystic kidney disease (ADPKD). *Clin Kidney J.* 2013; 6(5): 457-463.
10. Rangan GK, Tchan MC, Tong A, Wong at, Nankivell BJ. Recent advances in autosomal-dominant polycystic kidney disease. *Intern Med J.* 2016; 46(8):883-92.
11. Krishnappa V, Vinod P, Deverakonda D, Raina R. Autosomal dominant polycystic kidney disease and the heart and brain. *Cleve Clin J Med.* 2017;84(6):471–81.
12. Helal I, Al-Rowaie F, Abderrahim E, Kheder A. Update on the pathogenesis, management, and treatment of hypertension in autosomal dominant polycystic kidney disease. *Saudi J Kidney Dis Transpl*. 2017;28(2):253-260.
13. Chebib FT, Torres VE. Recent Advances in the Management of Autosomal Dominant Polycystic Kidney Disease. *Clin J Am Soc Nephrol.* 2018; 13(11):1765-76.
14. Chebib FT, Perrone RD, Chapman AB, Dahl NK, Harris PC, Mrug M, et al. A Practical Guide for Treatment of Rapidly Progressive ADPKD with Tolvaptan. *J Am Soc Nephrol*. 2018;29(10):2458–70.
15. Torra R. Recent advances in the clinical management of autosomal dominant polycystic kidney disease. F1000Res. 2019;8.

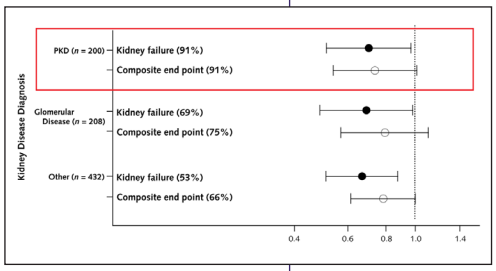
Table 4: Evidence Summary for Blood Pressure Targets in ADPKD

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
Klahr et al. 1995 (1)	• Subgroup study of ADPKD patients included in MDRD study (3-year RCT evaluating effect of lower BP and protein/phosphorus intake on GFR decline in 840 CKD patients) • BP measured monthly with random-zero sphygmonomanometer • Recommended BP medications: ACE-I +/- diuretics 1st line, with addition of CCB or others	• 200 ADPKD patients included in MDRD study with eGFR 13-55 mL/min • Study A: Patients with baseline eGFR 25 to 55 mL/min • Study B: Patients with baseline eGFR 13 to 24 mL/min	Low MAP (MAP ≤ 92 mm Hg if ≤ 60 years old or MAP ≤ 98 mm Hg if > 60 years old) (n=106)	Usual MAP (MAP ≤ 107 mm Hg if ≤60 years old or MAP ≤113 mm Hg if >60 years old) (n=94)	• Rate of eGFR decline • Renal function stop points (withdrawal from study): rapid decline in GFR (Study A only, to <50% of baseline if initial GFR ≤40 mL/min, or to a value ≤20 mL/min if baseline eGFR > 40 mL/min); ESRD requiring dialysis or transplant	• Mean follow-up MAP achieved was not associated with eGFR decline in Study A or B • Neither use of ACE-I nor other antihypertensives were associated with eGFR in Study A or B Study A: • -6.3 mm Hg difference in MAP (p<0.001), but substantial overlap in MAP distribution throughout study • 74% vs. 49% on ACE-I for >50% of follow-up period • 13 vs. 11 patients reached renal stop point • NSS difference in rate of eGFR decline Study B: • -3.9 mm Hg difference in MAP (p=0.01), but substantial overlap in MAP distribution throughout study • 42% on ACE-I for >50% of follow-up period in both groups	• No safety data reported • Minimal data available BP medication regimens and number of medications used to achieve target MAP • Numerous secondary analyses performed, increasing risk of chance findings • Differences in achieved BP between Low MAP and Usual MAP groups were small; therefore, may have been difficult to detect any effect of BP control on eGFR decline

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
						• 16 vs. 9 patients reached renal stop point • Rate of eGFR decline 4.9 mL/min/year vs. 3.9 mL/min/year (p=0.03), signaling a potential harmful effect of targeting low BP in advanced CKD	

Schrier et al. 2002 (2)	• 7-year, prospective, randomized study; randomization stratified by GFR
	• Patients randomized to enalapril or amlodipine for mean 2.1 years, but stopped due to loss of funding
	• BP measured at the research center by a trained professional and/or at home with BP cuff (mean of 3 sitting BPs used as the BP measurement)
		• 75 ADPKD patients with established HTN (BP≥140/90 mm Hg), LVH (LVMI >125 g/m^2 in men, >110 g/m^2 in women), eGFR > 30 mL/min/1.73 m^2
		• Mean age ~41 years
		• Mean BP ~143/96
		• Mean CrCl ~83 mL/min/1.73 m^2
			Rigorous BP control (<120/80 mm Hg) (n=41)	Standard BP control (135-140/85 mm Hg) (n=34)	• LVMI
					• 24h CrCl
						• Average MAP during study: 90 ± 5 mm Hg vs. 101 ± 4 mm Hg (p < 0.0001)
						• Mean BP at year 7:
						  • Men: 117/77 mm Hg vs. 131/84 mm hg
						  • Women: 123/77 mm Hg vs. 130/80 mm Hg
						• Mean number of BP medications needed: 2.7 ± 0.8 vs. 1.4 ± 0.6 (p < 0.0001)
						• Significant reduction in LVMI for both groups (p < 0.0001)
						• LVMI in normal range: 71% vs. 44%, (p<0.05)
						• Significant interaction between BP control group and gender on LVMI over time (p<0.05); rigorous BP control particularly important in men with LVH
							• 53 of the 79 patients completed the study through year 7
							• Applicable to ADPKD patients with LVH
							• No safety data reported

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
	• 1st line BP agent: enalapril or amlodipine (more patients received enalapril after medication randomization was terminated) • 2nd line BP agent: HCTZ, clonidine, or spironolactone					• Mean CrCl over time: NSS difference • Time to ESRD: 4.0 ± 1.4 years vs. 3.2 ± 1.8 years, (p=NSS)	
Schrier et al. 2003 (3)	Only select data from analyses pertaining to BP control are presented in this table Epidemiological study using mail-in questionnaires, phone calls, and follow-up visits at the research center to obtain information on patients' renal survival status	• 513 adult patients with ADPKD who participated in a longitudinal study at the research center between 1985 to 2001 and were between 18-60 years of age at their initial study visit At initial study visit, Males: • Mean age 36-39 years • Mean BP 127-136/80-82 mm Hg	Multiple linear regression analysis to determine association between MAP at initial study visit and renal survival • Adjusted for age, gender, urinary protein excretion, and gender (unclear whether any other potential confounders were included)			Note: MAP 93 mm Hg = 120/80 mm Hg • Male patients with MAP > 93 mm Hg were 10.0 times more likely to enter ESRD than those with MAP ≤ 93 mm Hg • Female patients with MAP > 93 mm Hg were 2.4 times more likely to enter ESRD than those with MAP ≤ 93 mm Hg • MAP was an independent predictor of progression to ESRD (p=0.0026)	• Large sample size • Analysis only used BP data from initial study visit • Likely several potential confounders that were not accounted for

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
		• Mean MAP 65-106 mm Hg • Mean SCr 124-177 umol/L • Mean UPE 105-409 mg/24h					
Sarnak et al. 2005 (4)	• Subgroup results of long-term follow up (additional 7 years) from MDRD study (3-year RCT evaluating effect of lower BP and protein/phosphorus intake on GFR decline in 840 CKD patients) • BP measured monthly with random-zero sphygmonometer during the study • Recommended BP medications: ACE-I +/- diuretics 1st line, with addition of CCB or others	• 200 ADPKD patients included in MDRD study with eGFR 13-55 mL/min • Study A: Patients with baseline eGFR 25 to 55 mL/min • Study B: Patients with baseline eGFR 13 to 24 mL/min	Low MAP during the study, (MAP ≤ 92 mm Hg if ≤ 60 years old or MAP ≤ 98 mm Hg if > 60 years old) (n=106)	Usual MAP during the study (MAP ≤ 107 mm Hg if ≤ 60 years old or MAP ≤ 113 mm Hg if >60 years old) (n=94)	• Kidney failure (dialysis initiation or transplant) • Composite outcome of kidney failure or all-cause mortality	• Plot of adjusted HR for Low MAP vs. Usual MAP below; confidence intervals not provided • In PKD, appears that there was reduced risk of kidney failure (statistically significant) • In PKD, appears that there was reduced risk of composite outcome (NSS)	• BP data is from duration of the study, not from long-term follow-up • No target BP or specific medication regimen was recommended after study completion • Numerous analyses performed, increasing risk of chance findings

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
Zeltner et al. 2008 (5)	• Post-hoc analysis of a 3-year, double-blind RCT comparing ramipril vs. metoprolol as 1st-line agent to achieve target of ≤135/85 mm Hg • For purpose of post-hoc analysis, used 24h ABPM measurement from 3-year follow-up visit • 2nd-line agent: felodipine • 3rd line agent: doxazosin and/or furosemide	• 37 ADPKD patients with HTN (casual BP ≥140/90 mm Hg or on BP medication), SCr < 352 mmol/L, no MI/stroke 12 months prior to study, no CHF • Mean age ~40 years • Mean BP 142-143/90-93 mmHg, • Mean eGFR 87-88 mL/min • Mean ACR 64.0-75.3 mg/mmol	Rigorous BP control = MAP ≤ 97 mm Hg (mean BP 125/78 mm Hg) achieved at 3 years (n=19)	Standard BP control = MAP >97 mm Hg (mean BP 136/86 mm Hg) achieved at 3 years (n=18)	• Change in eGFR • Change in albuminuria • Change in LVMI	• Lower loss of GFR (−1.7 ± 0.5 vs. −3.5 ± 0.9 mL/min/year, p=0.07). • Lower urinary albumin excretion (23.5 ± 6.7 vs. 94.8 ± 35.4 mg/g, p= 0.05). • No change in LVMI vs. significant increase • Lower LVMI (90.9 ± 4.7 vs. 110.5 ± 6.3 g/m^2, p= 0.017)	• Small sample size • Post-hoc analysis • Patients in standard BP control group had higher BP throughout the study and numerically lower renal function from the beginning, though difference in GFR was not significant • No data with regards to number of BP medications used in each group • No safety data reported
Cadnapaphorn-chai et al. 2012 (6)	• Primary objective was to assess effect of BP control with ACE-I on ADPKD progression and several comparisons analyzed; only the data on comparisons of BP targets in	Only hypertensive participant data listed below: • 28 patients aged 4-21 years with ADPKD (diagnosed by ≥1 renal cyst in setting of ADPKD family history, or multiple cysts	Target BP ≤ 50th percentile (HBP50) (n=14) 50% of this group also randomized to ACE-I	Target BP ≤ 90th percentile (HBP90) (n=14) 50% of this group also randomized to ACE-I	1° outcome: • Renal volume by U/S 2° outcomes include: • Micro-albuminuria • LVMI • SCr • 24h CrCl	• 4 dropouts in each group (did not want to continue participation; reasons not provided) • Number meeting BP target: 4/10 patients, vs. 7/10 patients • Mean BP at year 5: 125/67, vs. 137/77 mm Hg • Mean number of BP medications needed: 2.8 ± 0.3, vs. 1.6 ± 0.4	• Small sample size with high dropout rate (39%) • BP target not met in many patients • Multiple comparisons made in the entire study, increasing risk of false positive results

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS

	hypertensive participants is presented in this table
	• 5-year, single-centre, randomized clinical trial
	• BP measured at home (6 times, 3 min apart) using digital BP monitor at least monthly for medication adjustments
	• 1st line BP agent: enalapril if not previously taking, or alternative at discretion of physician
	• 2nd line BP agent: amlodipine
	• 3rd line BP agent: metoprolol
	• 4th line BP agent: HCTZ
	• 5th line BP agent: others as necessary
		that were clinically consistent with ADPKD) and normal renal function
		• Mean age 14 years
		• Mean BP 130/72 mm Hg
		• Mean 24h CrCl 130 mL/min/1.73 m^2
		• Mean UAE 23 mcg/d
		• Mean TKV corrected for BSA 289 mL/1.73 m^2
		• Mean LVMI 75 g/m^2
						• In both groups, compared to baseline:
						  • Increased renal volume over time
						  • No significant difference in microalbuminuria or LVMI
						  • Significant increase in SCr ($p<0.00001$) and 24h CrCl ($p<0.0001$)
						• HBP50 vs. HBP90:
						  • No significant differences in any parameter
							• No safety data reported

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS

Orskov et al. 2012 (7)	• Purpose was to determine association between low-birth-weight and age at onset of ESRD in PKD patients using multivariate analysis; only the data on associations between MAP and age of onset of ESRD is presented in this table
	• Retrospective study using hospital medical files and midwife protocols in Danish State Archives
		• 284 ADPKD patients who were born in Denmark, had reached ESRD, and had sufficient data for analyses
		• Mean follow-up period (time from first documented hospital contact to ESRD onset) of 4.8 years
		• Mean age at ESRD 54 years
		• HTN (MAP > 107 mm Hg or use of BP med during follow-up period) in 95%
		• Mean MAP of 108 mm Hg during follow-up period
		• RAAS blockade use in 69%
		• BB use in 58.4%
		• CCB use in 68%
		• Diuretic use in 80.4%
		• No BP meds in 5.7%
			• Multivariable linear regression analysis of factors associated with age at onset of ESRD
			• Factors included in multivariable analysis:
			  • Birth weight
			  • MAP
			  • Gender
			  • RAAS blocker
			  • BB
			  • CCB
			  • Diuretic
			  • Birth decade
						• For every mm Hg increase in average MAP, patients reached ESRD 0.1 year later (95% CI -0.2 to -0.07; p = 0.0005)
						  • However, range of MAPs was not provided; therefore, unable to determine MAP range to which this linear association applies
							• Clinically relevant endpoint
							• Major limitation is use of retrospective data
							• No data available before first hospital contact
							• Information not available on several potential confounders (eg. proteinuria, number and volume of renal cysts)

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS

Schrier et al. 2014 (8)
 	
HALT-PKD Study A
	In addition to comparing BP targets, also randomized patients to lisinopril + telmisartan or lisinopril + placebo in 2-by-2 factorial design; only data pertaining to BP targets comparisons are presented in this table
	• Multicenter, double-blind, placebo-controlled RCT with follow-up time of 5-8 years (mean follow-up of 5.7 years)
	• 1st line BP agent: lisinopril + placebo, or lisinopril + telmisartan
	• 2nd line BP agent: HCTZ
	• 3rd line BP agent: metoprolol
	• 4th line BP agents: non-DHP CCBs, clonidine, minoxidil, and/or hydralazine
	• BP measured at home
		• 558 ADPKD patients aged 15-49 years, with eGFR > 60 mL/min/1.73 m^2, and HTN (SBP ≥ 130 mm Hg and/or DBP ≥ 95 mm Hg or use of BP med in patients ≥ 18 years; BP ≥ 75th percentile or use of BP med in patients 15-17 years)
		• Mean age ~37 years
		• PKD1 genotype in ~74%
		• Mean eGFR ~91 mL/min/1.73 m^2
		• Median urinary albumin ~18 mg/24h
		• Mean TKV 1164-1264 mL
		• Mean home BP ~124/83 mm Hg
			Low BP target (95/60 to 110/75 mm Hg)
			(n=274)
				Standard BP target (120/70 to 130/80 mm Hg)
				(n=284)
					(Only select outcomes listed here)
					• Annual % change in TKV (measured with MRI)
					• Rate of change in eGR
					• Change in urinary albumin excretion
					• Change in renal blood flow
					• Change in renal vascular resistance
					• Change in LVMI
					• Adverse effects related to study medication
						• Difference in BP:
						  • Difference in home SBP at 96 months: 13.4 mm Hg
						  • Difference in home DBP at 96 months: 9.3 mm Hg
						• Percentage within target BP:
						  • In low-target group, SBP and DBP within target across all study visits in 40-66% and 58-75%, respectively
						  • In standard-target group, SBP and DBP within target across all study visits in 32-48% and 33-52%, respectively
						• BP medications:
						  • Mean daily lisinopril dose was more than 8 mg/day greater
						  • Median number of open-label medications prescribed was 2.0 vs. 1.0 (in addition to either lisinopril or lisinopril/telmisartan)
						  • Significantly greater proportion of patients using
							• 18.1% lost to follow-up, with similar proportions in each study group

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS

						different classes of BP agents, including diuretics (44.9% vs. 26.8%, p<0.001); beta- or alpha-blockers (31.4% vs. 14.4%, p<0.001); CCBs (10.2% vs. 5.3%, p=0.03)
						• Change in TKV:
						  • 14.2% slower annual increase (5.6% vs. 6.6%, p=0.006)
						  • From baseline, increase by 38.0% vs. 44.2%
						  • At 6 months, TKV 1636 ml [95% CI, 1489 to 1782] vs. 1788 mL [95% CI, 1639 to 1938]
						  • Effect of low BP on rate of TKV increase was greatest for men, patients with baseline TKV greater than median, and those with large kidneys (≥75th percentile) who were younger than 30 years
						• Change in eGFR:
						  • Overall change was similar (-2.9 vs. -3.0 mL/min/1.73 m^2 per year, p=0.55)	

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS

						• Change in urinary albumin excretion:
						  • -3.77% (95% CI, -5.71 to -1.78 per year) vs. 2.43% (95% CI, 0.48-4.41) (p<0.001)
						• Change in LVMI:
						  • -1.17 vs. -0.57 g per square meter per year, p<0.001
						• Change in renal blood flow:
						  • Declined similarly in both groups
						• Change in renal vascular resistance
						  • Increased more in standard BP group (p<0.001)
						• Adverse effects:
						  • Higher proportion with at least 1 episode of dizziness/ lightheadedness (80.7% vs. 69.4%, p=0.002)
						  • NSS difference in frequencies of death, serious CV or renal events, hyperkalemia, acute kidney injury, or cancer	

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
						• Mean BP at year 8 not provided, but appears to be ~120/80 mm Hg vs. ~110/70 mm Hg in Figure S1A in Supplementary Appendix	

Irazabal et al. 2017 (9)	• Post hoc analysis of HALT-PKD Study A (Schrier et al. 2014) (5)
	• Investigation of whether using an imaging classification of ADPKD would have increased the power to detect a beneficial treatment effect of rigorous BP control
		• 551 HALT-PKD participants with baseline MRI imaging and height information needed for imaging classification	Rigorous BP control (95/60 to 110/75 mm Hg)
			(n=271)
				Standard BP control (120/70 to 130/80 mm Hg)
				(n=280)
					• Annual % change in TKV
					• Rate of change in eGR
					• Change in urinary albumin excretion
					• Change in renal vascular resistance
					• Change in LVMI
						• Most patients were typical Class 1 patients, and all atypical Class 2 patients were Class 2A
						<u>Rigorous vs. Standard BP control:</u>
						• Annual % change in TKV:
						  • Lower in Class 1A to 1E
						  • Difference only significant in Class 1D (p=0.018)
						  • NSS difference in Class 2A patients
						  • When stratified by disease severity (Class 1A and 2A; 1B-1C; 1D-1E): Slower annual increase in Class 1D-1E (6.4% vs. 7.8%, p=0.034)
						• Rate of change in eGFR:
						  • In Class 1 patients: Overall, lower rate of eGFR decline across classes, particularly Class ID and IE, but difference NSS. After first 4 months,
							• Post-hoc analysis carrying risk of false positive result
							• Small sample sizes in different classification groups

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
						significantly lower in Class 1E only (p=0.036) • In Class 2 patients: NSS difference overall and after 4 months • When stratified by disease severity (Class 1A and 2A; 1B-1C; 1D-1E): Slower decline after first 4 months in Class 1D-1E (-3.36% vs.-4.45%, p=0.011) • Change in urinary albumin excretion: • Tended to decrease vs. increase in all classes, but statistically significant in Class 1A and 1C only (both p <0.01) • Change in renal vascular resistance: • Tended to decrease vs. increase in most classes, but difference only statistically significant in Classes 1C (p=0.023) and 1E (p=0.043) • Change in LVMI: • Tended to decrease in both groups,	

STUDY	STUDY DESIGN	ADPKD POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
						significantloy more in the low BP group compared to standard BP group in Class 1C only (p<0.001)	

Xue et al. 2015 (10)	• Meta-analysis of 10 studies
	• Studies were to be included only if they were RCTs; however, Zeltner et al. included despite non-randomization to BP targets
	• 3 studies included comparing BP targets: Schrier et al. 2002, Schrier et al. 2014, Zeltner et al. 2008
		See information for 3 included studies above	Standard BP control group (target 120/80-140/90 mm Hg)	Rigorous BP control group (target <120/80 mm Hg)	(Only select outcomes listed here)
					• LVMI
					• eGFR
					• Urinary albumin excretion
						• LVMI (2 studies, 517 patients):
						  • Greater decrease in LVMI in rigorous BP control group
						  • MD 14.56 g/m^2, 95% CI 2.06 to 27.06 g/m^2, p=0.02
						  • I^2 = 94%
						• eGFR (3 studies, 261 patients)
						  • Similar eGFR between groups
						  • Mean difference -6.39, 95%
						  • CI -17.67 to 4.90 g/m^2, p=0.27
						  • I^2 = 88%
						• Urinary albumin excretion (2 studies, 208 patients):
						  • Tended to be less in rigorous BP control group, but NSS
						  • MD -38.6, 95% CI -101.61 to 24.4, p=0.23
						  • I^2 = 98%
							• Inclusion of a study in which BP targets were not randomized
							• Lack of meaningful pooled results, as data from the end of follow-up were compared as mean differences, but study durations varied
							• High I^2 values for all pooled analyses, indicating that pooling the study results is inappropriate (this is expected, as study designs and populations varied)

ABPM = ambulatory blood pressure monitoring; ACE-I= angiotensin-converting enzyme inhibitor; ACR = albumin-to-creatinine ratio; ADPKD = autosomal dominant polycystic kidney disease; BP = blood pressure; CCB = calcium channel blocker; CHF = congestive heart failure; CI = confidence interval; CrCl = creatinine clearance; CV = cardiovascular; DBP = diastolic blood pressure; eGFR = estimated glo-merular filtration rate; ESRD = end-stage renal disease; GFR = glomerular filtration rate; HTN = hypertension; HCTZ = hydrochlorothiazide, hosp'n = hospitalization; LVMI = left ventricular mass index, LVH = left ventricular hypertrophy; MAP = mean arterial pressure; MD = mean difference; MI= myocardial infarction; MRI = magnetic resonance imaging; non-DHP CCB = non-dihydropyridine calcium channel blocker; NSS = non-statistically significant; PKD = polycystic kidney disease; QoL = quality of life; RCT = randomized controlled trial; SBP = systolic blood pressure; SCr = serum creatinine; TKV = total kidney volume; U/S = ultrasound

References

1. Klahr S, Breyer JA, Beck GJ, Dennis VW, Hartman JA, Roth D, et al. Dietary protein restriction, blood pressure control, and the progression of polycystic kidney disease. Modification of Diet in Re-nal Disease Study Group. *J Am Soc Nephrol*. 1995;5(12):2037-47.
2. Schrier R, McFann K, Johnson A, Chapman A, Edelstein C, Brosnahan G, et al. Cardiac and renal effects of standard versus rigorous blood pressure control in autosomal-dominant polycys-tic kid-ney disease: results of a seven-year prospective randomized study. *J Am Soc Nephrol.* 2002;13(7):1733-9.
3. Schrier RW, McFann KK, Johnson AM. Epidemiological study of kidney survival in autosomal dominant polycystic kidney disease. *Kidney Int*. 2003;63(2):678-85.
4. Sarnak MJ, Greene T, Wang X, Beck G, Kusek JW, Collins AJ, et al. The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of di-et in renal disease study. *Ann Intern Med*. 2005;142(5):342-51.
5. Zeltner R, Poliak R, Stiasny B, Schmieder RE, Schulze BD. Renal and cardiac effects of antihypertensive treatment with ramipril vs metoprolol in autosomal dominant polycystic kidney disease. *Nephrol Dial Transplant.* 2007;23(2):573–9.
6. Cadnapaphornchai MA, McFann K, Strain JD, Masoumi A, Schrier RW. Prospective Change in Renal Volume and Function in Children with ADPKD. *Clin J Am Soc Nephrol*. 2009;4(4):820-9.
7. Orskov B, Christensen KB, Feldt-Rasmussen B, Strandgaard S. Low birth weight is associated with earlier onset of end-stage renal disease in Danish patients with autosomal dominant polycystic kidney disease. *Kidney Int.* 2012;81(9):919–24.
8. Schrier RW, Abebe KZ, Perrone RD, Torres VE, Braun WE, Steinman TI, et al. Blood pressure in early autosomal dominant polycystic kidney disease. *N Engl J Med*. 2014;371(24):2255-66.
9. Irazabal MV, Blais JD, Perrone RD, Gansevoort RT, Chapman AB, Devuyst O, et al. Prognostic Enrichment Design in Clinical Trials for Autosomal Dominant Polycystic Kidney Disease: The TEMPO 3:4 Clinical Trial. *Kidney Int Rep*. 2016;1(4):213-20.
10. Xue C, Zhou C, Dai B, Yu S, Xu C, Mao Z, et al. Antihypertensive treatments in adult autosomal dominant polycystic kidney disease: network meta-analysis of the randomized controlled trials. *Oncotarget.* 2015;6(40):42515-29.