Supporting Evidence Document:
ANTIHYPERTENSIVE AGENTS IN ADPKD

BCRenal
Provincial Health Services Authority

Introduction

Due to the risks of cardiovascular complications and renal progression associated with hypertension in ADPKD, it is important to treat to blood pressure (BP) targets with appropriate therapies. Further information about BP targets is outlined in the "Blood Pressure Monitoring and Targets in ADPKD" Supporting Document.

Although non-pharmacological measures for BP control have not been specifically studied in ADPKD patients, they remain an important component of BP therapy. These include regular exercise, weight loss, smoking cessation, and sodium restriction. A multidisciplinary approach is key to provide optimal education about these measures.

However, antihypertensive agents are often necessary to reach BP targets in ADPKD patients. The magnitude of benefit of antihypertensive agents on cardiovascular and renal outcomes may differ depending on the class used. In addition, concerns with the effects of certain antihypertensive classes on disease progression have been outlined in numerous expert reviews (1-3).

Summary of the Evidence

A summary of published clinical studies involving antihypertensives in ADPKD is provided in Table 2.

Angiotensin-Converting Enzyme (ACE) Inhibitors or Angiotensin Receptor II Blockers (ARBs)

The renin-angiotensin-aldosterone system (RAAS) appears to play a large role in the pathogenesis of hypertension in ADPKD (1). It is thought that the compression of renal cysts on renal vasculature stimulates RAAS (1). This leads to increased angiotensin II, which not only increases BP, but also acts as a growth factor for cyst growth (1). Accordingly, RAAS blockade with ACE-inhibitors or ARBs is generally considered to be first-line therapy (1). This is in line with all published guidelines and expert reviews that provide recommendations for BP management in ADPKD, as indicated in Table 1.

Due to the general consensus that RAAS blockade is the cornerstone of BP management in ADPKD, the majority of studies evaluating antihypertensives have compared RAAS blockade with other antihypertensive classes (1), and select studies are summarized in the subsequent antihypertensive class sections below.

Only one study randomized patients to RAAS blockade or no RAAS blockade specifically in the ADPKD population, and this was done in 57 young patients aged 4-21 years who were either normotensive with severe ADPKD or borderline hypertensive (4). Patients were randomized to enalapril (or losartan if enalapril was not tolerated) or to treatment with no ACE-inhibitor to reach a target BP of ≤50th or ≤90th percentile (4).

After 5 years, there were no significant differences in renal volume, microalbuminuria, or left ventricular mass index between groups (4). A mild decline in CrCl from baseline was found in the no ACE-inhibitor treatment group, while no significant change was found in the ACE-inhibitor group (4). No safety data was reported. This study was limited by its lack of blinding, small sample size, and high dropout rate. Furthermore, the patients included in this trial were not hypertensive, and the results may have been different had the trial been conducted in a hypertensive population.

To our knowledge, there have been no clinical studies published that compare RAAS blockade to placebo or to no treatment specifically in the adult ADPKD population. A patient-level meta-analysis by Jafar et al. pooled 142 ADPKD patients (mean age 48 years) from 8 studies that compared ACE-inhibitors to any other antihypertensive agent in nondiabetic CKD patients (5). The agents included in the "control group" of the meta-analysis were: placebo, nifedipine, atenolol/acebutolol, and "not specified" (5). ACE-inhibitors were shown to be more effective in reducing proteinuria compared to the control group (5). ACE-inhibitors were also found to be associated with a lower risk of kidney disease progression, defined as a composite of doubling of baseline serum creatinine or onset of kidney failure; however, the relative risk was non-significant (RR 0.73, 95% CI 0.41-1.29) (5). Tests for interaction revealed that ACE-inhibitors had a greater effect on lowering proteinuria and slowing disease progression in patients with higher baseline proteinuria (5). Of note, the mean protein excretion of patients included in this meta-analysis was 0.92 g/day, which is higher than the level usually seen in the ADPKD population (5). In addition, due to the diversity of agents included in the control group, the results of this study are difficult to interpret.

The issue of whether ACE-inhibitors or ARBs should be preferred in ADPKD was evaluated in two small studies of 32 and 20 adult ADPKD patients (6-7). Both were 12-month, prospective, randomized trials (6-7). When comparing the ACE-inhibitor and ARB treatment groups, neither study found any difference in renal function (CrCl or eGFR) at the end of 1 year (6-7). There were also no differences between groups with regards to BP control or left ventricular mass index, which were outcomes that were evaluated in one of the studies (6). Although ACE-inhibitors and ARBs appear to have similar effects, ACE-inhibitors are more frequently used in studies. In addition, a Markov-state decision model in one study suggested that, compared to ARBs, ACE-inhibitors are more cost-effective and prolong survival by 1.39 years (8).

The safety of RAAS blockade has not been well-reported in ADPKD studies. However, as in the general population, the risks of hyperkalemia and acute kidney injury are important considerations.

Combination of ACE-inhibitors and ARBs

HALT-PKD Study A and Study B were two large, randomized, double-blind, placebo-controlled studies that compared the combination of ACE-inhibitor and ARB (lisinopril and telmisartan), versus an ACE-inhibitor alone (lisinopril and placebo) (9-10). Study A was conducted in patients with early ADPKD, and the primary outcome was annual percentage change in total kidney volume (9). Study B was conducted in patients with late ADPKD, and the primary outcome was the composite of time to death, end-stage renal disease, or a 50% reduction from baseline eGFR (10).

In both studies, the rates of adverse events were low and similar between the two groups; however, no benefit of dual RAAS blockade was found over the ACE-inhibitor alone (9-10).

Dual RAAS blockade with ACE-inhibitors and ARBs is therefore not recommended for BP management in ADPKD patients, and this has been indicated in a

number of guidelines and expert reviews (3, 11-12).

Diuretics

Increased aldosterone levels and associated sodium retention are thought to contribute to the pathogenesis of hypertension in ADPKD patients (1). Consequently, diuretics, which promote sodium excretion, have been considered to be reasonable second-or third-line agents by numerous experts (1-2, 11, 13). However, there is also a concern that diuretics may increase RAAS activation through volume depletion, leading to increased ADPKD progression. Cautious use has therefore been recommended in a couple expert reviews (1, 3).

Only one prospective study examining clinical outcomes with diuretics has been published. This was a historical, single-center prospective, non-randomized study of 33 hypertensive ADPKD patients who were followed for a mean of 5.2 years (14). Patients who were taking diuretic(s) without an ACE-inhibitor were compared to those taking an ACE-I without any diuretics (14). Although BP control was similar between groups, the decline from baseline and annual decline in CrCl was significantly higher in the diuretic group (14). In addition, urinary protein excretion increased significantly from baseline in the diuretic group, while no significant change was seen in the ACE-inhibitor group (14). Plasma sodium and potassium remained stable in both groups (14), and no other safety data was provided. However, all patients were taking ACE-inhibitors or diuretics at baseline, and it is therefore likely that they were already tolerating these agents. This study was limited by its small sample size and non-randomized design. In addition, the diuretic group had higher diastolic BP, lower CrCl, and higher urinary protein excretion at baseline, which may have contributed to the results.

To summarize, the concern that diuretics worsen ADPKD progression is only theoretical at this time. Because no studies have been published comparing diuretics to placebo or to no treatment, there is currently no data to inform on whether diuretics have any detrimental effect on ADPKD progression. In addition, one low-quality study suggested that diuretics are inferior to ACE-inhibitors for renal outcomes, but further studies are needed to confirm this finding.

Calcium Channel Blockers (CCBs)

Cyclic AMP (cAMP) is responsible for cyst cell proliferation in ADPKD, and it is thought that cAMP's effects in this condition are mediated by reduced intracellular calcium levels (1). There is a concern that blockade of calcium entry into renal cells by CCBs may worsen ADPKD progression (15), and cautious use has been recommended in a few expert reviews (1-3). This concern has been supported by a study in which verapamil was tested on ADPKD rats (15). Compared to control-treated rats, those that were administered verapamil had greater renal cell proliferation and apoptosis, kidney weight, and cyst index (15).

To our knowledge, there have been no clinical trials comparing CCBs to placebo or to no treatment in humans. In addition, there have been no clinical trials evaluating the effects of non-dihydropyridine CCBs compared to other antihypertensives.

Four clinical trials have been conducted to compare the effects of dihyropyridine CCBs to those of RAAS blockade in ADPKD, and they have yielded mixed results (16-19). The only trial with results favoring CCB therapy was a study by Kanno et al., which found that amlodipine was associated with a significantly lower reduction in CrCl from baseline when compared to enalapril after 2 years (16). A sub-analysis of a 7-year study by Schrier et al. showed no significant difference in 24-hour CrCl when comparing patients who received enalapril or amlodipine for at least 80% of the study

duration (17). In contrast, two studies concluded that CCBs were associated with worse outcomes when compared to ACE-inhibitors or ARBs (18-19). In the first study by Ecder et al., the annual mean decline in CrCl was higher in the amlodipine group compared to the enalapril group (annual mean decline of 4.2 mL/min/1.73 m^2 vs. 2.8 mL/min/1.73 m^2); however, the difference between groups did not meet statistical significance (18). In addition, a significant decrease in albumin-to-creatinine ratio was seen in the enalapril group, while proteinuria remained stable in the amlodipine group (18). The albumin-to-creatinine ratio was significantly higher in the amlodipine group at the end of the study (18). Similarly, in a 3-year study by Nutaraha et al., amlodipine was compared to candesartan and was associated with a significantly greater decline in CrCl, as well as a significantly higher degree of proteinuria (19). All of the four aforementioned studies were limited by very small sample sizes, which ranged from 24 to 69 patients (16-19). In addition, in the study by Nutarahara et al., many of the patients had missing data at various timepoints during the study, including at baseline (19).

Three retrospective studies have also provided evidence that CCBs may be associated with worse outcomes compared to RAAS blockade, though not all studies included information on whether the CCBs were within the dihydropyridine or non-dihydropyridine classes. In a small study by Mitobe et al., rate of eGFR reduction was positively associated with dihydropyridine CCB therapy, but not RAAS blockade therapy, after a mean treatment duration of 2.4 years (20). Furthermore, a retrospective study by Orskov et al. found that both CCBs and RAAS blockade were associated with a later onset of end-stage renal disease (ESRD) (21). The two classes were not compared directly, but results were more favorable with RAAS blockade (4.3 delay in onset of ESRD with RAAS blockade, vs. 2.1 years with CCB) (21). Finally, in a study by Patch et al., RAAS blockade and CCB prescriptions were independently associated with lower mortality, but the incident rate ratio was somewhat lower with RAAS blockade [0.53 (95% CI 0.35-0.80) with CCBs, vs. 0.44 (95% CI 0.17-0.42) with RAAS blockade] (22). These studies were limited by their retrospective designs, and it is likely that the analyses did not adjust for all potential confounders.

Limited or no safety data was reported in all of the aforementioned studies.

In summary, the concern that CCBs lead to accelerated ADPKD progression is theoretical at this time. No studies have been published comparing CCBs to placebo or to no treatment, and there is therefore currently no data to inform on the effects of CCBs on ADPKD. Studies comparing CCBs to RAAS blockade are of low-quality, but they collectively suggest that CCBs are associated with worse outcomes.

Beta-Blockers

Due to the theoretical concerns with diuretics and calcium channel blockers that are outlined above, beta-blockers have been recommended as second-line agents in a number of expert reviews (2-3, 13).

Two published studies have evaluated clinical outcomes with beta-blockers in hypertensive ADPKD patients (23-24). In the first study by van Dijk et al., 28 hypertensive ADPKD patients completed a 3-year trial in which they were randomized to enalapril or atenolol (up to a maximum dose of 20 mg/day and 100 mg/day, respectively) (23). In the second study by Zeltner et al., 37 hypertensive patients completed a 3-year trial in which they were randomized to ramipril or to metoprolol (up to maximum dose of 5 mg/day or 100 mg/day, respectively) (24). In both studies, no significant differences were found in mean arterial pressure, decline in eGFR, or change in albumin-to-creatinine ratio when comparing the ACE-inhibitor and beta-blocker groups (23-24). In addition, no significant

difference in left-ventricular mass index was found in the study by Zeltner et al. (24). Very limited safety data were provided in both of these studies. The trials were limited by their small sample sizes and by the low doses of ACE-inhibitors used. The maximum dose of metoprolol used in the study by Zeltner et al. was also lower than typically recommended.

In summary, limited and very low-quality data suggest that beta-blockers have similar effects on renal outcomes compared to ACE-inhibitors in ADPKD. Further studies are needed to confirm this finding.

Other Antihypertensives

To our knowledge, there have been no published studies evaluating other commonly-used antihypertensives (e.g. alpha-blockers, direct vasodilators) in ADPKD.

Choice of Antihypertensive(s) in BP Management

With the exception of the use of RAAS blockade as first-line therapy, antihypertensive regimens employed in ADPKD studies have varied widely.

The best evidence to inform on BP management in ADPKD is HALT-PKD Study A, which randomized 558 hypertensive patients aged 15-49 years of age with an eGFR > 60 mL/min/1.73 m^2 to a standard or low BP target and to either ACE-inhibitor/placebo or an ACE-inhibitor/ARB combination (9). 2nd-, 3rd-, and 4th-line antihypertensives were respectively: hydrochlorothiazide; metoprolol; and non-dihydropyridine CCBs, clonidine, minoxidil, and/or hydralazine (9).

Compared to the standard BP target group, patients in the low BP target group had a significantly lower annual percentage increase in total kidney volume, a similar overall change in eGFR, a greater reduction in left ventricular mass index, and a greater reduction in urinary albumin excretion (9). Dizziness and lightheadedness were also more common in the low target BP group (9). This study therefore provided evidence that targeting a lower BP in young patients with preserved renal function is effective in slowing ADPKD progression.

The proportions of patients who used certain antihypertensives were much greater in the low BP target group compared to the standard BP target group (9). These antihypertensives included diuretics (44.9% vs. 26.8%, $p<0.001$) and beta- or alpha/beta-blockers (31.4% vs. 14.4, $p<0.001$) (9). This suggests that the addition of diuretics and/or beta-blockers to RAAS blockade may be effective in reducing ADPKD progression through improved BP control.

The proportion of patients who used CCBs was also significantly greater in the low BP target group compared to the standard target BP group (10.2% vs. 5.3%, $p<0.001$) (9). However, the proportions of CCB-users were small in both arms. It is therefore less likely that CCBs contributed to the better outcomes seen in the low BP target group.

Statements/Recommendations

- RAAS blockade with ACE-inhibitors or ARBs is generally recommended as first-line therapy for hypertension in ADPKD patients.
  - This recommendation is based on the postulation that RAAS activation plays a major role in the pathogenesis of hypertension in ADPKD.
  - There is limited evidence to support that RAAS blockade is superior to other antihypertensive classes for reducing ADPKD progression.
    - However, findings from low-quality studies collectively do suggest that CCBs

are associated with more rapid decline in renal function compared to RAAS blockade.
    - Compared to other antihypertensive classes, RAAS blockade may be more effective in reducing proteinuria; however, the clinical relevance of proteinuria reduction in ADPKD is unclear.
  - ACE-inhibitors have been most commonly used than ARBs in studies and are the preferred first-line agents, but ARBs may be used if ACE-inhibitors are not tolerated.
- Based on the HALT-PKD studies, there is no role for dual RAAS blockade with an ACE-inhibitor and ARB.
- There are concerns that diuretics and CCBs may increase ADPKD progression based on their mechanisms of action. However, due to the absence of studies comparing them to placebo or to no treatment, there is currently no data to inform on whether these agents are harmful.
- There is limited data available to guide the choice of antihypertensive if RAAS blockade is not tolerated or if additional antihypertensive(s) are needed to achieve BP targets.
  - Due to the theoretical concerns about diuretic and CCB use in ADPKD, some experts suggest beta-blockers as the second-line agent of choice. However, there is limited data to support this.
  - In HALT-PKD Study A, thiazide diuretics and beta-blockers were added to RAAS blockade as second- and third-line agents, respectively. For patients who meet HALT-PKD Study A inclusion criteria (15-49 years old with eGFR > 60 mL/min/1.73m^2), this may be a reasonable approach until further data is available.
- In all cases, antihypertensive regimens should be individualized. Considerations when making decisions about regimens should include the presence of comorbidities that are indications for specific antihypertensives, medication side effect profiles, CKD stage, and pill burden.

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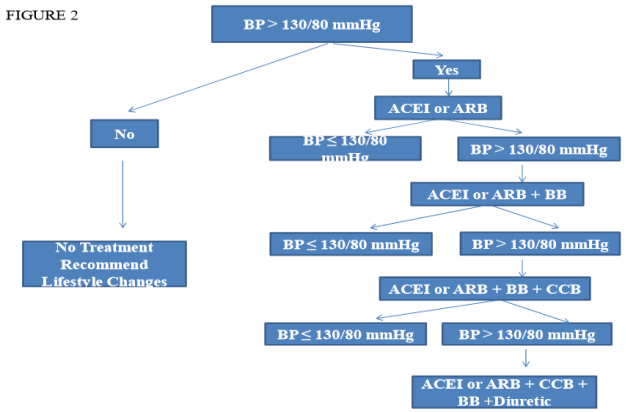
Table 1: Statements/Recommendations Regarding Antihypertensive Agents in ADPKD

PUBLICATION TYPE	PUBLICATION	YEAR OF PUBLICATION	STATEMENT/RECOMMENDATION
Guideline	Spanish guidelines for the management of autosomal dominant polycystic kidney disease (1)	2014	• "Pharmacological regimens for hypertension should include a RAAS inhibitor as the first option based on its theoretical advantages (C)."
	KHA-CARI Autosomal Dominant Polycystic Kidney Disease Guideline: Pharmacological Management (2)	2015	• "We recommend that ACEi be considered as first-line antihypertensive therapy (1B) and if intolerant, that ARB be considered as second-line antihypertensive therapy (1C)."
	KHA-CARI guideline recommendations for the diagnosis and management of autosomal dominant polycystic kidney disease (3)	2016	• "Management of hypertension: ACEi therapy has demonstrated safety and antihypertensive effectiveness with improvements in proteinuria and left ventricular mass index. There is no evidence of the benefit of dual ACEi and angiotensin receptor blockers (ARB) therapy in ADPKD. Other meds that may be considered are ARBs, beta blockers, calcium channel blockers and diuretics although individualization in the setting of comorbid illness, stage of renal disease and clinical circumstance is required."
	European ADPKD Forum multidisciplinary position statement on autosomal dominant polycystic kidney disease care (4)	2018	• "Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are the first-line antihypertensives in ADPKD."
	Assessing Risk of Disease Progression and Pharmacological Management of Autosomal Dominant Polycystic Kidney Disease: A Canadian Expert Consensus (5)	2017	• No specific recommendations for choice of antihypertensive meds
	Updated Canadian Expert Consensus on Assessing Risk of Disease Progression and Pharmacological Management of Autosomal Dominant Polycystic Kidney Disease (6)	2018	• No specific recommendations for choice of antihypertensive meds

PUBLICATION TYPE	PUBLICATION	YEAR OF PUBLICATION	STATEMENT/RECOMMENDATION
Review Article	Fall and Prisant (7)	2005	• "[Blood pressure] treatment should include the use of angiotensin-converting enzyme inhibitors."
	Sans-Axter et al. (8)	2013	• "Even though a nonpharmacological approach should not be neglected, RAAS inhibitors are the cornerstone of hypertension treatment." • "…both dihydropyridine and non-dihydropyridine CCBs should probably be avoided as first- and probably second-line treatment in patients with ADPKD. However, considering that ADPKD patients show resistant hypertension and CCBs are good antihypertensive drugs, they should certainly be third-line treatment" • "Because aldosterone levels are greater in hypertensive ADPKD patients than in essential hypertensives, and higher aldosterone levels may lead to sodium retention, diuretics should be considered as second-line treatment in hypertensive ADPKD. It must be noted, however, that diuretic treatment may lead to extra activation of the RAAS owing to volume depletion. In hypertensive ADPKD patients with normal renal function, thiazide diuretics are the first choice. In those with impaired renal function and glomerular filtration rate <30 mL/min/1.73 m2, long-acting loop diuretics must be the first choice." • "To our knowledge, other drug treatments (e.g. alpha-blockers, direct vasodilators) have not been compared with RAAS inhibitors and may play a secondary role in hypertension treatment in this population."
	Rangan et al. (9)	2016	• "[Hypertension] is mediated by increased intra-renal angiotensin II production in cystic epithelial cells… Hence, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are the preferred first-line meds."
	Krishnappa et al. (10)	2017	• "Early diagnosis and aggressive management of high blood pressure, specifically with meds that block the renin-angiotensin-aldosterone system, are necessary to prevent left ventricular hypertrophy and progression of renal failure in ADPKD." • "ACE inhibitors are first-line drugs in hypertensive ADPKD patients." • "ARBs can be considered, but there is no role for dual ACE inhibitor and ARB therapy. A study found ACE inhibitors to be more cost-effective and to decrease mortality rates to a greater extent than ARBs." • "Beta-blockers or calcium channel blockers should be considered instead if ACE inhibitors and ARBs are contraindicated, or as add-on drugs if ACE inhibitors and ARBs fail to reduce blood pressure adequately." • "Diuretics are third-line meds. Thiazides are preferred in ADPKD patients with normal renal function and loop diuretics in those with impaired renal function."

	Helal et al. (11)	2017	• "…an ACEI or ARB should be the initial antihypertensive med… Patients who develop a significant decline in renal function may be more safely treated with another med such as a beta-blocker or calcium channel blocker; we prefer to use a beta blocker as a second med given the potentially detrimental effects of calcium blockers on cyst formation." • "Diuretics, used in conjunction with inhibitors of the RAAS, may be effective in reducing BP in • ADPKD patients, particularly those with established CKD where the capacity to excrete sodium is reduced, and BP is maintained through intravascular volume expansion. In hypertensive ADPKD patients with normal kidney function, thiazide diuretics are the first choice. In those with impaired kidney function, long-acting loop diuretics must be the first choice. Diuretics should be considered as second- or third-line treatment in hypertensive ADPKD." • "To the best of our knowledge, alpha blockers and direct vasodilators have not been tested and compared with RAAS inhibitors in ADPKD population." • Suggested treatment algorithm:  Figure 2. Treatment algorithm of hypertension in ADPKD. ADPKD: Autosomal dominant polycystic kidney disease, ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blockers, CCB: Calcium channel blockers, BB: β-Blockers, BP: Blood pressure.

	Chebib et al. (12)	2018	• "Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers increase kidney blood flow at early stages of the disease and are the first-line therapy for ADPKD." • "Dual renin-angiotensin blockade had no beneficial effect compared with ACE inhibition alone." • "It is not clear which antihypertensive drug class should be used as second line. Combined α/β blockers have good metabolic and hemodynamic profiles and are well tolerated. β-blockers or α 1 adrenergic antagonists are preferred for patients with comorbid conditions, such as angina or benign prostatic hyperplasia." • "Calcium channel blockers and diuretics should be used cautiously because of hypothetical concerns that they might worsen disease progression." • "By order of preference: 1. ACEI/ARB 2. α/β or cardioselective β-blocker 3. Dihydropyridine CCB 4. Diuretic"
	Torra et al. (13)	2019	• "First-line management of hypertension should include a blocker of the renin–angiotensin–aldosterone system (angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers)" • "Second- and third-line treatments should be diuretics and beta-blockers." • "Calcium channel blockers (particularly the dihydropyridine class) should be considered if blood pressure is not controlled by the other meds."

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Table 2: Evidence Summary of Antihypertensive Agents in ADPKD

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
Chapman et al. 1990 (1)	Comprised of 1 short-term study (examining plasma renin activity after captopril x 1 dose) and 1 long-term study in both patients with and without HTN; only information on the long-term study in hypertensive patients is presented in this table • 6-week prospective study • Follow-up BP measurements performed by patients at home BID after careful instruction and evidence of competent self-measurement	2 groups with HTN [defined as BP >140/90 in sitting position on 3 separate occasions, or previous diagnosis of HTN and treatment with BP med(s)]: 1) PKD patients with HTN (n=13) • PKD defined as ≥5 renal cysts distributed bilaterally as determined on U/S 2) Essential HTN patients (n=9) Overall: • Mean age ~35 years • Mean CrCl 110-113 mL/min/1.73 m^2 • Mean MAP (upright) ~105 mm Hg	Enalapril 5 mg/day; dose increased until BP 110/70 mm Hg, MAP reduction of 30 mm Hg, or enalapril dosage of 20 mg/day reached	Baseline	• MAP • BSA • 24h sodium excretion • CrCl • Inulin clearance • PAH clearance (measure of effective renal plasma flow) • Renal vascular resistance	• Similar mean daily dose of enalapril between groups (HTN and PKD 15.8 ± 1.9 mg/day, essential HTN 19.4 ± 0.6 mg/day) • Similar and significant decreases in MAP in both groups • No change in BSA, 24h sodiums excretion, creatinine clearance, or inulin clearance in either group • Significant changes for the following outcomes in hypertensive patients with PKD but not in patients with essential HTN: • PAH clearance ($p<0.005$ for PKD patients) • Filtration fraction ($p<0.02$) • Renal vascular resistance • Similar rate and severity of side effects in both groups: • Fatigue 12.9% • Headache 12.1% • Cough 9.7%	• Although this was an ADPKD study, included patients may not have been limited to ADPKD patients based on PKD inclusion criteria • Very small sample size • Short follow-up period • Use of surrogate markers as outcomes

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
Kanno et al. 1996 (2)	• 2-year, prospective study • Target BP: Sitting SBP < 150 mm Hg, sitting DBP < 90 mm Hg • 2nd-line BP med: If study med is CCB, arotinoliol (alpha/beta blocker) 10-20 mg/day; If study med is ACE-I, trichlor-methiazude (diuretic) 2-8 mg/day	• 35 Japanese patients with PKD (defined as ≥5 renal cysts distributed between kidneys on U/S) who had been treated with conventional BP meds (eg. diuretics, BB, or alpha-methyldopa) • Mean age 56-60 years • Mean SCr 177-203 umol/L • Mean SBP ~155/105 mm Hg	CCB: Nifedipine-R 10-30 mg or nicardipine-LA 10-60 mg twice daily (n=14)	ACE-I: Enalapril 5-10 mg daily or captopril-R 37.5-75 mg twice daily (n=12)	Change in CrCl (CrCl recorded as average of 3 CrCl measured endogeously)	26 patients completed the study (14 in CCB group, 12 in ACE-I group); results presented only for these patients Dropouts: • 7 patients for non-medical reasons (distribution of these patients among treatment groups not described) • 2 patients in ACE-I group due to rapid increases in SCr within 6 months; resolved with change from ACE-I to CCB Need for additional BP meds: • 3 patients in CCB group vs. 2 patients in ACE-I group ADRs: • 7 patients in ACE-I group had dry cough BP: • Decreased significantly from baseline in both groups [154 ± 4/104 ± 5 to 144 ± 3/88 ± 6 mm Hg ($p<0.05$), vs. 158 ± 8/107 ± 6 to 142 ± 4/85 ± 3 mm Hg ($p<0.05$)]	• Although this was an ADPKD study, included patients may not have been limited to ADPKD patients based on PKD inclusion criteria • No information provided on blinding • No information on whether patients were randomized • Small sample size with 26% dropout rate • ITT analysis not done • 2nd-line med differed according to treatment group

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
						• No significant difference between groups CrCl: • Decreased significantly from baseline in both groups [44.2 ± 3.6 to 41.0 ± 3.8 mL/min ($p<0.05$), vs. 51.9 ± 3.9 to 46/4 ± 3.5 mL/min ($p<0.05$)] Change in CrCl: • Significantly lower in CCB group when expressed as mL/min/year [-1.5 ± 0.4 vs. -2.7 ± 0.3 mL/min/year ($p<0.05$)] • No significant difference when expressed as percentage decrease (7.2 ± 0.8% vs. 10.2 ± 1.2%)	
Ecder et al. 2000 (3)	• 5-year, prospective, randomized study • Target MAP < 107 mm Hg • BP measured 3 times in sitting position by research nurse coordinator; reported BP	• 24 ADPKD patients with HTN (BP > 140/90 mm Hg in sitting position or taking BP meds) • Mean age ~42 years • Mean CrCl 77-83 mL/min/1.73 m^2	Amlodipine, max 10 mg/d (n=12)	Enalapril, max 20 mg/d (n=12)	Measured at year 1, 3, and 5: • MAP • CrCl • ACR	Mean dose: • Amlodipine: 9 mg/d • Enalapril: 17 mg/d Additional BP meds in amlodipine group: • HCTZ: 10 patients • Clonidine: 5 patients • Spironolactone: 4 patients • Furosemide: Not reported, assume 0 patients	• Small sample size • No information provided on blinding • Limited safety data provided

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
	was mean of first 2 measurements unless MAPs differed by > 8 mm Hg, in which case 2 closest BP measurements were used • 2nd-line BP med: HCTZ, clonidine, furosemide, or spironolactone	(all had CrCl > 50 mL/min/1.73 m^2) • Mean BP 136-140/93-94 mm Hg				Additional BP meds in enalapril group: • HCTZ: 9 patients • Clonidine: 4 patients • Spironolactone: 5 patients • Furosemide: 2 patients ADRs: • None necessitating withdrawal of drugs in any patients MAP: • Statistically significant decrease from baseline in both groups (5-year data: amlodipine 109 ± 3, to 97 ± 3 mm Hg; enalapril 108 ± 3, to 94 ± 3 mm Hg) • No significant difference between groups CrCl: • Statistically significant decrease from baseline in both groups (5-year data: amlodipine 83 ± 5, to 69 ± 3 7 mL/min/1.73 m^2; enalapril 77 ± 6, to 56 ± 4 mL/min/1.73 m^2) • Annual mean decline 2.8 mL/min/1.73 m^2 in amlodipine group vs. 4.2 mL/min/1.73 m^2 in	

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
						enalapril group; NSS difference ACR: • No significant change from baseline in amlodipine group (5-year data: 68 ± 21 mg/g, to 148 ± 74 mg/g) • Significant decrease from baseline in enalapril group at year 1 (23 ± 4 mg/g, to 13 ± 3 mg/g) that was sustained until end of study at year 5 (14 ± 6 mg/g) • In enalapril group, men showed a significantly greater anti-albuminuric effect than women • Significantly higher ACR in amlodipine group vs. enalapril group at year 1 and 5	
Ecder et al. 2001 (4)	• Historical, single-center, prospective, non-randomized study with mean follow-up of 5.2 years • BP measured by a research nurse using a mercury	• 33 hypertensive ADPKD patients receiving either ACE-I without any diuretics, or diuretics without any ACE-I; excluded patients with CrCl < 40 mL/	Diuretic without ACE-I (n=14) Types of diuretics (n): • Loop (6) • Thiazide (9) • Potassium-sparing (5)	ACE-I without diuretics (n=19) Types of ACE-I (n): • Enalapril (8) • Lisinopril (7) • Captopril (4) Ramipril (3)	(Select ones listed here): • BP control • CrCl • Change in CrCl • UPE • Plasma potassium and sodium	BP control: • SBP increased significantly from baseline in both groups (127 to 141 mm Hg, vs. 125 to 132 mm Hg); NSS difference between groups • DBP remained stable in both groups	• Non-randomized; patients were already taking study medication at baseline and therefore were likely already tolerating them • Small sample size

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
	• sphygmomanometer 14 times during 2-day research visits throughout study • BP target not specified, but same between the two groups	• min/1.73 m^2 at first visit • Mean age 41-47 years • Mean BP 125-127/81-86 mm Hg (higher DBP in diuretic group at baseline) • Mean CrCl 74-83 mL/min/1.73 m^2 (higher CrCl in ACE-I group at baseline, but NSS difference) • Mean UPE 125-168 mg/d (higher UPE in diuretic group at baseline, but NSS)	Additional BP meds: • 9 patients (64%) required additional BP meds • BB in 5 patients (36%) • CCB in 4 patients (29%) • Clonidine in 1 patient (7%)	Additional BP meds: • 4 patients (21%) required additional BP meds • CCB in all 4 patients (21%)		CrCl: • Decreased significantly from baseline in both groups • 74 to 46 mL/min/1.73 m^2 ($p<0.0001$), vs. 83 vs. 71 mL/min/1.73 m^2 ($p=0.0005$) Change in CrCl: • Significantly higher decrease in CrCl from baseline in diuretic group (28.4 vs. 12.7 mL/min/1.73 m^2, $p<0.0001$) • Significantly higher annual decrease in CrCl in diuretic group (5.3 vs. 2.7 mL/min/1.73 m^2, $p<0.05$) UPE: • Increased significantly from baseline in diuretic group (168 to 503 mg/d, $p<0.05$) • No significant change from baseline in ACE-I group (125 to 198 mg/d, p=NS) Plasma sodium and potassium: • Remained stable in both groups	• Long duration of follow-up • Better outcomes in ACE-I group may be related to baseline differences (higher DBP, lower CrCl, and higher UPE in diuretic group), as well as better BP control in ACE-I group (at 5-year follow-up, 141/88 mm Hg in diuretic group, vs. 132/84 mm Hg in ACE-I group)

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
Nakamura et al. 2001 (5)	• 6-month, randomized prospective study • No BP target • Method of BP measurement not described	• ADPKD patients with micro-albuminuria • Excluded patients with SCr > 133 umol/L or 24h CrCl < 70 mL/min • Group A and C: 12 patients with normal BP. Mean age 47 years; UAE ~131 ug/min; CrCl 102-108 mL/min; BP ~113/76 mm Hg • Group B and D: 10 patients with HTN (>145/85 mm Hg). Mean age 52 years; UAE 136-142 ug/min; CrCl 96-103 mL/min; BP 156-158/94-102 mm Hg	Dilazep 300 mg/d (vasodilator and anitplatelet med) • Group A - normal BP (n=6) • Group C - HTN (n=5)	Placebo • Group B - normal BP (n=6) • Group D - HTN (n=5)	UAE	• Little change in SCr, BUN, BP, BUN, or 24h CrCl in all groups • Group A - normal BP on dilazep: Significant decrease in UAE at 3 and 6 months from 130 ± 52 ug/min to 82 ± 34 ug/min ($p<0.05$) and 46 ± 26 ug/min ($p<0.01$), respectively • Group B - normal BP on placebo: No statistically significant change in UAE • Group C - HTN on dilazep: Slight decrease in UAE that was not statistically significant (from 132 ± 56 um/min to 118 ± 40 ug/min at 6 months) • Group D - HTN on placebo: No statistically significant change in UAE (from 136 ± 42 ug/min to 142 ± 46 ug/min at 6 months	• Dilazep not commerically available in Canada • Small sample size • No information provided on blinding • No safety data provided • Use of surrogate marker as outcome

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
Schrier et al. 2002 (6)	Only data pertaining to subanalysis comparing BP meds are presented in this table • 7-year, prospective, randomized study that compared rigorous vs. standard BP control; patients also randomized to enalapril or amlodipine for mean 2.1 years, but stopped due to loss of funding • Subanalysis of patients performed on the patients who received either one of enalaprin or amlodipine for at least 80% of the study time • 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)	Overall study: • 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 Subanalysis comparing patients who received either one of enalapril or amlodipine for at least 80% of study time: • 69 of the above patients • Mean age 41-43 years • Mean LVMI 159 g/m^2 • Mean MAP 109-103 mm Hg • Mean 24h CrCl 79-84 mL/min/1.73 m^2	Enalapril for at least 80% of the study time (n=49 in subanalysis)	Amlodipine for at least 80% of the study time (n=20 in subanalysis)	• LVMI • CrCl	BP control: • NSS difference in mean BP levels LVMI: • Larger decrease in ACE-I group; decreased from 159±25 to 106±25 g/m^2 ($p<0.001$) in enalapril group, vs. 159±25 to 133±33 g/m^2 ($p<0.05$) in amlodipine group • LVMI in normal range at 7-year follow-up in 67% vs. 36% ($p<0.05$) • Significant interaction between BP control and BP med over time ($p<0.01$), i.e. rigorous BP control with enalapril led to the greatest reduction in LVMI over time 24h CrCl: • NSS difference between groups	• Nonrandomized; more patients received enalapril • Small sample size • No safety data reported

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
	• BP target either <120/80 mm Hg or 135-140/85 mm Hg • 2nd line BP agent: HCTZ, clonidine, or spironolactone						
Schrier et al. 2003 (7)	Only data from analyses pertaining to BP meds in hypertensive patients 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	• 346 adult hypertensive 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, Hypertensive males: • Mean age 38-40 years • Mean UPE 305-474 mg/d • Mean SCr 305-474 umol/L Hypertensive females: • Mean age 40-42 years	Comparison of two hypertensive cohorts: • Early cohort: Initial study visit between June 1985-May 1992 (n=177) • Later cohort: Initial study visit between June 1992-May 2001 (n=169) Antihypertensives at the initial study visit that were compared between the two cohorts: • ACE-I • CCB • Diuretics • Alpha-blockers • BB Outcome compared between the two cohorts: • Renal survival			All results below are comparing later vs. early cohort, unless otherwise specified Antihypertensive use in initial study visit: • Significantly higher use of ACE-I and CCB • Significantly lower BB use • Lower diuretic use, but difference was only statistically significant in males • Lower alpha-blocker use, but NSS difference • No significant differences in number of antihypertensive medications used BP control at initial study visit: • Similar SBP • DBP higher in early cohort, p<0.0001 • MAP higher in early cohort, p<0.0001	• Large sample size • Analyses only used antihypertensive data from initial study visit • Authors concluded that aggressive BP control using RAAS inhibition may delay progression to ESRD; however, they did not address CCB use, which also increased in the later cohort • Study was unable to account for all potential factors that may have contributed to the longer median survival time in the later cohort

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
		• Mean UPE 267-276 mg/24h • Mean SCr 159-194 umol/L				Median survival time to ESRD: • Males: 63 years vs. 53 years, p=0.0220 • Females: 60 years vs. 54 years, p=0.0177	

van Dijk et al. 2003 (8)	• 3-year, prospective, randomized clinical trial; design differed for baseline normotensive and hypertensive patients (hypertension defined as SBP > 160 mm Hg, DBP > 95 mm Hg, or use of BP med)
	• Study in normotensive patients was double-blind
	• Study in hypertensive patients was open-label
	  • Target BP ≤140/85 mm Hg
	  • 2nd-line BP med: HCTZ to max 25 mg/d
		• Patients aged 18-70 years with ADPKD (defined by U/S criteria) and plasma creatinine < 225 umol/L
		• Excluded patients with MI or CVA in past 6 months, other renal disease,DM, CHF, PVD, NSAID use
		• Normotensive group: 61 patients completed trial (of 69 randomized patients). Mean age 37 years, plasma creatinine 89 umol/L, BP 133/88 mm Hg
			Sample sizes indicated only include patients who completed the trial
			
			Normotensive group:
			• Enalapril 5 mg/d, then increased to 10 mg/d if DBP did not decrease by > 10 mm Hg or if DBP > 70 mm Hg (n=32)
			
			Hypertensive group:
			• Enalapril up to max 20 mg/d (n=13)
				Sample sizes indicated only include patients who completed the trial
				
				Normotensive group:
				• Placebo (n=29)
				
				Hypertensive group:
				• Atenolol up to max 100 mg/d (n=15)
					• MAP
					• GFR decline (GFR measured by inulin infusion)
					• Effective renal plasma flow (measured by PAH infusion)
					• ACR
						<u>Normotensive group:</u>
						• Dropouts (not included in primary analyses): 1 for drug-related cough, 6 became hypertensive (all in placebo group), 2 for personal reasons
						• Enalapril vs. placebo - analyses only of patients who completed the trial:
						  • MAP decreased in enalapril and increased in placebo group, but NSS difference (-3 ± 2, vs. +2 ± 2 mm Hg)
						  • Similar GFR decline from baseline (-9 ± 1, vs. -7 ± 3 mL/min; p=0.4)
						  • GFR decline by >20% in 3 patients vs. 1 patient
						  • No significant difference in decrease in effective renal plasma flow
							• Small sample size with dropout rate of 12% and 20% in normotensive and hypertensive groups, respectively
							• Primary analyses were not ITT
							• Low dose of enalapril studied (max recommended dose is 40 mg/d)
							• Safety data not provided for patients who completed the study

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
	• 3rd-line BP med: felodipine to max 20 mg/d • BP measurements were recorded as average of 3 office BP readings measured with a random-zero sphygmomano-meter	• Hypertensive group: 28 patients completed trial (of 35 randomized patients). Mean age 44-30 years, plasma creatinine 78 umol/L, BP 144/97mm Hg				• Slight increase in ACR from baseline in placebo group (0.39 ± 0.50 to 0.68 ± 1.01 mg/mmol) vs. stable ACR in enalapril group (0.46 ± 0.68 to 0.42 ± 0.48 mg/mmol); NSS difference between groups • Enalapril vs. placebo - secondary analysis of all randomized patients: • NSS difference in slope of GFR decline (p>0.05) <u>Hypertensive group:</u> • Dropouts (not included in primary analyses): • 5 in atenolol group (1 for dialysis-dependence, 2 for uncontrollable HTN, 1 for chronic infection, 1 death due to subarachnoid hemorrhage) • 2 in enalapril group (1 for psychological problems, 1 for enlarged polycystic liver requiring NSAID treatment)	

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

						• Enalapril vs. atenolol - analyses only of patients who completed the trial:
						  • Fewer patients needed addition of HCTZ (4 patients vs. 7 patients in atenolol group) and of felodipine (0 patients in enalapril group, vs. 2 patients in atenolol group)
						  • Greater decrease in MAP, but NSS difference (-11 ± 3, vs. -3 ± 3 mm Hg)
						  • Similar decline in eGFR from baseline (-12 ± 2, vs. -12 ± 3 mL/min)
						  • GFR decline by >20% in 1 patient vs. 4 patients
						  • Similar decrease in effective renal plasma flow
						  • NSS difference in change in ACR from baseline (0.39 ± 0.31 to 1.18 ± 1.45, vs. 0.33 ± 0.28 to 0.49 ± 0.59)	

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
						• Enalapril vs. atenolol - secondary analysis of all randomized patients (last observation carried forward): • NSS difference in slope of GFR decline (p>0.05)	

Jafar et al. 2005 (9)	• Patient-level meta-analysis
	• Included RCTs of nondiabetic CKD patients that:
	  • Included hypertensive PKD patients;
	  • compared the effects of BP meds, including ACE-I, to regimens without ACE-I; and
	  • Had a minimum planned follow-up period of 1 year
		• From a database of 11 RCTs with a total 1860 patients, included 8 studies that had a total of 142 PKD patients and a mean follow-up duration of 2.3 years
		• Mean age 48 years
		• Mean BP 149/94
		• Mean SCr 265 umol/L
			ACE-I (n=68)	Control (n=74)
				• Placebo in 4 studies
				• Nifedipine in 1 study
				• Atenolol/ acebutalol in 2 studies
				• Not specified in 1 study
					• Decline in urine protein excretion from baseline to follow-up
					• Kidney disease progression, defined as combined endpoint of doubling in SCr from baseline or need for long-term dialysis
						BP control:
						• Decline in SBP and DBP greater by 6.3 and 6.6 mm Hg, respectively, in ACE-I vs. control group (p<0.001, for each)
						
						Protein excretion:
						• Mean decline of 0.33 g/ day in ACE-I group, vs. increase of 0.19 g/day in control group (p<0.001)
						• Treatment effect diminished but remained significant after adjusting for baseline characteristics and change in BP/ proteinuria during follow-up (0.34 g/day greater reduction in ACE-I vs. control group)
						
						Kidney disease progression:
						• 29% in ACE-I group, vs. 41% in control group (p=0.17)
							• Unclear whether all included patients had ADPKD, as opposed to other types of PKD
							• Short mean follow-up duration Results can only be generalized to patients with more advanced PDK
							• Included patients had a higher degree of proteinuria than usually seen (mean 0.92 g/d)
							• Control groups varied widely across studies

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
						• Treatment effect remained insignificant after adjusting for baseline characteristics and change in BP/ proteinuria during follow-up Interactions of treatment effect with baseline urine protein: • Benefit of ACE-I increased with baseline urine protein levels for both decline in urine protein excretion (interaction p <0.001) and kidney disease progression (interaction p=0.03)	

Nutahara et al. 2005 (10)	• 36-month, multicenter, prospective, randomized clinical trial
	• Target SBP < 130 mm Hg and DBP < 85 mm Hg
	• BP measurement method not described
		• 49 ADPKD patients aged 20-70 years with previously treated or untreated HTN (sitting SBP > 140 mm Hg and/or DBP > 90 mm Hg)	Amlodipine 2.5-10 mg/d (n=25)	Candesartan 2-8 mg/day (n=24)	• 1° outcome: Doubling of SCr or 50% reduction in CrCl
					
					• Change in:
					  • SCr
					  • CrCl
					  • UPE
					  • UAE
						Dropouts/missing data:
						• At end of study, outcomes only reported for 9-24 patients in amlodipine group, vs. 13-24 patients in candesartan group (number of patients included varied depending on the outcome)
							• Small sample size
							• Analyses reported to be ITT, but analyses appear to have excluded dropouts and patients with missing data
							• Incomplete data at all time points

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
	• 2nd-line BP med: propranolol or carvedilol	• Excluded patients with SCr > 177 umol/L • Mean age ~48 years • Mean CrCl ~70 mL/min/1.73 m^2 • Mean UPE 116-148 mg/day • Mean UAE 66-91 mg/day				Need for additional BP meds: • 9 patients vs. 3 patients ADRs: • None necessitating withdrawal of study drug in either group BP: • Decreased significantly in both groups, but no significant difference between groups; BP data not provided 1° outcome: • 6 of 25 (24%) in amlodipine group, vs. 1 of 24 (4.2%) in candesartan group; p <0.05 Change in SCr: • Significantly higher in amlodipine group at 24 and 36 months (36-month data: 151 ± 79, vs. 111 ± 41 mmol/L; p = 0.046) Change in CrCl: • Significantly larger decrease in amlodipine group at 36 months (-20.9 ± 13.1, vs. -4.8 ± -13.8 mL/min/1.73 m^2; p<0.001)	during the study, including baseline • Patients in amlodipine group had higher proteinuria at baseline (amlodipine vs. candesartan: Mean UPE 148 mg/d vs. 116 mg/d; Mean UAE 91 mg/d vs. 66 mg/d) • Limited safety data provided

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
						UPE: • In amlodipine group, increased from mean 148±187 mg/d at baseline to 458±419 mg/d at 36-months • In candesartan group, increased from mean 116±102 mg/d at baseline to 154±176 mg/d at 36 months • Significantly higher in amlodipine group at 36 months (458 ± 419, vs. 154 ± 176 mg/day; p = 0.019) UAE: • In amlodipine group, increased from mean 91±67 mg/d at baseline to 66±63 mg/d at 36 months • In candesartan group, decreased from mean 66±63 mg/d to 49±37 mg/d at 36 months • Significantly higher in amlodipine group at 12, 24, and 36 months (36-month data: 287 ± 238, vs. 49 ± 37 mg/d; p = 0.001)	

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
Zeltner et al. 2008 (11)	• 3-year prospective, randomized, double-blind study • Target mean 24h ABPM measurement < 135/85 mm Hg • 2nd-line BP med: felodipine 5-10 mg/day • 3rd line BP med: doxazosin and/ or furosemide (doses not provided)	• 46 ADPKD patients with HTN (casual BP ≥140/90 mm Hg or on BP medication), SCr < 352 mmol/L • Excluded patients with MI/stroke 12 months prior to study or CHF • Mean age ~40 years • Mean BP 142-143/90-93 mmHg, • Mean eGFR 87-88 mL/min • Mean ACR 6.4-7.5 mg/ mmol	Ramipril 2.5 mg/day; increase to max 5 mg/day as needed to reach target BP (final n=17; 7 dropped out)	Metoprolol 50 mg/day; increase to max 100 mg/ day as needed to reach target BP (final n=20; 2 dropped out)	1° outcome: Doubling of SCr, 50% reduction in GFR, or need for RRT • GFR • ACR • LVMI	• 37 patients completed the study; results presented only for these patients • Dropouts: 7 patients in ramipril group (1 due to uncontrollable HTN, 6 due to ADRs) vs. 2 patients in metoprolol group (1 due to dialysis dependence, 1 due to non-adherence) • Need for additional BP meds: 8 patients in ramipril group vs. 10 patients in metoprolol group • Total number of BP meds: Similar number (1.7 ± 0.2 vs. 1.8 ± 0.2; p=NS) • Similar MAP reduction (-8 ± 2 mm Hg vs. -6 ± 2 mm Hg; p=NS) • 1° outcome: 2 vs. 3 patients • GFR: Similar reduction (mean -2.5 ± 0.7 mL/ min/yr vs. -2.9 mL/min/ yr; p=NS) • ACR: No significant difference (42.6 ± 12.3 mg/g vs. 70.3 mg/g; p=NS)	• Small sample size with unexpectedly high (20%) dropout rate • ITT analysis not done • Low doses of ramipril and metoprolol used (usual max doses are 10-20 mg/d and 200 mg/d, respectively)

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
						• LVMI: No significant difference (102.6 ± 6.8 vs. 100.3 ± 5.4 g/m^2; p=NS)	

Mitobe et al. 2010 (12)	• Single-centre, retrospective study (specific methods of obtaining data not described)
	• Periods in which prescriptions for CCB and/or RAAS-inhibition had not changed for ≥ 1 year were selected for data collection; mean treatment duration evaluated was 2.4 years
		• 31 outpatients with ADPKD (diagnosed based on family history and various methods of imaging)
		• Mean age 50 years
		• Mean baseline eGFR 34 mL/min/1.73 m^2
		• Mean baseline annual eGFR decline -2.7 mL/min/1.73 m^2 per year
		• Mean BP 125/78
			• Purpose of study was to use an ANCOVA to determine association between change in eGFR per year and:
			  • CCB (n=14; all patients on DHP CCB)
			  • RAAS-inhibition (n=18; 16 patients on ARB, 3 patients on ACE-I)
			• Multivariable ANCOVA was adjusted for:
			  • Baseline eGFR
			  • Mean DBP throughout treatment
			  • Mean SBP throughout treatment
						BP throughout treatment:
						• Mean SBP 125 mm Hg
						• Mean DBP 78 mm Hg
						
						After adjusting for baseline eGFR, mean SBP, and mean DBP:
						• No significant association between RAAS-inhibition and change in eGFR per year
						• Only CCB was significantly associated with reduction in eGFR per year (adjusted coefficient -1.79, p=0.02)
							• Major limitation is retrospective design
							• Small sample size
							• Several potential confounders not included in multivariable ANCOVA
							• Results cannot be generalized to non-DHP CCBs
							• Results possibly cannot be generalized to ACE-I

Ulusoy et al. 2010 (13)	• 12-month prospective, randomized clinical trial • BP target not specified	• 32 ADPKD patients aged 18-70 years with CrCl > 30 mL/min/1.73 m^2 and stage 1-2 hypertension	Losartan 50 mg/d; if tolerated, increased to 100 mg/d (n=19)	Ramipril 2.5 mg/d; if tolerated, increased to 5 mg/d, then 10 mg/d (n=13)	• BP • CrCl • LVMI	BP control: • Both groups reached target BP • Statistically significant difference in SBP, DBP, and MAP from baseline in both groups	• Small sample size • Short duration of follow-up • No information provided on use of additional BP meds • No safety data provided

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
	• BP measured at home and in office (office BP measured with mercury sphygmomano-meter twice on both arms) • 2nd line BP med: amlodipine • 3rd line BP med: doxazosin • 4th line BP med: rildmelidine dihydrogen phosphate	according to JNC VII (BP ≥140/90 mm Hg) or taking BP meds • Excluded patients with DM or CHF • Mean age ~50 years • Mean BP 150-156/94-98 mm Hg • Mean LVMI 117-120 g/m^2 • Mean CrCl 76-80 mL/ min/1.73 m^2				• Change from baseline in losartan group: Mean BP 156/99 mm Hg to 117/73 mm Hg, p<0.0001 • Change from baseline in ramipril group: Mean BP 150/94 mm Hg to 120/74 mm Hg, p<0.001 • NSS differences in SBP, DBP, or MAP between groups CrCl: • NSS difference from baseline in either group • NSS difference between groups LVMI: • Statistically significant decrease from baseline in both groups • Change from baseline in losartan group: Mean LVMI 117.3 g/m^2 to 106.9 g/m2, P=0.007 • Change from baseline in ramipril group: Mean LVMI 117.3 g/m^2 to 106.9 g/m^2, P<0.001 • NSS difference between groups	

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

Patch et al. 2011 (14)	• Retrospective cohort study using the UK General Practice Research Database
	• Patient data collected using diagnostic codes from medical records and prescription data
		• 1877 ADPKD patients aged > 15 years in UK General Practice Research Database between 1991 and 2008	• Purpose of study was to use a Poisson regression model to determine association between 5 antihypertensive classes and:
			  • Death
			  • New RRT event
			• 5 antihypertensive classes included in regression model:
			  • RAAS drugs (ACE-I, ARB)
			  • BB
			  • CCB
			  • Diuretics
			  • Other (centrally acting drugs, alpha-blockers, vasodilators)
			• Regression model was adjusted for:
			  • Age
			  • Sex
			  • Year of entry to cohort Calendar year of study
			  • Coronary heart disease
			  • Stroke
			  • Diabetes
			  • Hyperlipidemia
			  • Prescription of lipid lower drugs, including statins and others
						Use of antihypertensive classes from 1991-2008:
						• Proportion of patients prescribed 1 class, 2 classes, 3 classes, and 4 or 5 classes increased
						• Proportion of patients prescribed each of the 5 classes increased, but proportion prescribed RAAS drugs increased substantially from 7% to 46%
						
						All incident rate ratios below are using "drug class not prescribed" as the reference.
						
						Death:
						• Trend toward decreasing mortality as the number of antihypertensive classes prescribed increased ($p<0.001$)
						  • Peak benefit found at 3 antihypertensive classes; incident rate ratio 0.11 (95% 0.06-0.21) compared to 0 classes
						• RAAS drugs, BB, CCB, and diuretics independently
							• Major limitation is retrospective design
							• Reliance on medical codes and prescription data, which may not be accurate
							• Large sample size

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
						associated with lower mortality • Compared to BB and CCB, lower incident rate ratios with RAAS drugs and diuretics • No independent association between other antihypertensives and mortality New RRT event: • Associated strongly with more intensive antihypertensive therapy, suggesting strong confounding by indication	
Cadnapaphorn-chai et al. 2012 (15)	Several analyses done; only the data comparing ACE-I vs. no ACE-I are presented in this table • 5-year, single-centre, randomized, clinical trial • Target BP: randomized to ≤ 50th percentile or ≤ 90th percentile • BP measured at home (6 times, 3 min apart) using digital BP monitor	• 57 patients aged 4-21 years with ADPKD (diagnosed by ≥1 renal cyst in setting of ADPKD family history, or multiple cysts that were clinically consistent with ADPKD) and normal renal function • Patients randomized to ACE-I or no	ACE-I (enalapril); losartan could be used as alternative if unable to tolerate enalapril (n=30 in total)	No ACE-I (n=27 in total)	1° outcome: • Renal volume by U/S 2° outcomes include: • Micro-albuminuria • LVMI • 24h CrCl	Borderline hypertensive group (n=27): • 10 dropouts (6 in ACE-I group vs. 4 patients in no ACE-I group); specific reasons not provided • No significant differences in renal volume, microalbuminuria, or LVMI when comparing ACE-I vs. no ACE-I • No significant change in 24h CrCl over time in ACE-I group • Mild 24h CrCl decline from baseline in no ACE-I group (p<0.03)	• Small sample size with high dropout rate • Not blinded • Multiple comparisons made with data from the entire study, increasing risk of chance findings • No information provided on the use of additional BP meds in the ACE-I and no ACE-I groups • No safety data reported

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
	at least monthly for medication adjustments • 2nd line BP med: amlodipine • 3rd line BP med: metoprolol • 4th line BP med: HCTZ • 5th line BP med: others as necessary	ACE-I were either borderline hypertensive, or normotensive with severe ADPKD (BP <75th percentile and >10 renal cysts) • Borderline hypertensive group (n=27): Mean age 12 years, BP 119/68, 24h CrCl 127 mL/min/1.73 m^2, TKV corrected for BSA 190 mL/1.73 m^2, LVMI 71 g/m^2, UAE 23 mcg/d • Normotensive with severe ADPKD group (n=30): Mean age 12 years, BP 109/64, 24h CrCl 135 mL/min/1.73 m^2, TKV corrected for BSA 188mL/1.73 m^2, LVMI 61 g/m^2, UAE 31 mcg/d				Normotensive with severe ADPKD group (n=30) • 5 dropouts (2 in ACE-I group vs. 3 patients in no ACE-I group); specific reasons not provided • No significant differences in renal volume, microalbuminuria, LVMI, or CrCl when comparing ACE-I vs. no ACE-I	

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
Nakamura et al. 2012 (16)	• 12-month prospective, blinded, randomized trial • BP measured manually • BP target < 130/80 mm Hg • With the exception of ACE-I and ARBs BP meds at baseline were maintained at the same dosages and no other BP meds were added	• 20 ADPKD patients aged 20-80 years with micro-albuminuria, preserved renal function, and HTN (BP > 140/90 mm Hg on ≥2 occasions or on BP med) • Excluded patients with SCr > 88 mmol/L, eGFR < 60 mL/min, current smokers, CVA within past 6 months, CHF, PVD, IHD • All patients were on BP meds at baseline • Mean age ~58 years • Mean BP ~159/98 • Mean eGFR ~67 mL/min/1.73 m^2 • Mean UAE ~91 ug/min	Telmisartan 80 mg daily (n=10) Baseline BP meds in this group (n): • Alpha-blocker (0) • BB (2) • CCB (6) • Diuretics (4) • Other (3)	Enalapril 10 mg daily (n =10) Baseline BP meds in this group (n): • Alpha-blocker (3) • BB (2) • CCB (7) • Diuretics (4) • Other (3)	At 6 and 12 months, change in: • SBP • DBP • SCr • eGFR • UAE • Serum HMGB1 • Serum IL-6 • UrinaryOHdG	No numerical data provided for results below Change from baseline: • SBP and DBP decreased significantly in both groups • Little change in SCr in either group • UAE and urinary 8-OHdG decreased significantly in both groups • Serum HMGB1 and IL-6 decreased significantly in both groups Telmisartan vs. enalapril: • No significant difference in SCr or eGFR • Significantly greater decrease in UAE and urinary 8-OHdG at 6 and 12 months ($p<0.05$ for all comparisons) • Significantly greater decrease in serum HMGB1 and IL-6 at both 6 months ($p<0.01$) and 12 months ($p<0.05$) ADRs: None in either group	• Small sample size • Blinding process not described • Surrogate markers used as outcomes • Short follow-up period • Dosage of enalapril used was low compared to that of telmisartan (max recommended dose is 80 mg for telmisartan, vs. 40 mg/d for enalapril)

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

Orskov et al. 2012 (17)	Primary objective 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 BP meds 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
						Only results related to BP meds listed below:
						• Treatment with RAAS blockade during follow-up period associated with a later onset of ESRD by 4.3 years (95% CI 2.6-6.0; $p < 0.0001$)
						• Treatment with CCB during follow-up period associated with a later onset of ESRD by 2.1 years (95% CI 0.5-3.7; $p = 0.01$)
						• No significant associations between age at onset of ESRD and BB or diuretic use
							• 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	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
Ulusoy et al. 2012 (18)	• Single-centre retrospective study of data over 5 years • Specific methods not described • Target BP ≤ 130/80 mm Hg	• 18 ADPKD patients aged 18-70 years from a single nephrology clinic with HTN (≥140/90 mm Hg) and CrCl ≥ 30 mL/min • 2nd-line BP med that was permitted for study inclusion: amlodipine 5-10 mg or doxazosin 4-8 mg • Excluded patients with DM, CHF, otherrenal disorders, or surgery in preceding 5 years, and smokers • Mean age 50 years • Mean BP 156/98 • Mean CrCl 91 mL/min • Mean TKV 1275 cm^3	Initial HTN treatment with losartan (n=11) Losartan dosage was 100 mg/d in all patients in this group Additional BP meds in this group (n): • None (7) • Amlodipine (3) • Amlodipine + doxazosin (1	Initial HTN treatment with ramipril (n=7) Ramipril dosage ranged 2.5-10 mg/d Additional BP meds in this group (n): • None (5) • Amlodipine (2)	• BP • CrCl • Renal volume	BP: • Target BP achieved at 1 year and maintained at end of year 5 • No significant difference between groups CrCl: • Losartan group: Annual decrease of 6.59 mL/min over 5 years • Ramipril group: Annual decrease of of 1.33 mL/min over 5 years • No significant difference between groups in mean change in CrCl from baseline to 1 year (p=0.53) or to 5 years (p=0.06) Renal volume: • Losartan group: Annual increase in TKV 252.04 ± 271.10 cm^3 over 5 years • Ramipril group: Annual increase in TKV 167.36 ± 144.74 cm^3 over 5 years • No significant difference between groups in increase in renal volumes at 1 or 5 years	• Major limitation is retrospective design • Small sample size • Safety data not available/ provided

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
Schrier et al. 2014 (19) HALT-PKD Study A	In addition to comparing BP meds, also randomized patients to standard or low BP targets in 2-by-2 factorial design; only data pertaining to BP med 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) • BP measured at home • BP target either standard target (120/70 to 130/80 mm Hg) or low target (95/60 to 110/75 mm Hg) • 1st line BP med: lisinopril + placebo, or lisinopril + telmisartan • 2nd line BP med: HCTZ	• 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	Lisinopril 5 mg/d, increased as needed to max 40 mg/d + Telmisartan 40 mg/d, increased as needed to max 80 mg/d (n=273)	Lisinopril 5 mg/d, increased as needed to max 40 mg/d + Placebo (n=285)	1° outcome: • Percentage change in TKV over time 2° outcomes (select ones listed here): • Rate of change in eGFR • Urinary aldosterone excretion • Urinary albumin excretion • Renal blood flow • LVMI • Frequency of all-cause hospital-izations • Quality of life • Frequency of pain associated with ADPKD • Adverse effects related to study medication	Study retention: • 75.8% completed study according to protocol • 8.7% discontinued study medication before end of the study • 6.1% modified consent to less than full study participation • 18.1% lost to follow-up BP control: • Significantly lower BP in lisinopril/telmisartan group at 4-month and 12-month visits only • Significantly greater diuretic use in lisinopril/placebo group, compared to lisinopril/telmisartan group (41.4% vs. 29.7%, p=0.004) • Mean lisinopril dose was 5 mg/d higher in lisinopril/placebo group 1° outcome: • Similar rates between groups (6.0% per year vs. 6.2% per year, respectively) • TKV increased by 40.5% vs. 42.5%, respectively • No significant subgroup interactions when stratifying for or age, sex,	• Long follow-up duration • Use of a surrogate marker for primary outcome • Large sample size, but close to 20% lost to follow-up • Multiple comparisons made, increasing the risk of false positive results

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
	• 3rd line BP med: metoprolol • 4th line BP meds: non-DHP CCBs, clonidine, minoxidil, and/or hydralazine					baseline TKV • Marginal benefit in annual TKV increase for patients with baseline eGFR < 80 mL/min/1.73 m^2 in lisinopril/telmisartan group, compared to those in telmisartan/placebo group (5.7% per year, vs. 6.9% per year; p=0.006) 2° outcomes: • Similar rate of eGFR decline in both groups (-3.00 mL/min/1.73 m^2 per year, vs. -2.86 mL/min/1.73 m^2 per year; p=0.55) • Unchanged urinary albumin excretion in both groups • Similar decline in urinary aldosterone • Significant and similar decline in LVMI • Similar increase in renal blood flow and renal vascular resistance • NSS differences in physical component scores of SF-36, but significantly better mental component scores in lisinopril/telmisartan group (p=0.02)	

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
						• Lower risk of hospitalization in lisinopril/telmisartan group (HR 0.71; 95% CI 0.53 to 0.93) • Risk of having kidney stones decreased each month in lisinopril/telmisartan group (OR 0.99; 95% CI 0.98 to 1.00), as compared to no change in lisinopril/placebo group (OR 1.00, 95% CI 0.55 to 1.01) ADRs: • Rates of ADRs were low and overall similar, including rates of AKI and cancer • Higher rate of hyperkalemia in lisinopril/telmisartan group, though rates were low (4.0% vs. 1.8%)	
Torres et al. 2014 (20) HALT-PKD Study B	• Multicenter, double-blind, placebo-controlled RCT with follow-up of 5-8 years (mean 5.2 years)	• 486 ADPKD patients aged 18-64 years, eGFR 25-60 mL/min/1.73 m^2, with HTN or high-normal BP	Lisinopril 5 mg/d, increased as needed to max 40 mg/d + Telmisartan 40 mg/d, increased as needed to max 80 mg/d (n=244)	Lisinopril 5 mg/d, increased as needed to max 40 mg/d + Placebo (n=242)	1° outcome: • Composite of time to death, ESRD, or a 50% reduction from baseline eGFR	Study retention: • 85.2% vs. 90.1% completed study according to protocol • 5.8% discontinued study medication and/or reduced number of study visits/assessments • 6.4% lost to follow-up	• Use of clinically relevant outcomes • Large sample size with high rate of study completion • Long duration of follow-up

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
	• BP measured at home • Target BP 110-130/70-80 mm Hg • 2nd-line BP med: furosemide • 3rd-line BP med: non-dihydropyridine CCB, clonidine, minoxidil, and/or hydralazine	(HTN defined as SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg on 3 separate occasions, or use of BP med) • Mean age 49 years • 81% with PKD1 genotype • Mean SCr 141 umol/L • Mean aldsterone 10 ug/24h • Median urinary albumin 29 mg/24 h			2° outcomes include: • Rate of change in urinary albumin and aldosterone • Frequency of all-cause hospitalization • Frequency of hospitalization for CV causes • Quality of life • Incidence of pain • Frequency of symptoms related to ADPKD • Adverse study medication effects	BP control: • SBP and MAP within target range throughout trial in 73-86% and 70-83% of patients, respectively • DBP in target range for only 56-65% of patients • Lower SBP in lisinopril/telmisartan group, compared to lisinopril/placebo group; difference 1.23 mm Hg (95% CI 0.15 to 1.63, p=0.02) • Patients in lisinopril/placebo group received diuretics and beta or alpha/beta blockers more frequently than lisinopril/telmisartan group (46.7% vs. 37.7% and 21.0% vs. 23.0%, respectively) 1st outcome: • NSS difference; HR 1.08 (95% CI 0.82-1.42) • NSS differences in any components of composite outcome (death, ESRD, 50% reduction in eGFR) • Mean eGFR decline after adjusting for informative censoring was -3.91 mL.min/1.73 m2 per year, vs. -3.87 mL/min/1.73 m^2 per year	• High rate of achieved BP targets

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
						• No significant subgroup interactions when stratifying for age, sex, baseline eGFR, or baseline urinary albumin 2° outcomes: • NSS differences in any ADRs: • Similar rates of ADRs, include episodes of hyperkalemia or AKI, which were mostly mild • Deaths in 1.6% vs. 2.1%; none thought to be due to study medications or trial	

Xue et al. 2015 (21)	• Network meta-analysis of 10 studies comparing BP meds in adult ADPKD patients
	• Studies were to be included only if they were RCTs; however, Ulosoy 2010 was included despite non-randomization to BP meds
		See information for 10 included studies above; total N = 1386	• Comparison between various BP med treatments
			• BP med treatments included in analyses:
			  • ACE-I
			  • ARB
			  • ACE-I + ARB
			  • BB
			  • CCB
					• SBP
					• DBP
					• MAP
					• LVMI
					• eGFR
					• UAE
						BP :
						• No significant differences between all treatments in SBP (7 studies), DBP (7 studies), or MAP (5 studies)
						LVMI:
						• Similar LVMI lowering effect in all treatments (4 studies)
						eGFR:
						• No difference of GFR between all treatments (7 studies)
						UAE:
						• UAE compared in 7 studies
						• Increased UAE with CCB compared to RAAS
							• Inclusion of a study in which BP meds were not randomized
							• Most ADPKD patients included were prescribed combinations of BP meds that varied across studies, making it difficult to isolate the effect of each antihypertensive class

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
	• 10 studies included: Ecder et al. 2000 (3), Nakamura et al. 2001 (5),Schrier et al. 2002 (7), van Dijk et al. 2003 (8), Nutahara et al. 2005 (10), Zeltner et al. 2008 (11), Ulusoy et al. 2010 (13), Nakamura et al. 2012 (16), Schrier et al. 2014 (19), Torres et al. 2014 (20)					inhibition treatments and BB Direct comparisons between antihypertensive classes: • I^2 > 80% for all pooled analyses • Compared to CCB, ACE-I associated with significantly lower SBP (1 study), DBP (1 study), MAP (1 study), and LVMI (1 study) • Compared to CCB, RAAS inhibition associated with significantly lower UAE (1 study comparing ACE-I vs. CCB, 1 study comparing ARB vs. CCB)	• High I^2 values for all direct comparisons, indicating that pooling the study results is inappropriate (this is expected, as study designs, populations, and follow-up durations varied)
Sung et al. 2017 (22)	Several analyses done; only data from comparisons pertaining to RAAS blockade exposure are presented in this table • Population-based cohort study with mean follow-up duration of 9 years	• 2647 ADPKD patients in the Taiwan National Health Insurance Research Database • Median age 46 years (IQR 37-55 years)	• Multivariable Cox proportional hazard regression analysis of factors associated with CVA (defined as ischemic or hemorrhagic stroke) • Factors included in multivariable analysis ("exposure" defined as regimen duration >3 months based on prescription data): • Gender • Age • Hypertension • Diabetes mellitus • Dyslipidemia			Compared to no exposure to RAAS blockade or statin: • Lower risk of CVA with RAAS blockade exposure alone (adjusted HR 0.37; 95% CI 0.28-0.50) • Even lower risk of CVA with combined statin + RAAS blockade exposure (adjusted HR 0.19; 95% CI 0.11-0.31)	• Reliance on ICD-9-CM codes and prescription data, which may not be accurate • Some patient data were not available (eg. laboratory values, lifestyle factors, body mass index, functional capacity)

STUDY	STUDY DESIGN	POPULATION	INTERVENTION	CONTROL	OUTCOMES	RESULTS (INTERVENTION VS. CONTROL, UNLESS OTHERWISE SPECIFIED)	COMMENTS
			• RAAS blockade exposure (n = 1595; 60.3% of patients) • RAAS blockade defined as ACE-I, ARB, direct renin inhibitor, and/or mineralocorticoid receptor antagonist • Statin exposure (n = 702; 26.5% of patients)				• Only collected prescription data on statins and RAAS blockade; therefore, did not adjust for any other potential medication-related confounders • RAAS blockade definition comprised of several different BP med classes and no information provided on number of patients prescribed each class; therefore, difficult to interpret results pertaining to RAAS blockade • No safety data available

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Papizh et al. 2018 (23)	Only abstract available • 12-month, non-randomized, prospective cohort study comparing GFR in patients on ACE-I vs. not on ACE-I • BP measured by ABPM • Normal BP defined as <90th percentile; high-normal BP defined as 90-95th percentile; high BP defined as >95th percentile	• 34 pediatric ADPKD patients and CKD Stage 1 • Median age 12.5 years (IQR 9-15)	ACE-I (n=19) • 84.2% with high BP at baseline No ACE-I (n=15) • 100% with normal BP at baseline	Baseline	• BP • Change in eGFR (calculated using Schwartz formula)	ACE-I group: • BP at baseline: 42.1% with high BP, 15.8% with high-normal BP; 42.1% with normal BP • No significant decrease in eGFR from baseline overall [126 (103.1;129) vs. 117.3 (110.9;131), p=0.68)] • No significant decrease in eGFR within each BP classification group No ACE-I group: • BP at baseline, 33.3% with high BP; 66.7% with normal BP • Significantly lower GFR from baseline overall [130 (104.5;142.3) vs. 108 (102.9;120), p=0.01)] • Decrease in GFR in patients with both high BP [(130 (113;133) vs. 108 (102.9;120), p= 0.04] and normal BP [127.5 (104;143.5) vs. 108.6 (105;122.4), p=0.05)]	• Small sample size • Non-randomized and unblinded • Short follow-up period • No comparisons done between ACE-I and No ACE-I groups; however, may have been inappropriate to make comparisons due to baseline differences • No safety data provided

ABPM = ambulatory blood pressure monitoring; ACE-I = angiotensin-converting enzyme inhibitor; ACR = albumin=to-creatinine ratio; ADR = adverse drug reaction; ARB = angiotensin II receptor blocker; BB = beta-blocker; BID = twice daily; BP = blood pressure; BSA = body surface area; CCB = calcium channel blocker; CHF = congestive heart failure; CVA = cerebrovascular accident; DHP = dihydropyrine; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; GFR = glomerular filtration rate; HTN = hypertension; HMGB1 = high mobility group box-1 protein; IHD = ischemic heart disease; IL-6 = interleukin-6; ITT = intention-to-treat; MAP = mean arterial pressure; MI = myocardial infarction; NS = non-significant; UPE = urinary protein excretion; OHdG = 8-hydroxydeoxyguanosine; PAH = p-aminohippurate clearance; PKD = polycystic kidney disease; PVD = peripheral vascular disease; RAAS = renin-angiotensin-aldosterone system; RRT = renal replacement therapy; SBP = systolic blood pressure; TKV = total kidney volume; UAE = urinary albumin excretion; UPE = urinary protein excretion; U/S = ultrasound

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