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Improving Awareness & Patient Outcomes

Hypertension in Autosomal Dominant Polycystic Kidney Disease (ADPKD), Chronic Kidney Disease (CKD), & the General Population (GP)

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Improving Awareness & Patient Outcomes

This program is paid for by

Otsuka Pharmaceutical Development & Commercialization, Inc.

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Objectives

1. Describe the pathophysiology of ADPKD and hypertension (HTN)
2. Compare and contrast the pathophysiology of HTN in the general population (GP), ADPKD, and CKD
3. Discuss unique risk factors and complications of ADPKD
4. Discuss HTN management in the GP and in patients with ADPKD and CKD

1.Rahbari-Oskoui F, et al. *Nephrol Dial Transplant*. 2014;29(12):2194-2201. 2. Chapman AB et al. *Adv Chronic Kidney Dis*. 2010;17(2):153-163.

HTN In ADPKD

HTN is the first ADPKD complication in **30%** of patients[1]

HTN affects **20%** of ADPKD patients <20 years old[1]

> 60% of ADPKD patients (all ages) have HTN prior to kidney function decline[2]

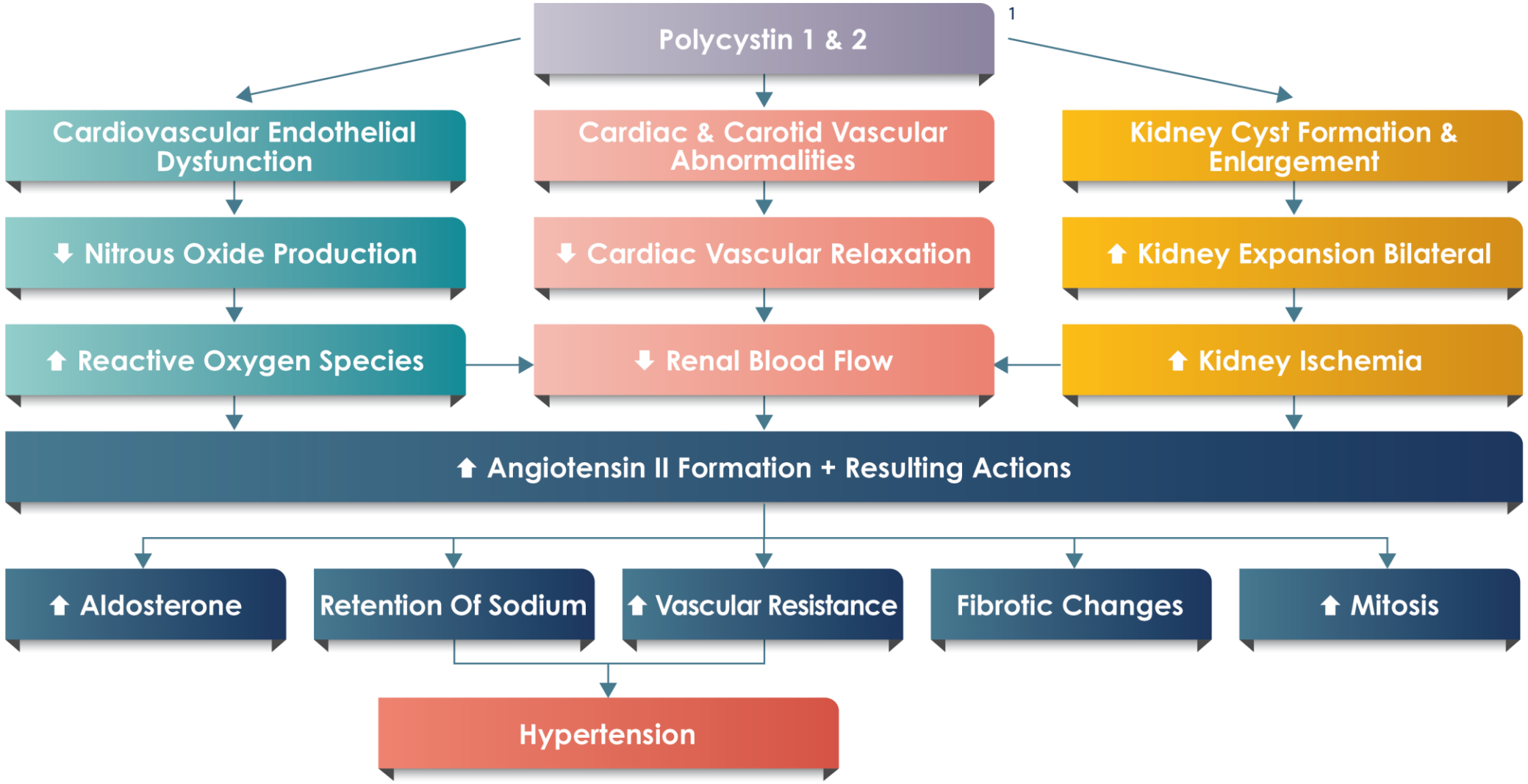
Earlier onset is linked to a *PKD1* mutation and a parent having ADPKD and HTN[1,2]

Hypertensive ADPKD patients with preserved kidney function have:[2]

- ⬆ Greater total kidney volume (TKV)[2]
- ⬆ Higher proteinuria[2]
- ⬇ Decreased renal blood flow[2]

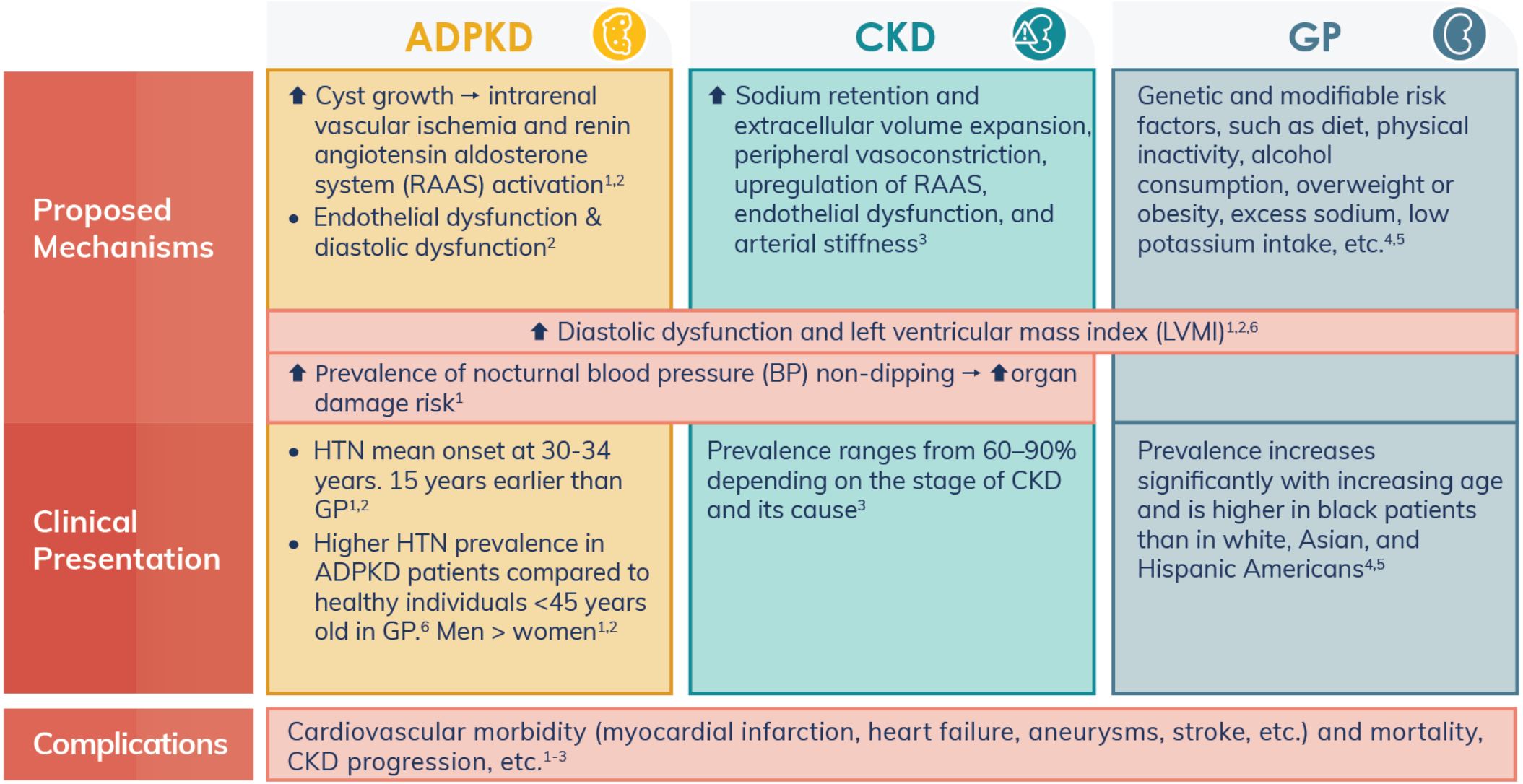
1.Rahbari-Oskoui F, et al. *Nephrol Dial Transplant*. 2014;29(12):2194-2201. 2. Chapman AB, et al. *Adv Chronic Kidney Dis*. 2010;17(2):153-163.

Pathophysiology of HTN in ADPKD



Reference: 1. Chapman AB et al. Adv Chronic Kidney Dis. 2010;17(2):153-163.

Proposed HTN Mechanisms



References: 1.Rahbari-Oskoui F, et al. Nephrol Dial Transplant. 2014;29(12):2194-2201. 2. Chapman AB et al. Adv Chronic Kidney Dis. 2010;17(2):153-163. 3. Ku E, et al. Am J Kidney Dis. 2019;74(1):120-131. 4. Whelton PK, et al. Hypertension. 2018;71:e13–e115. 5. Whelton PK et al. Hypertension. 2018;71:e140–e144. 6. Kelleher CL, et al. Am J Hypertens. 2004;17(110 :1029-1034.

Proposed Mechanisms

ADPKD	CKD	GP
⬆ Cyst growth → intrarenal vascular ischemia and renin angiotensin aldosterone system (RAAS) activation[1,2] • Endothelial dysfunction & diastolic dysfunction[2]	⬆ Sodium retention and extracellular volume expansion, peripheral vasoconstriction, upregulation of RAAS, endothelial dysfunction, and arterial stiffness[3]	Genetic and modifiable risk factors, such as diet, physical inactivity, alcohol consumption, overweight or obesity, excess sodium, low potassium intake, etc.[4,5]
⬆ Diastolic dysfunction and left ventricular mass index (LVMI)[1,2,6]		
⬆ Prevalence of nocturnal blood pressure (BP) non-dipping → ⬆organ damage risk[1]		

References: 1.Rahbari-Oskoui F, et al. Nephrol Dial Transplant. 2014;29(12):2194-2201. 2. Chapman AB et al. Adv Chronic Kidney Dis. 2010;17(2):153-163. 3. Ku E, et al. Am J Kidney Dis. 2019;74(1):120-131. 4. Whelton PK, et al. Hypertension. 2018;71:e13–e115. 5. Whelton PK et al. Hypertension. 2018;71:e140–e144. 6. Kelleher CL, et al. Am J Hypertens. 2004;17(110 :1029-1034.

	ADPKD	CKD	GP
Clinical Presentation	• HTN mean onset at 30-34 years. 15 years earlier than GP[1,2] • Higher HTN prevalence in ADPKD patients compared to healthy individuals <45 years old in GP.[6] Men > women[1,2]	Prevalence ranges from 60–90% depending on the stage of CKD and its cause[3]	Prevalence increases significantly with increasing age and is higher in black patients than in white, Asian, and Hispanic Americans[4,5]
Complications	Cardiovascular morbidity (myocardial infarction, heart failure, aneurysms, stroke, etc.), and mortality, CKD progression, etc.[1-3]		

References: 1.Rahbari-Oskoui F, et al. Nephrol Dial Transplant. 2014;29(12):2194-2201. 2. Chapman AB et al. Adv Chronic Kidney Dis. 2010;17(2):153-163. 3. Ku E, et al. Am J Kidney Dis. 2019;74(1):120-131. 4. Whelton PK, et al. Hypertension. 2018;71:e13–e115. 5. Whelton PK et al. Hypertension. 2018;71:e140–e144. 6. Kelleher CL, et al. Am J Hypertens. 2004;17(110 :1029-1034.

ADPKD and Aneurysm

- ADPKD is associated with a 5-fold increased risk of intracranial aneurysms (ICAs) and incidence rate of 9-12%[1]
- Median age for ICA rupture is significantly lower than the general population (41.5 vs 51 years old)[1]
- Family history of ICA was the only risk factor for screening with magnetic resonance angiography (MRA)[1]
- Recent studies have identified additional risk factors and a lower prevalence than previously reported [4.65% (3.56-5.74)[1]

1. Lefevre S, et al. *Nephrol Dial Transplant*.2020;0:1-11 2. Niemczyk M, et al. *Kidney Blood Press Res*. 2014;39(6):630-635.

Risk Factors for ICA Screening in ADPKD

- Female sex [HR 1.8; 95% CI (1.2-2.7), p=0.005][1,2]
- Age >45 years old, especially in females[2]
- Family history of ICAs[1,2]
- PKD2 vs PKD1 mutation [HR 0.4; 95% CI (0.2-0.8), p=0.009][1]
- Early onset-hypertension (<35 years old) [HR 2.2; 95% CI (01.5-3.2), p≤0.001][1]
- Smoking [HR 2.1; 95% CI (1.2-3.7), p=0.009][1]
- Significant BP changes using ambulatory blood pressure monitoring (ABPM), such as high nocturnal SBP or DBPmax, nocturnal non-dipping, etc)[2]

1. Lefevre S, et al. *Nephrol Dial Transplant*.2020;0:1-11. 2. Niemczyk M, et al. *Kidney Blood Press Res*. 2014;39(6):630-635.

Hyperaldosteronism and CV risk in ADPKD patients

- HTN in ADPKD patients may be due to renal ischemia leading to activation of RAAS system. Primary aldosteronism (PA) can also be a cause of HTN due to decreased renin levels and increased aldosterone levels.[1]
- HTN increases CV risk[1]
- This study enrolled 27 patients and split into 2 groups:[1]
  - Group A (normal Primary aldosterone concentration (PAC) - 18 patients[1]
  - Group B (PA) - 9 patients[1]
- Diagnosis of PA was made using fasting PAC and plasma renin activity (PRA)[1]

1. Lai S, et al. *Medicine*. 2016;95:29

Hyperaldosteronism and CV risk in ADPKD patients

- Statistically significant differences between the two groups included:[1]
  - Higher mean value of LVMI, homeostasis model assessment for insulin resistance (HOMA-IR) and homocysteine (Hcy) found in Group B (PA)[1]
  - Lower value of flow mediated dilation (FMD) and 25-OH-VitD compared to group A (normal PAC)[1]
  - Group B had a higher prevalence of non-dipper pattern using ABPM[1]
- Patients with ADPKD and PA have a high cardiovascular risk. This study had a higher percent of PA patients with ADPKD than the general population. Screening of PA in ADPKD patients along with CV risk factors should be performed.[1]

1. Lai S, et al. Medicine. 2016;95:29

Antihypertensive Medications and Mortality in Patients with ADPKD: A Population-Based Study

- Retrospective cohort study of patients with ADPKD from 1991-2008
- Prescription and intensity of antihypertensive agents increased significantly over time with the greatest increase in RAASi followed by CCB[1]
- Mortality was significantly lower in patients who were on antihypertensive medications with a trend of lower mortality with increasing number of drug classes[1]

1. Patch C, et al. *Am J kidney Dis*. 2011;57(6):856-862.

Calcium Channel Blocker (CCB) vs RAASi in PKD patients

- Retrospective study of 32 ADPKD patients treated with CCB vs RAASi[1]
  - Medication couldn't be changed for 1 year and addition of diuretic was not permitted[1]
  - CCB group showed a statistically significant reduction in yearly eGFR change compared to RAASi group[1]
    - CCB was only variable shown to reduce eGFR out of SBP, DBP, confounding factors, RAASi and baseline eGFR[1]
  - CCB may affect renal function negatively in PKD patients and avoidance of CCB is recommended unless treating resistant HTN[1]
    - Animal model with PKD showed increase in cyst growth with verapamil[1]
    - Study with normal human kidney cells showed cell proliferation and cyst formation when treated with a CCB[1]
    - CCB could possibly block Ca^{2+} entrance into the cell therefore further decreasing intracellular calcium in PKD patients[1]

1. Mitobe M, et al. *Clin Exp Nephrol*. 2010; 14:573-577

Landmark Trials

HALT-PKD Study A (2014)[1] **(n=558)**	Double-blind, placebo controlled, RCT, 15-49 years old with ADPKD and HTN, eGFR >60 mL/min/1.73 m^2, 2x2 factorial: • Lisinopril +telmisartan vs lisinopril + placebo • Standard BP target (120/70-130/80 mmHg) vs Low BP (95/60 mmHg-110/75 mmHg)	• Angiotensin converting enzyme inhibitor (ACE-I)/angiotensin receptor blocker (ARB) combination did not significantly reduce the rate of TKV increase • Intensive BP control was associated with a slower TKV increase [5.6% vs 6.6%, (p=0.006)], no overall change in eGFR, a greater decline in LVMI, and greater reduction in urinary albumin excretion compared to standard BP
HALT-PKD Study A Secondary Analysis (2018)[2] **(n=477)**	• Low (n=225) vs high dose (n=252) RAAS inhibition using median daily equivalent dose of RAASi	• High dose group did not have a slower increase in TKV and chronic eGFR slope decline was similar to the low dose group. A higher SBP was associated with a greater eGFR decline. • ADPKD progression based on eGFR decline and TKV increase was improved with intense BP control compared to pharmacological RAASi intensity
HALT-PKD Study B (2017)[3] **(n=486)**	• Double-blind, placebo controlled, RCT, 18-65 years old with ADPKD and HTN or high normal BP, eGFR 25-60 mL/min/1.73 m^2 • Lisinopril vs lisinopril + telmisartan with doses titrated to achieve BP of 110/70 to 130/80 mmHg.	• No significant difference in composite primary outcome of time to death, ESRD, or 50% reduction from the baseline eGFR between two groups. • No difference in overall rate of change in eGFR • No significant difference in rate of hospitalization or secondary outcomes (frequency of symptoms related to ADKPD, quality of life and incidence of pain.

1. Shrier RW, et al. *New Engl J Med*. 2014;371:24:2255-2266 2. Brosnahan GM, et al. *Current Hypertension Reviews*. 2018;14:39-47. 3. Torres VE, et al. *N Engl J Med*. 2014;371:24:2267-2276.

Landmark Trials

SPRINT Trial (2015)[1] **n=9361**	• Multi-center, open-label, RCT • SBP 130-180 mmHg, ≥50 years old, high CV risk, eGFR 20-60 mL/min/1.73 m^2, no diabetes or prior stroke • Intensive-treatment (SBP <120mmHg) vs Standard (SBP <140 mmHg)	• Trial stopped early due to significantly lower rates of fatal and nonfatal major CV events and all-cause mortality in the intensive-treatment group compared to the standard group. • Hypotension, syncope, electrolyte abnormalities, and acute kidney injury were significantly higher in intensive treatment group (SBP <120 mmHg).
PREVENT-ADPKD (2021)[2] **n=184**	• 3-year RCT, 18-67 years old, ADPKD, eGFR≥30 mL/min/1.73 m^2, Mayo Class 1B-1E • Prescribed water intake uOsm goal ≤270 mOsm/Kg vs ad libitum	• There was no significant difference between annualized height-adjusted TKV rate of growth, eGFR decline, or copeptin levels. Only 52.3% of patients achieved the 24-hr uOsm goal ≤270 mOsm/Kg and was not associated with additional adverse events.

1. SPRINT Research Group. *N Engl J Med*. 2015;373:2103-16. doi: 10.1056/NEJMoa1511939. 2. Rangan, GP, et al. *N Engl J Med*. 2022 ;1(1):doi:10.1056/EVIDoa2100021

HTN Management

	ADPKD	CKD	GP
Lifestyle Modifications 1st-line	• **Sodium:** <2g/day or <5g sodium chloride/day[1], protein restriction to 0.8–1.0 g/kg ideal body weight[2] • **Dietary Approaches to Stop Hypertension (DASH Diet):** ⬆ fruits and vegetables, ⬇ saturated and unsaturated fats.[3] **CKD 4&5:** Hyperkalemia concern.[1] • **Fluids:** Moderate Alcohol (men, ≤2 drinks; women ≤1)[4] ⬇ Caffeine Intake,[5,3] **ADPKD hydration goal:** ~3L/day.[5,6] • **Smoking Cessation**[1,3,4,5] • **Weight Loss:** waist-to-height ratio <0.5 to avoid obesity[3] • **Exercise:** 90-150 minutes of aerobic exercise weekly[4]		
Medications*	**1st-line:** ACE-I/ARB[2,5,7] **2nd-line:** Beta blockers (mild RAAS effect)[5] **3rd-line:** Calcium channel blockers (CCB) with caution[5] **4th-line:** Diuretics with caution (+RAASi)[5]	**1st-line:** ACE-I/ARB for patients with high BP, CKD and severely or moderately increased albuminuria with or without diabetes[1] **Other drugs:** Based on comorbidities[4]	• Thiazide diuretics, ACE-I/ARB, CCB (choice based on comorbidities)[8,9] • For Stage II HTN (>140/90 mmHg), can consider starting with 2 agents from two different classes[8,9]
Goals	• **KDIGO*:** Systolic Blood Pressure (SBP) 95–110 mmHg may be more beneficial than 120–130 mmHg[1] • **Expert Opinion:** Mayo Class 1C-1E & 18-50 y.o.: <110/75 mmHg; others: <130/80 mmHg[2]	**KDIGO:** SBP <120 mmHg, if tolerated[1]	• **2017 Multisociety Guideline:** <130/80 mmHg for adults 18-65 y.o.[3,4,8] • **ISH*:** <65 y.o.: <130/80 mmHg, but >120/70 mmHg; >65 y.o.: <140/90 mmHg as tolerated[3,4]

References: 1. KDIGO. Kidney International. 2021;99(3S):S1-287. 2. Radhakrishnan Y, et al. Kidney Res Clin Pract. 2022;41(4):422-431. 3. Unger T, et al. Hypertens. 2020;75(6):1336-1357. 4. Ku E, et al. Am J Kidney Dis. 2019;74(1):120-131. 5. Rahbari-Oskoui F, et al. Nephrol Dial Transplant. 2014;29(12):2194-2201. 6. Rangan, GP, et al. N Engl J Med. 2022;1(1):doi:10.1056/EVIDoa2100021 7. Chapman AB et al. Adv Chronic Kidney Dis. 2010;17(2):153-163. 8. Whelton PK, et al. Hypertension. 2018;71:e13–e115. 9. Whelton PK et al. Hypertension. 2018;71:e140–e144.

*Based on expert opinion for ADPKD

ADPKD CKD GP

Lifestyle Modifications 1st-line

Sodium: <2g/day or <5g sodium chloride/day[1]

Diet

- **Protein restriction:** 0.8–1.0 g/kg ideal body weight[2]
- **Dietary Approaches to Stop Hypertension (DASH Diet):**
  ⬆ fruits and vegetables, ⬇ saturated and unsaturated fats.[3]
- **CKD 4&5:** Hyperkalemia concern[1]

Fluids

- Moderate Alcohol (men, ≤2 drinks; women ≤1)[4]

⬇ Caffeine Intake[3,5]

- **ADPKD hydration goal:** ~3L/day.[5,6]

Smoking Cessation[1,3,4,5]

Weight Loss: Waist-to-height ratio <0.5 to avoid obesity[3]

Exercise: 90-150 minutes of aerobic exercise weekly[4]

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*Based on expert opinion for ADPKD

	ADPKD	CKD	GP
Goals	• **Kidney Disease Improving Global Outcomes (KDIGO):** Systolic Blood Pressure (SBP) 95–110 mmHg may be more beneficial than 120–130 mmHg[1] • **Expert Opinion:** Mayo Class 1C-1E & 18-50 y.o.: <110/75 mmHg; others: <130/80 mmHg[2]	**KDIGO:** SBP <120 mmHg, if tolerated[1]	• **2017 Multisociety Guideline:** <130/80 mmHg for adults 18-65 y.o.[3,4,5] • **2020 International Society of Hypertension Global Hypertension Practice Guidelines (ISH):** <65 y.o.: <130/80 mmHg, but >120/70 mmHg; >65 y.o.: <140/90 mmHg as tolerated[3,5]

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